NUMBER 61 AUGUST 2008

CODE OF PRACTICE REVIEW

PMCPA Prescription Medicines Code of Practice Authority

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

CODE AWARENESS WEEK 2008

Code Awareness Week 2008 will take place from 29 September-3 October 2008. All member companies of the ABPI and non-member companies that have agreed to comply with the Code are encouraged to support Code Awareness Week by allocating time for sales representatives and others who have contact with external stakeholders to promote the Code to customers, doctors, pharmacists, nurses and NHS management as part of their regular programme of calls this week. This would send a powerful signal of the industry's ongoing commitment to high standards of ethical behaviour. The week will also provide an excellent opportunity to reinforce the importance of the Code amongst your own staff.

It is up to individual companies how much time is allocated to awareness activities during the week. The PMCPA will provide briefing material, key messages and leave pieces for the week.

So if your company hasn't yet signed up to participate, please do so today by emailing nmacmahon@pmcpa.org.uk.

COMPLIANCE WITH UNDERTAKINGS

An undertaking, given in acceptance of a ruling of a breach of the Code, is an important document. It includes an assurance that all possible steps will be taken to avoid similar breaches of the Code in future. It is very important for the reputation of the industry that companies comply with undertakings.

On occasion, a journal advertisement found to be in breach of the Code has subsequently been published again some time later due to the erroneous use of an old electronic copy of it stored by a third party. Companies are advised to make certain that their procedures are such that they ensure that materials which are no longer acceptable are not used again, no matter how they have been stored or by whom.

Any oral communications with third parties regarding the withdrawal of journal advertisements should always be confirmed in writing. It is helpful if the message from the company includes the following:

- A full explanation of which advertisement is to be destroyed and why. Agencies should know that the changes are due to a breach of the Code and not just a 'tweak' to the campaign.

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PUBLIC REPRIMAND AND SUSPENSION FOR ROCHE

Roche Products Limited has been publicly reprimanded by the Code of Practice Appeal Board for breaches of the Code in relation to the inappropriate supply of a prescription only medicine to a bogus health professional and the funding for a new private clinic. The Appeal Board was extremely concerned about this case particularly with reference to Roche's disregard for patient care.

Roche has now been suspended from membership of the ABPI for a minimum of six months by the ABPI Board of Management.

The ABPI Board considered that funding the new clinic, and Roche not taking any action in relation to the supply of a medicine to an existing clinic following the visit by a Roche employee posing as a new patient in 2003, were very serious matters.

The suspension took effect from 14 July 2008 with re-entry conditional upon an audit which the company will undergo in September proving satisfactory to the ABPI Board. Roche will be required to comply with the Code during the period of suspension.

Full details can be found at page 37 of this issue of the Review in the report for Cases AUTH/2099/2/08 and AUTH/2100/2/08.

CODE OF PRACTICE TRAINING

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

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

The next Code of Practice seminar dates on which places remain available are:
Friday, 12 September
Friday, 10 October

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.

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- A clear instruction that old copies of the advertisement must be destroyed with the inclusion of reference codes or some other easy way for the third party to correctly identify the material at issue.
- A request for written confirmation that copies have been destroyed forthwith. Agencies should only be given a very short time limit within which to provide such confirmation

Companies are advised to keep written records of action taken to withdraw material.

USE OF PATIENT CASE STUDIES

Companies may illustrate their promotional material with relevant patient case studies but everything which the company states, or the patient states, about the disease or response to treatment will be subject to the Code. Particular attention must be paid to Clauses 3.2 and 7. Patients chosen must be typical in terms of their condition and response to therapy; for example, those at the severe end of the disease spectrum with an outstanding response to treatment should therefore not be chosen. Asking patients to participate in videos and the like can be difficult as the company will be responsible under the Code for whatever the patient says, no matter how sincerely held are their views.

Patients can be paid if they have given up their own time to provide case study material to a company. Such payment should fairly reflect the time and effort involved.

ARE YOUR JOB BAGS IN ORDER?

When called upon to audit a company's procedures relating to the Code, the Authority will produce, on the day of the audit, a number of journal advertisements, up to three years old, and request the relevant job bags. It is rare to find the certification of these job bags wholly in order. Common errors include one reference number being used for a number of different layouts/sizes, the advertisement being certified in one form and printed in another, the certificate only being signed by one person and in some cases the certificate post dating the publication date.

Clause 14 sets out the requirements for certification and guidelines on the certification of promotional material are included in the guidelines on company procedures in the Code booklet. Using this information, companies might find it useful to periodically audit their own certification process – perhaps rewarding the brand team with the best kept job bags!

CASE AUTH/2091/1/08

GE HEALTHCARE v GUERBET LABORATORIES

Dotarem exhibition panel

GE Healthcare complained about the claim 'Dotarem The MR Gadolinium Complex with the highest Stability' used on an exhibition panel used by Guerbet Laboratories to promote Dotarem (gadoteric acid).

GE Healthcare considered that the claim of 'highest stability' implied a clinical benefit of Dotarem over other products. The relationship between the stability of gadolinium-based contrast media (GdCM) and their propensity to cause nephrogenic systemic fibrosis (NSF) had been widely debated. GE Healthcare was unaware of any evidence of a clinical benefit, safety or otherwise, linked to a higher stability, especially when the claim might be based on *in vitro* measurements in a non-physiological environment. GE Healthcare alleged that the claim was misleading.

The Panel noted that the issue of stability of GdCM and the development of NSF had been examined. The use of some agents was associated with a higher risk of NSF than others. Dotarem was one of the three agents considered the most stable and least likely to cause NSF. The risk of NSF with three other agents (MultiHance, Primovist and Vasovist) remained under investigation. The public assessment report (PAR) for GdCM stated that NSF and the role of GdCM was an emerging science. The Dotarem summary of product characteristics (SPC) included a statement in relation to patients with impaired renal function that there was a possibility that NSF might occur with Dotarem which should only be used in such patients after careful consideration.

The supplementary information to the Code stated that the extrapolation of, *inter alia*, *in-vitro* data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. It was also stated that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. The Panel noted that it was an accepted principle under the Code that all claims related to the clinical situation unless otherwise stated.

The Panel considered that the claim at issue 'Dotarem The MR Gadolinium Complex with the highest Stability' implied a clinical benefit as a consequence of its stability over less stable agents which had not been proven. In that regard the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

Upon appeal by Guerbet, the Appeal Board considered that the claim 'Dotarem The MR Gadolinium Complex with the highest Stability' was true. The claim could be substantiated with the available physicochemical data and no contrary data had been provided. The Appeal Board ruled no breach of the Code in this regard.

The Appeal Board considered that even when a claim was true, the context in which it was used was very important. It was an accepted principle under the Code that claims etc related to the clinical situation unless otherwise stated. The claim at issue had been used with clinicians who would be familiar with the ongoing debate regarding stability and NSF. In Appeal Board's view the claim could be interpreted to mean that the 'highest stability' resulted in the 'highest safety'. In that regard the Appeal Board noted the statements from the various regulatory organisations, in particular the PAR which stated 'NSF and the role of gadolinium-based contrast media is an emerging science. The exact disease mechanism has yet to be elucidated, but physicochemical properties of gadolinium-containing agents *might* (emphasis added) affect the amount of free gadolinium released in patients with renal impairment'. The PAR concluded that the data did not *suggest* that the risk of NSF in patients with advanced renal impairment was the same for all GdCM. The non-ionic linear chelates (Omniscan and optiMARK) were associated with the highest risk because they were *more likely* to release free gadolinium than the cyclical chelates (Gadovist, ProHance and Dotarem) which were the most stable and *likely* to have the lowest risk of NSF.

The Appeal Board noted the submission that the claim at issue had been used for many years without complaint. Stability of GdCM had, however, only relatively recently been postulated to be linked to the development of NSF. In that regard the claim had taken on a new relevance for clinicians and the Appeal Board considered that within the context of the current scientific debate it implied a clinical benefit for Dotarem as a consequence of its stability which had not been proven. The Appeal Board considered that, as used, the claim was misleading and it upheld the Panel's rulings of breaches of the Code.

GE Healthcare Limited complained about the claim 'Dotarem The MR Gadolinium Complex with the highest Stability' on an exhibition panel used by Guerbet Laboratories Ltd to promote Dotarem (gadoteric acid).

COMPLAINT

GE Healthcare considered that the claim of 'highest stability' implied a clinical benefit of Dotarem over other products. GE Healthcare was unaware of any evidence of a clinical benefit, safety or otherwise, linked to a higher stability, especially when the claim might be based on *in vitro* measurements in a non-physiological environment. GE Healthcare alleged that the claim was misleading in breach of Clauses 7.2, 7.3 and 7.4 of the Code.

GE Healthcare considered that Guerbet had used the claim at a clinical meeting to imply a benefit in the clinic and noted that the Code stated that care must be taken to ensure that data from *in vitro* and animal studies were not extrapolated to the clinical situation unless there were data to show that they were of direct relevance and significance (Clause 7.2). GE Healthcare knew of no clinical data which substantiated this. The findings from laboratory and animal studies on the relative stability of some gadolinium-based contrast media (GdCM) were variable and the methodology frequently lacked validation. In fact, even the definition of stability in this context was unclear as many different definitions were used in the literature.

- Nephrogenic systemic fibrosis (NSF), GdCM and stability: There had been considerable discussion since early 2006 on the chemical stability of the gadolinium (Gd)-chelate used to provide contrast in magnetic resonance imaging (MRI) studies and whether this was a factor in the development of the rare, but potentiality serious, chronic, disabling condition nephrogenic system fibrosis in patients with severe renal impairment. Three types of stability constant had been defined for GdCM: the thermodynamic (Ktherm), conditional (Kcond), and selectivity (Ksel). Ktherm was measured at very high pH values incompatible with life. Kcond was the stability constant at physiologic pH (pH 7.4). Ksel was the stability at pH 7.4 toward exchange of the Gd3+ ion in a chelate for another ion such as H^+, Zn^{2+}, Cu^{2+}, etc. These three stability constants were measured *in vitro*, and in water (or calculated from data measured in water), rather than a physiological solution or blood. They applied to pure chelates only and not to commercial formulations of GdCM because they did not take into account factors such as extra ligand. They were contradictory in their predictions of GdCM stability, and as they did not necessarily reflect the stability of the Gd complex *in vivo*, it was not surprising that they did not correlate well with measures of acute toxicity.

  Furthermore, there was no clear correlation between the numbers of reported NSF cases for the various GdCM and their thermodynamic stability. This seemed to question a relationship between NSF and the thermodynamic stability of GdCM, a suggestion which was made repeatedly by Guerbet.

  Although the exhibition panel in question did not overtly tie stability to the risk of NSF, the stability claim was clearly designed with discussion of NSF in mind; there was no other reason to raise the issue. That a number of independent authors had raised the issue of stability as a possible factor in the potential differences in the risk of NSF did not excuse this line of promotion by Guerbet, when there was no clinical evidence to support this theory.

- NSF and the Medicines and Healthcare products Regulatory Agency (MHRA): in intercompany correspondence, Guerbet referred to the updated public assessment report (PAR) regarding NSF and GdCM issued in June 2007 by the MHRA in co-operation with the Committee for Medicinal Products for Human Use (CHMP) Pharmacovigilance Working Party (PhVWP). GE Healthcare was concerned about the PAR, and did not believe that it could or should be used to justify Guerbet's claims. The PAR was not clinical research, but a collection and comment on some of the NSF data. Certain hypotheses regarding the physiochemical stability of Gd chelates and the development of NSF were presented in the PAR as fact or substantiated theories, rather than hypotheses that were still the subject of considerable scientific investigation, because no causative mechanism for NSF had yet been identified.

  Different Gd chelates exhibited different levels of thermodynamic stability *in vitro*, but GE Healthcare knew of no data to demonstrate that this had any clinical consequences given that the amount of free Gd released *in vivo* appeared to be negligible for all compounds. It was not known whether transmetallation (substitution of the Gd ion in the Gd/chelate complex for another heavy metal ion) played a role in the development of NSF. No published studies had found transmetallation of GdCM or metabolism of free Gd after use of GdCM in humans. Some studies did not use commercial formulation and no studies had used analytical methods capable of distinguishing between complexed and free Gd.

  Regarding Kimura *et al* (2005), cited by Guerbet, GE Healthcare noted that any link between zinc elimination and stability or transmetallation, was unproven. The authors stated that excess ligand was also considered to be responsible for the increase in urinary zinc excretion (which was not clinically significant). In fact, relating to gadodiamide, it was far more likely that zinc elimination in the urine was due to excess chelate, as the affinity of zinc for the chelate was in the region of 30,000 times lower than the affinity of Gd for the chelate. Therefore it seemed highly unlikely, and was certainly not proven, that zinc would displace Gd from the Gd-chelate complex when there was an excess of free ligand (as in the commercial formulation of Omniscan GE Healthcare's product).

- Research and an evolving clinical situation: GE Healthcare noted that much of the research conducted to date was in animals or *in vitro*, and the relevance of such studies to humans must be judged very carefully. Furthermore, the human studies must be viewed in light of the entire body of knowledge on GdCM for proper interpretation. To date, it had still not been shown that Gd whether free or chelated, caused NSF. Furthermore, recent case reports of NSF occurring in association with purportedly more stable cyclic GdCM continued to throw doubt upon the physiochemical stability hypothesis.

RESPONSE

Guerbet submitted that kinetic and thermodynamic stability data were acceptable measures of stability assessed by the MHRA and the European Pharmacovigilance Working Group during their recent assessment of agent stability and investigation into the causes of NSF. The detailed PAR published by the MHRA in June 2007 stated 'Cyclic molecules offer better protection and binding to Gd compared with linear molecules. For example, the ionic cyclic chelate gadoterate meglumine has a much longer dissociation half-life and higher thermodynamic stability than the non-ionic chelate gadodiamide'.

Guerbet considered that this report was a definitive collation, review and assessment of all of the current data relating to NSF and the stability of GdCM made by the definitive group of decision makers and experts. The meetings that took place at the EMEA and the subsequent document had been used not only in the UK, but across Europe to influence and change practice relating to choice of GdCM based upon the agents' stability and potential for contribution to cause of NSF. Guerbet was surprised that GE Healthcare did not accept the importance of this report, especially when the clinical evidence upon which it was based had contributed to a review of and significant changes to the safety data contained within the summaries of product characteristics (SPCs) for all Gd agents and in particular GE Healthcare's product Omniscan.

Further the MHRA PAR stated that 'The non-ionic linear chelates (Omniscan and OptiMARK) are associated with the highest risk of NSF because they are more likely to release Gd from the chelate complex in patients with severe renal impairment than are other agents. By contrast, the cyclical chelates (Gadovist, ProHance and Dotarem) are considered the most stable and likely to have the lowest risk of NSF'. The stability data to which the report referred included kinetic and thermodynamic measurements and was purely based on irrefutable physicochemical facts. GE Healthcare's opinion that the stability data could not be extrapolated to the clinical setting contradicted the European Pharmacovigilance Working Group and eminent scientists/clinicians called as experts to this issue.

To further support the claim of 'highest stability' Guerbet submitted that when comparing an ionic agent against a non-ionic agent: 'The simple removal of one anionic donor atom (carboxylate) and replacement by a non-ionic functional group (amide or ester) resulted in a decrease in stability of the resulting Gd complex by about three orders of magnitude' (Brücher and Sherry, 2001). More simply, an agent would be more stable if it was ionic rather than non-ionic.

In addition and as an overview, Guerbet noted that Morcos (2007) stated:

> 'Currently, there are seven extracellular Gd-CA available for clinical use (Table 1). They are all chelates containing Gd ion (Gd+++). The configuration of the molecules is either linear or cyclic. They are available as ionic or non ionic preparations. Understanding the synthesis of metal chelates is somewhat difficult especially for those of us who have no deep knowledge in chemistry. However, the author of the article attempted to present some of the chemical principles involved in the production of Gd chelate in a simplified manner and hopefully without important compromise of scientific accuracy. The gadolinium ion has nine coordination sites (coordination sites represent the number of atoms or ligands directly bonded to the metal centre such as Gd++. A ligand is a molecule or atom that is bonded directly to a metal centre. The bonding between the metal centre (Gd+++) and the ligands is through valent bonds in which shared electron pairs donated to the metal ion by the ligand). In the ionic linear molecule such as Gd-DTPA, Gd+++ is coordinated with 5 carboxyl groups and 3 amino nitrogen atoms. The remaining vacant site is coordinated with a water molecule which is important in enhancing the signal by the contrast agent in T1 weighted MR imaging (Figure1). In the non ionic linear molecule such as gadodiamide and gadoversetamide the number of carboxyl groups are reduced to three as the other two carboxyl groups have been replaced by non ionic methyl amide (Figure 2). Although both amide carbonyl atoms are directly coordinated to Gd+++ the binding is weaker in comparison to that of carboxyl groups. This will result in weakening the grip of the chelate on the Gd+++ and decreasing the stability of the molecule. The other feature which influences the binding between the Gd+++ and the chelate is the configuration of the molecule; the cyclic molecule offers a better protection and binding to Gd+++ in comparison to the linear structure.'

This meant that an ionic macrocylic gadolinium agent would have the highest stability. As Dotarem was the only ionic macrocyclic gadolinium agent available for MRI it was therefore the agent with the highest stability. GE Healthcare knew this and in fact the team that worked on Omniscan published 'The benefits of high kinetic and thermodynamic stability offered by structurally preorganized and rigid metal

chelates such as DOTA macrocycles for use as magnetic resonance imaging contrast agents are well established' (Varadarajan *et al* 1994).

Guerbet stated that the exhibition panel in question made no clinical claims for Dotarem; in fact it did not promote any licensed indication and purely stated a physiological fact.

Guerbet was not surprised by GE Healthcare's assumption that Guerbet implied extrapolation to the clinical setting. This statement was made from the practices of GE Healthcare. It was interesting that this assumption arose from a company that depicted a sign leading to a renal unit/ITU to promote one of its own products; this appeared to be far more evocative advertisement than any that Guerbet had produced.

There was no evidence to support the assumption that Guerbet promoted in a similar way to GE Healthcare or that the exhibition panel suggested anything other than the physiological stability of the molecule. Guerbet noted that it had presented the stability of the Dotarem molecule in various promotional pieces at international events for many years and this was the first formal complaint about the issue of stability.

PANEL RULING

The Panel noted that the issue of stability of GdCM and the development of NSF had been examined. The use of some agents was associated with a higher risk of NSF than others. Dotarem was one of the three agents considered the most stable and least likely to cause NSF. The risk of NSF with three other agents (MultiHance, Primovist and Vasovist) remained under investigation. The PAR for GdCM stated that NSF and the role of GdCM was an emerging science. The Dotarem SPC included a statement in relation to patients with impaired renal function that there was a possibility that NSF might occur with Dotarem which should only be used in such patients after careful consideration.

The supplementary information to Clause 7.2 stated that the extrapolation of, *inter alia*, *in-vitro* data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. It was also stated that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. The Panel noted that it was an accepted principle under the Code that all claims related to the clinical situation unless otherwise stated.

The Panel considered that the claim at issue 'Dotarem The MR Gadolinium Complex with the highest Stability' implied a clinical benefit as a consequence of its stability over less stable agents which had not been proven. In that regard the claim was misleading and could not be substantiated. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

APPEAL BY GUERBET

Guerbet appealed the Panel's rulings for the following reasons:

1 The claim 'highest stability' had not been made in connection with the current debate on NSF – evidenced by the fact that Guerbet was using the claim 8 years before NSF was first reported and almost 10 years before a link between NSF and Gd based agents was proposed.

Guerbet submitted that NSF was first reported in 1997. A causal connection between NSF and use of Gd based agents was first proposed in 2006. Guerbet had been using the claim that Dotarem was the most stable Gd based agent since its launch in France in 1989 (promotional items from 1992, 1995, 2000, 2005, and 2006 were provided). The high stability of Dotarem was an important, material property of the agent independent of the current debate on NSF. It had been known for many years that free Gd was poorly tolerated in the body. It was therefore desirable under the precautionary principle to seek to maximise the stability of gadolinium based agents to reduce the release of free gadolinium.

Guerbet submitted that given its consistent use of the term pre-dated awareness of NSF, it was self evident that the claim 'highest stability' was not intended to suggest that use of Dotarem was less likely to result in NSF. As a competitor of Guerbet, GE Healthcare must have been aware of the long standing use of this claim. But it was not until 2007 when independently of any statement by Guerbet the Commission on Human Medicines (CHM) and the EMEA both suggested a possible link between the stability of gadolinium based agents and NSF, that GE Healthcare complained.

2 The claim 'highest stability' was factually correct and scientifically substantiated.

Guerbet noted that Clause 7.2 required that information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis.

Guerbet submitted that it was true that Dotarem had the highest kinetic and thermodynamic stability of any MR gadolinium complex. This stability resulted from its ionised macrocyclic structure, which was unique. The greater stability of Dotarem was recognised by the MHRA, which stated in the PAR that 'the cyclical chelates … (including) Dotarem …are considered to be the most stable' issued in cooperation with the European

Pharmacovigilance Working Party ('PhVWP') of the Committee for Medicinal Products for Human Use (CHMP). This conclusion was based on a review of all existing material, including the articles cited by GE Healthcare in support of its arguments. The material included *in vitro*, *in vivo* and human studies.

Guerbet submitted that the MHRA was even more unequivocal in its question and answer document released in February 2007, which stated that 'Dotarem has a molecular charge and a cyclical structure, and is least likely to release free Gd into the body'. In the nearly 20 years since Dotarem was first introduced in Europe, no competitor except for GE Healthcare had objected to the 'highest stability' claim. GE Healthcare only objected to this claim when the MHRA and the European Pharmacovigilance Working Group linked stability with the risk of NSF.

Guerbet provided a detailed review of the scientific literature on the favourable stability of Dotarem. The claim made by GE Healthcare that the data on relative stability was variable and lacking in validation was simply unfounded.

3 Guerbet's advertising did not state that Dotarem's stability characteristics had clinical implications.

Guerbet's advertising did not state that Dotarem's high stability had any clinical significance. Guerbet made no claim about the relative clinical performance of gadolinium products either expressly or by implication. It did not even mention NSF (which was unsurprising since, as set out above, Guerbet was using this claim long before the first case of NSF was identified or any link between NSF and stability was posited). It merely educated health professionals about the product's stability.

Guerbet submitted that a clinician reading the exhibition panel would appreciate that a comment on 'stability' would be based on preclinical data. It might be that those professionals who were aware of MHRA's and the PhVWP's recommendations would appreciate the potential significance of those characteristics, but if that was the case they would already be aware of the MHRA's and PhVWP's conclusion that Dotarem appeared to have a lower risk of NSF. The clinician could not make a link to NSF without being aware of the independent literature on NSF and the guidance of the regulator. They would also be aware of any continuing debate from the literature. Any extrapolation made to the clinical setting would be a matter for the clinician's own judgment based on the scientific literature and the guidance given by the regulatory authorities.

4 While Guerbet did not make this claim, the regulator had concluded that there might be a link between stability and incidence of NSF.

Guerbet submitted that in February 2007, after reviewing all available evidence, the EMEA concluded that there might be a link between stability and NSF. The PAR of February 2007 stated that 'there were differences in the stability of the gadolinium complex of the different substances that may impact on their propensity to trigger NSF'.

Guerbet submitted that in February 2007, the MHRA sent a circular to health professionals on gadolinium containing MRI contrast agents and NSF which stated:

> **'Mechanism**
> The mechanism by which some gadolinium-containing contrast agents are more likely to trigger NSF than other agents is not understood fully, but is thought to be related to their different physicochemical properties that affect the extent to which they release free gadolinium ions. Deposition of free gadolinium ions in tissues and organs might stimulate NSF through induction of fibrosis…'

Guerbet submitted that the MHRA also issued a questions and answers document in February 2007, which went into more detail on the relationship between the stability of different structures and the risk of NSF. It stated

> 'Gadolinium-containing contrast agents have different properties that affect their behaviour in the body. Contrast agents such as Omniscan and OptiMARK that carry no molecular charge and are arranged in a linear structure with excess chelate seem to be more likely to release free gadolinium ions (Gd3+) into the body. Those that carry a molecular charge and have a linear structure (eg, Magnevist, MultiHance, Primovist, and Vasovist), and those that carry no molecular charge and have a cyclical structure (eg, Gadovist and ProHance), seem to be less likely to release free Gd3+ into the body. **Dotarem has a molecular charge and a cyclical structure, and is least likely to release free Gd3+ into the body…'** (emphasis added by Guerbet).

'… Current evidence suggests that the risk of developing NSF may be related to the structure of the gadolinium-containing contrast agent …. Most cases of NSF have been associated with agents Omniscan and OptiMARK, which have similar structures. A small number of cases have been associated with Magnevist, and, to date, no cases of NSF have been associated with some gadolinium-containing contrast agents. This issue will be monitored closely as evidence accumulates, and new advice will be issued when necessary' and

'… The UK Commission on Human Medicines (CHM) and one of its expert advisory groups reviewed the issue of NSF and gadolinium-based contrast agents in January, 2007. CHM proposed a step-wise approach to restricting the use of gadolinium-based contrast agents in patients with kidney disease, in liver-transplant patients, and in neonates. They advised that Omniscan (and OptiMARK) should not be given to these patients, and that Magnevist, MultiHance, Vasovist,

Primovist, Gadovist, ProHance should not be given to these patients unless regarded clinically essential. For Dotarem, a warning for its use in at-risk patients was also proposed.

Guerbet submitted that in June 2007, the MHRA in conjunction with the PhVWP issued a revised PAR to take account of new evidence. This conclusion as to stability did not change. The report stated that:

> 'A review of the available data does not suggest that the risk of NSF in patients with advanced renal impairment is the same for all gadolinium-based contrast agents. Distinct physicochemical properties affect their stabilities and thus the release of free gadolinium ions, and pharmacokinetic properties influence how long the contrast agent remains in the body…'

Guerbet submitted that the non-ionic linear chelates (Omniscan and OptiMARK) were associated with the highest risk of NSF because they were more likely to release Gd from the chelate complex in patients with severe renal impairment than were other agents. By contrast, the cyclical chelates (Gadovist, ProHance, and Dotarem) were considered the most stable and likely to have the lowest risk of NSF.

Guerbet submitted that in August 2007, the MHRA issued a Drug Safety Update which stated:

> 'The exact mechanism by which a gadolinium-containing contrast agent can cause NSF is not known. However, under some conditions gadolinium ions (Gd3+) are released from chelate complexes through a process of transmetallation with endogenous ions in the body and can accumulate in the skin and other tissues. Gadolinium-containing MRI contrast agents have different levels of NSF risk based on their physicochemical and pharmacokinetic properties (see table). Risk of NSF is considered to be highest with Omniscan and OptiMARK, which have a linear chemical structure with excess chelate, carry no molecular charge, and seem more likely to release free Gd3+ into the body. Those that are cyclical in structure (eg, ProHance, Gadovist, and Dotarem) are least likely to release free Gd3+ into the body. Between these two groups are those that carry a molecular charge and have a linear structure (eg, Magnevist, MultiHance, Primovist, and Vasovist).'

Guerbet submitted that the European Society of Urogenital Radiology had also issued guidance to its members which stated:

> ***'CHOICE OF GADOLINIUM AGENT***
>
> There are differences in the incidence of NSF with the different Gd-CM, which appear to be related to differences in physico-chemical properties and stability. Macrocyclic gadolinium chelates, which are preorganized rigid rings of almost optimal size to cage the gadolinium ion which have high stability.'

Guerbet submitted that the guidance commented on the structure and risks of the different agents available. The MHRA referred health professionals to this guidance.

Guerbet submitted that in conclusion, the consensus of the European medical community and medical regulators on a review of all the available evidence was that there was a possible link between NSF and stability, and that Dotarem was in the class of agents (macrocyclic gadolinium chelates) with the highest stability. Within this class, Dotarem was the only agent with a molecular charge. The MHRA described Dotarem as the most stable because of its molecular charge and cyclical structure. This information had been made widely available by the MHRA on its website and through circulation to health professionals.

5 There was a strong public interest in advertising the comparative stability of Dotarem. This public interest had been recognised by the MHRA, the European Pharmacovigilance Working Group, and experts in the field.

Guerbet submitted that the PAR stated that on the basis of current evidence, the use of GdCM in at-risk patients should be restricted based on their physicochemical and pharmacokinetic properties. Further, the CHM and the PhVWP recommended that relevant health professionals (ie, radiologists, nephrologists, and all physicians who might request MRI radiological investigations in patients with severe renal impairment such as geriatricians and cardiologists) should be given this new information promptly.

The PAR stated that 'It is imperative that radiologists, nephrologists and other healthcare professionals receive guidance on how to avoid [NSF]'. It concluded 'The cyclical chelates [including Dotarem] are considered to have the most stable structure and are likely to be associated with the lowest risk of NSF'.

Guerbet submitted that having regard to the objectives of the Code, that the pharmaceutical industry should behave in a professional, ethical and transparent manner to ensure the appropriate use of medicines and support the provision of high quality care – it was not clear how the use of a claim which was factually accurate, and related to a property considered by the regulator to be important, could be misleading. Indeed, such a communication was in the public interest, as demonstrated by the PhVWP's and the MHRA's efforts to communicate the relative stability characteristics of gadolinium based agents, and the possible relevance of those characteristics, to the medical sector. Indeed, it was preposterous to claim that clinicians had been misled by Guerbet when the regulator itself was widely promoting the importance of stability and the relevance of difference in stability.

6 The Code should not be used as a vehicle to

suppress information which was of public interest and which might assist the promotion of public health.

As set out above, the pharmaceutical industry should behave in a professional, ethical and transparent manner to ensure the appropriate use of medicines and support the provision of high quality care. GE Healthcare sold Omniscan (gadodiamide), a competing GdCM which had been associated with NSF. As GE Healthcare itself recognised, NSF was more strongly linked with some products than with others. An open letter to health professionals issued in September 2007 by GE Healthcare, Bayer Health, Bracco and Mallinckrodt, stated that 'The extent of risk for NSF following exposure to any specific gadolinium-based contrast agent is **unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide'** (emphasis added by Guerbet).

Guerbet submitted that the MHRA and the PhVWP had concluded that on the available evidence, it appeared that the link between NSF and Omniscan might be related to its stability characteristics.

Against this background, it was clear that GE Healthcare might be commercially motivated to suppress statements about Dotarem's favourable stability. However, it was inappropriate to use the complaints procedure to achieve this aim.

In summary Guerbet submitted that it had claimed that Dotarem had the highest stability for nearly 20 years; the claim was true and had been accepted by regulators (the PhVWP in European level and the MHRA in the UK) after a review of all of the available evidence. Guerbet did not claim that Dotarem's stability characteristics had any clinical significance. However, a link between Dotarem's superior stability characteristics and safety had been made by UK and European regulators. Again, this conclusion had been reached on the basis of a review of all of the available evidence and not as a result of any claim by Guerbet. This link had been widely promoted by UK and European regulators, in view of the public interest considerations. Guerbet submitted that clinicians who knew about this link from regulatory communications or from the literature might appreciate on the basis of the current state of the evidence that Dotarem's stability characteristics were potentially relevant to the risk of NSF. However, they would appreciate the ongoing debate as to the cause of NSF and would be able to use their clinical judgment. It was illogical and contrary to the purposes of the Code to require Guerbet to stop promoting a feature of its products which the regulator itself considered might be instrumental in lowering the risk of a fatal condition.

COMMENTS FROM GE HEALTHCARE

GE Healthcare stated that Guerbet's appeal had failed to assuage its concerns regarding the use of preclinical and *in vitro* data to imply a clinical benefit. This was particularly the case given that the relationship between these *in vitro* measurements and the clinical syndrome of NSF remained to be established. GE Healthcare concurred with the Panel's ruling which concluded that Guerbet's activities in this regard were misleading and in breach of Clauses 7.2, 7.3 and 7.4. Specifically, the Panel highlighted that the extrapolation of, *inter alia*, *in vitro* data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance and that where a clinical or scientific issue had not been resolved, particular care must be taken to ensure that the issue was treated in a balanced manner.

GE Healthcare submitted that Guerbet had approached its appeal primarily from two contradictory positions. The first was that its claims for having the highest stability were not intended to imply a clinical benefit and the second that having the highest stability did result in a clinical benefit with regards to NSF.

1 The fact that the claim that Dotarem had the highest stability for nearly 20 years

GE Healthcare alleged that the stability of all gadolinium agents was well established, many with data from two decades of research and clinical use. All the available GdCM were extremely stable in their commercial formulations. Despite gadolinium being toxic in its free form, clinical experience from more than 120 million doses of the supposedly less stable linear formulations of these compounds had demonstrated that GdCM had an excellent safety record (Murphy *et al* 1999).

GE Healthcare noted that whilst this promotional activity had not been complained about in the past, this did not mean that the activity was justified. Clause 14.5 reasonably required that promotional items were re-certified at intervals of no more than two years. This reflected the constant evolution of both regulations and scientific/clinical knowledge. Over the past two years, NSF had developed to become a topical safety issue which formed much of the debate around GdCM.

To date, the role of stability in the aetiology of NSF remained unproven and contentious (Penfield *et al* 2008). This was, in part because stability claims were based upon *in vitro* assays performed at non-physiological conditions. There were no *in vivo* measures of stability. Nor were there any *in vitro*, *in vivo* or clinical demonstrations that stability was related to NSF's aetiology. The supplementary information to Clause 7.2 stated that care must be taken to ensure that data from *in vitro* and animal studies were not extrapolated to the clinical situation unless there were data to show that they were of direct relevance and significance. In the light of this, GE Healthcare was concerned about the opportunistic and increased activities by Guerbet to promote stability as a differentiator.

There were a number of questions that remained unanswered and cast doubt on the hypothesis that the stability or transmetallation of GdCM played a role in NSF: Firstly, if cyclic GdCM were effectively inert and did not transmetallate, what explained recent reports of NSF occurring in association with these purportedly more stable agents (Penfield *et al*)? Secondly, if the linear agents exhibited instability or transmetallation *in vivo* and this was responsible for the association with NSF then why was there no evidence of NSF patients exhibiting any of the other signs of gadolinium toxicity that might be expected such as impaired liver function? Finally, if the linear GdCM were potentially unstable in renally impaired patients, and if this was the cause of NSF, then why did more than 95% of end stage renal disease patients who received linear GdCM not develop NSF (Penfield *et al*)?

Thus, the association between the stability of GdCM and their propensity to cause NSF remained unclear. The supplementary information to Clause 7.2 stated that where a scientific opinion had not been resolved, particular care must be taken to ensure that the issue was treated in a balanced manner. Since its initial description, NSF had been reported in association with both linear and cyclic GdCM, regardless of stability (Penfield *et al*). Hence, the continuing promotion of Dotarem as a safe option on account of its stability represented an imbalanced and misleading view.

The exhibition panel in question promoted Dotarem as 'The MR Gadolinium Complex with the highest Stability'. Although it did not overtly claim a clinical significance in relation to stability, Guerbet's use of the superlative 'highest' in its claim clearly showed that it was trying to differentiate Dotarem from other products in this class. This differentiation could only be to encourage health professionals to choose Dotarem over the other products and it was counter-intuitive to suggest that no clinical benefit was implied.

GE Healthcare fully supported the Panel's view that it was an accepted principle under the Code that all claims related to the clinical situation unless otherwise stated. The promotional material did not state that the claims regarding stability should be viewed other than from a clinical perspective which further supported the belief that the material was misleading. In fact, as noted below, recent promotional material for Dotarem made clinical inferences by carrying headings such as 'Maximised stability for minimal biological impact in patients'.

2 Guerbet suggested that its claim that Dotarem had the highest stability was true and had been accepted by regulators.

GE Healthcare alleged there had been considerable discussion since early 2006 on the chemical stability of the gadolinium (Gd)-chelate, and whether this was a factor in the development of NSF in patients with severe renal impairment. Three questions were pertinent to Guerbet's claim that Dotarem was 'The MR Gadolinium Complex with the highest Stability'. Firstly, of the various methods employed to measure stability, which was of the greatest accuracy? Secondly, what were the actual comparative stabilities in the clinically relevant setting? Thirdly, were these of relevance to the commercial formulations of GdCM? GE Healthcare addressed all three questions in detail and concluded that Guerbet's allusion to the fact that its claim was accepted by the regulators bordered upon an over-statement. The guidance from these regulators (and published literature) was phrased in terminology which made it clear that the aetiology of NSF was not understood. These also made it clear that the impact of stability upon an agent's propensity to trigger NSF was not certain.

3 Guerbet purported not to claim that Dotarem's stability characteristics had any clinical significance.

GE Healthcare noted that this was contrary to the basic understanding that all promotional materials had a clinical purpose and thus relevance. Guerbet would not have used the claim at a clinical meeting if the intention was not to imply a benefit in the clinical situation. The Code stated that care must be taken to ensure that data from *in vitro* and animal studies were not extrapolated to the clinical situation unless there were data to show that they were of direct relevance and significance (Clause 7.2). GE Healthcare was not aware of any preclinical or clinical data which substantiated this. Where laboratory and animal data on the relative stability of some GdCM had been examined, the findings were variable and the methodology frequently lacked validation.

GE Healthcare alleged that the exhibition panel in question did not make it clear that the claim of 'highest stability' was based on laboratory data. Guerbet's statement that clinicians reading the panel would appreciate that a comment on stability would be based on preclinical data was, as with its implied claim, without any evidence to support it. As stated above, the Panel noted that it was 'an accepted principle under the Code that all claims related to the clinical situation unless otherwise stated'. Guerbet's material provided no such statement to deflect a recipient of such material from assuming that it was clinically supported.

Guerbet's suggestion that its claim had no intended clinical relevance was also contradicted by the company's other promotional activities eg Guerbet's symposium at the European Congress of Radiology (ECR) in Vienna (March 7 – 10), was entitled 'From kinetic stability to patient benefits'. Within this symposium, as well as being the main area of discussion in the chairman's opening remarks, two of the three presentations covered NSF. In addition, Guerbet's promotional material for Dotarem at the ECR was headed 'Maximised stability for minimal biological impact in patients', which clearly implied clinical benefit (which had not been substantiated).

This symposium represented only the latest of a series of similar activities by Guerbet. Amongst its promotional materials was a CD entitled 'Nephrogenic Systemic Fibrosis and Gadolinium contrast agents'. In this CD, was a presentation entitled 'Possible mechanisms for the induction of NSF and stability of gadolinium complexes'.

GE Healthcare stated that although none of the above actually provided any evidence that stability was related to the risk of developing NSF, this clearly demonstrated that Guerbet's strategy was to lead health professionals to believe that Dotarem was a safer product than other GdCM on the basis of a claim to highest stability.

4 Guerbet had claimed that a link between Dotarem's superior stability characteristics and safety has been made by UK and European regulators.

Much of the rest of Guerbet's appeal seemed to hinge upon the updated PAR regarding NSF and Gadolinium containing MRI contrast media issued on 26 June 2007 by the MHRA in cooperation with the CHMP PhVWP and the guidelines also published in 2007 by the European Society of Urogenital Radiology (ESUR) safety committee.

GE Healthcare had a number of concerns regarding both the PAR and ESUR guidelines. Firstly, neither the PAR, nor the ESUR guidelines were clinical research, but rather a collection of, and comment on some of the data on NSF existing at that time. The discussion within these publications regarding the physiochemical stability of Gd chelates and the development of NSF were hypotheses that were still the subject of considerable scientific investigation, because no causative mechanism for NSF had been identified to date. Secondly, it should be noted that since their publication, increasing data suggested that NSF was a risk associated with the use of any gadolinium agent, irrespective of stability. Finally, it ought to be noted that both these organisations had relied upon the advice of some of the same expert clinicians. Thus, it could not be suggested that Guerbet's claims were supported by a diverse expert field. The FDA's guidance underlined the uncertainty within the field and was clear that NSF was a risk associated with GdCM (FDA website). The FDA made no distinction between agents irrespective of structure or claimed stability. This position had been supported by the manufacturers of those products available in the US as evidenced by communications sent to health professionals in that country.

GE Healthcare submitted that the majority of the advice published by the ESUR and PhVWP, differentiating between the various GdCM was based on a perceived difference in the incidence of spontaneous reports for the various products. Spontaneous reporting could be misleading and it was important to consider not only relative market share but also how this exposure had looked over the past few years and the time over which the cases of NSF had been reported. It was also important to consider the exposure of the various products to those patients at greatest risk and the doses used of these products.

1 How long had a product been available?
2 Has the product been available in those markets from which most cases were reported?
3 Was the product licensed for either angiography or whole body imaging (the procedures that tended to be linked to both patients with renal insufficiency and higher doses)?
4 Did the product, in any of the major markets, have a pre-existing contraindication in patients with severe renal insufficiency (thereby limiting any historical exposure to patients at greatest risk)?

For example, GE Healthcare stated that Dotarem had never been sold in the USA, the market from which the majority of reports had arisen, and during the time that reports had been received, it had been contraindicated in patients with severe renal impairment (those at risk of NSF) in Germany, the largest single market in Europe. Estimation of true incidence would require the number of NSF cases associated with a given contrast medium, n, divided by the number of patients at risk for NSF who were exposed to the contrast medium, N. Neither figure was known for any GdCM.

GE Healthcare stated that possible differences in the general safety profiles between GdCM were difficult to assess given the low overall incidence and the vagaries of reporting. In a large, retrospective study (Murphy *et al*), adverse events were reported infrequently, and could vary greatly – by up to 9,000 fold agent-to-agent. No statistical differences between the agents studied were found indicating that there was no difference in overall toxicity of the compounds. However, of the three agents principally noted, Omniscan had the fewest allergic and non-allergic reactions.

As stated in supplementary information to Clause 7.2, if Guerbet insisted upon using these opinions of regulatory bodies in its promotional activities, care should be taken to ensure that emerging opinions of an unresolved issue were presented in a balanced manner. Given the current discrepancy between the guidance of the FDA and PhVWP, and the discord between the statements of the guidelines when they were published and current data, the position of UK and European regulators could or should not be used to justify the claims made by Guerbet.

5 Guerbet claimed that the link had been widely promoted by UK and European regulators.

The above statement was used by Guerbet in defence of its promotional activities. This was not a legitimate defence. It was entirely appropriate for

regulatory authorities to issue assessment reports and safety updates. In general, references to regulatory authorities should not be used promotionally. Similarly, pharmaceutical companies had ultimate responsibility for their promotional activities.

6 Guerbet assumed that clinicians …will appreciate the ongoing debate as to the cause of NSF and would be able to use their clinical judgement

GE Healthcare alleged that as with many of the claims discussed in relation to this complaint, this was unsubstantiated. Additionally, the assumption of what clinicians would or would not believe did not remove Guerbet's responsibility for its promotional materials and activities.

7 Guerbet stated that it was contrary to the purposes of the Code to require it to stop promoting a feature of its products which the regulator considered might be instrumental in lowering the risk of NSF

GE Healthcare agreed with Guerbet that the Code was not a vehicle to suppress information. The basis of this complaint was, as stated by the Panel, that these promotional activities were in breach of Clauses 7.2, 7.3 and 7.4. This had come about because of Guerbet's use of preliminary and contradictory *in vitro* or animal data to suggest superior clinical benefit with Dotarem beyond other GdCM. As Guerbet stated in its appeal, the regulatory authorities reported only an association between GdCM and NSF and stability was a factor which had been suggested but not proven to be instrumental in lowering the risk of NSF. Indeed, NSF cases had since been described in association with cyclic agents (including Dotarem).

In conclusion, GE Healthcare alleged that theories regarding stability were largely based on thermodynamic stability which did not reflect physiological conditions. There was no clear correlation between the numbers of reported NSF cases for the various GdCM and their thermodynamic stability. This questioned the relationship between NSF and the thermodynamic stability of GdCM, a suggestion which was made repeatedly by Guerbet.

GE Healthcare alleged that these theories attempted to explain the differences in reported numbers early in the history of the reported association between gadolinium and NSF. They could be argued to not have the same credibility now that reported numbers had changed with a decreasing proportion of cases being associated with Omniscan and reports of cases associated with the supposedly more stable macrocyclic GdCM. The claim of 'highest stability', presented within clinical forums, could lead the reader to conclude that this led to a clinical benefit of the product over other products. GE Healthcare concurred with the Panel that this was misleading and in breach of Clauses 7.2, 7.3 and 7.4.

Furthermore, although this complaint arose from the use of panels at a local meeting, materials based upon a similar theme but overtly linked to a claimed clinical benefit were in general use, suggesting that Guerbet's underlying motivation was indeed to link stability claims with a clinical benefit which was currently unsubstantiated.

APPEAL BOARD RULING

The Appeal Board considered that the claim 'Dotarem The MR Gadolinium Complex with the highest Stability' was true. The claim could be substantiated with the available physicochemical data and no contrary data had been provided. The Appeal Board ruled no breach of Clause 7.4. The appeal on this point was successful.

The Appeal Board considered that even when a claim was true, the context in which it was used was very important. It was an accepted principle under the Code that claims etc related to the clinical situation unless otherwise stated. The claim at issue had been used with clinicians who would be familiar with the ongoing debate regarding stability and NSF. In Appeal Board's view the claim could be interpreted to mean that the 'highest stability' resulted in the 'highest safety'. In that regard the Appeal Board noted the statements from the various regulatory organisations, in particular the PAR which stated 'NSF and the role of gadolinium-based contrast media is an emerging science. The exact disease mechanism has yet to be elucidated, but physicochemical properties of gadolinium-containing agents *might* (emphasis added) affect the amount of free gadolinium released in patients with renal impairment'. The PAR concluded that the data did not *suggest* that the risk of NSF in patients with advanced renal impairment was the same for all GdCM. The non-ionic linear chelates (Omniscan and optiMARK) were associated with the highest risk because they were *more likely* to release free gadolinium than the cyclical chelates (Gadovist, ProHance and Dotarem) which were the most stable and *likely* to have the lowest risk of NSF.

The Appeal Board noted the submission that the claim at issue had been used for many years without complaint. Stability of GdCM had, however, only relatively recently been postulated to be linked to the development of NSF. In that regard the claim had taken on a new relevance for clinicians and the Appeal Board considered that within the context of the current scientific debate it implied a clinical benefit for Dotarem as a consequence of its stability which had not been proven. The Appeal Board considered that, as used, the claim was misleading and it upheld the Panel's rulings of breaches of Clauses 7.2 and 7.3. The appeal on these points was unsuccessful.

Complaint received **29 January 2008**

Case completed **16 May 2008**

CASE AUTH/2093/1/08

GENERAL PRACTITIONER v PFIZER

Lipitor journal advertisement

A general practitioner complained about a Lipitor (atorvastatin) journal advertisement issued by Pfizer. The advertisement showed a photograph of a fireman together with the text 'What's terrifying for them is everyday for me. I need to act quickly but decisions can never be rushed. You don't often get a second chance to rescue someone. For a few minutes, the family inside is more important than my own'. The product logo included the strapline 'My life. Your decision'.

Lipitor was indicated, *inter alia*, as an adjunct to diet for the reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides in primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other non pharmacological measures was inadequate. It was also indicated for reducing the risk of cardiovascular events in certain diabetic patients.

The complainant stated that the advertisement had the potential to mislead with regard to Lipitor's role; was it for the acute management of coronary events such as myocardial infarction (MI) or the chronic management of raised cholesterol which aimed to reduce the lifetime risk of developing CHD?. The image of a fireman associated with wording such as 'terrifying', 'act quickly', 'You don't often get a second chance to rescue someone' and 'few minutes' suggested that Lipitor was indicated not only for the chronic management of elevated cholesterol but was also for the management of acute cardiovascular events associated with elevated cholesterol. This was clearly not so.

The complainant agreed that 'decisions can never be rushed' but the advertisement implied that the failure to delay prescribing [sic] Lipitor somehow equated to a therapeutic crisis. To promote Lipitor by analogy to the work of the emergency fire rescue services was wholly inappropriate and misleading. Fireman often had to make split second life-or-death decisions often without recourse to second chances. However, in the complainant's experience, the treatment of raised cholesterol was not an acute condition/emergency situation and often offered the opportunity to revise/tailor treatment strategies which were not solely dependent on medicines but also involved dietary and lifestyle changes.

If one accepted the premise that Lipitor treatment was somehow analogous with an emergency rescue scenario where there might only be a 'few minutes' to make the right decision without recourse to a second chance, then one might ask whether this advertisement invited prescribers to disregard the summary of product characteristics (SPC) which stated that 'Liver function tests should be performed before the initiation of treatment and periodically thereafter'. The SPC highlighted other equally important examples as to why Lipitor could not be considered to be an acute/rescue treatment and required prescribers to take a more thorough and responsible approach to implementing treatment. The advertisement was inconsistent with the licensed indications of Lipitor. It was also alarmist and irresponsible.

The Panel noted Pfizer's submission that the purpose of the advertisement was to position Lipitor as a cholesterol lowering agent for patients at high cardiovascular risk. Whilst the Panel accepted that there was a certain urgency attendant to lowering the cholesterol of such patients it did not accept, as implied by the advertisement, that the degree of urgency was immediate and similar to that faced by a fireman in an emergency. For patients with raised cholesterol levels (other than type 2 diabetics) Lipitor was indicated only when diet or other non-pharmacological measures had failed. The SPC referred to the need to perform liver function tests before the initiation of therapy. Prescribers would often have additional opportunities to tailor treatment ie a 'second chance'. The SPC stated that adjustment of dose should be made at intervals of 4 weeks or more. The Panel considered that the advertisement was misleading as alleged. Breaches of the Code were ruled.

Upon appeal by Pfizer, the Appeal Board noted that despite Pfizer's submission regarding the purpose of the advertisement, there was no reference to high risk patients; it appeared to be relevant to all patients with hypercholesterolaemia.

The Appeal Board considered that the advertisement exaggerated the urgency to prescribe which was incompatible with advice given to prescribers in the Lipitor SPC. For patients with raised cholesterol levels (other than type 2 diabetics) Lipitor was indicated only when diet or other non-pharmacological measures had failed and the SPC also referred to the need to perform liver function tests before the initiation of therapy. The degree of urgency was not similar to that faced by a fireman in an emergency.

The Appeal Board considered that the advertisement was misleading as alleged and upheld the Panel's rulings of breaches of the Code.

The Panel did not accept that the advertisement

was inconsistent with the Lipitor SPC as alleged. It did not consider that it promoted Lipitor for an unlicensed indication ie that Lipitor was an acute/rescue treatment. No breach of the Code was ruled.

A general practitioner complained about Lipitor (atorvastatin) journal advertisement (ref LIP2933e) issued by Pfizer Limited. The advertisement showed a photograph of a fireman together with the text 'What's terrifying for them is everyday for me. I need to act quickly but decisions can never be rushed. You don't often get a second chance to rescue someone. For a few minutes, the family inside is more important than my own'. In addition the product logo in the bottom right hand corner included the strapline 'My life. Your decision'.

Lipitor was indicated, *inter alia*, as an adjunct to diet for the reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides in primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other non pharmacological measures was inadequate. It was also indicated for reducing the risk of cardiovascular events in diabetic patients with at least one additional risk factor without clinically evident coronary heart disease irrespective of whether cholesterol was raised.

COMPLAINT

The complainant stated that it was widely recognised that the treatment of elevated cholesterol was an important risk factor in the management coronary heart disease (CHD) and that statins, such as Lipitor, had an important role to play. However, the advertisement had the potential for readers to be misled regarding what this precise role was; was it the acute management of coronary events such as myocardial infarction (MI) or the chronic management of raised cholesterol which aimed to reduce the lifetime risk of developing CHD?. The image of a fireman associated with wording such as 'terrifying', 'act quickly', 'You don't often get a second chance to rescue someone' and 'few minutes' suggested that Lipitor was indicated not only for the chronic management of elevated cholesterol but was also for the management of acute cardiovascular events associated with elevated cholesterol. This was clearly not the case and was not supported by the prescribing information.

Whilst the complainant agreed that 'decisions can never be rushed', he alleged that the advertisement clearly also aimed to create a misleading impression that the failure to delay prescribing [sic] Lipitor somehow equated to a therapeutic crisis. To promote Lipitor by analogy to the work of the emergency fire rescue services was wholly inappropriate and misleading. Yes, fireman often had to make split second life-or-death decisions to rescue individuals or families and often without recourse to second chances. However, in the complainant's experience, the treatment of raised cholesterol to help reduce the risk of cardiovascular events was not managed as an acute condition/ emergency situation and often offered the opportunity to revise/tailor treatment strategies which were not solely dependent on medicines but also involved dietary and lifestyle changes.

The complainant stated that if one accepted the premise that Lipitor treatment was somehow analogous with the emergency rescue scenario depicted in the advertisement, where there might only be a 'few minutes' to make the right decision without recourse to a second chance, then one might reasonably ask whether this advertisement invited prescribers to disregard Section 4.4 of the Lipitor summary of product characteristics (SPC) which stated 'Liver function tests should be performed before the initiation of treatment and periodically thereafter'. Indeed, consideration of the SPC in its entirety clearly highlighted other equally important examples as to why Lipitor could not be considered to be an acute/rescue treatment and required prescribers to take a more thorough and responsible approach to implementing this particular treatment. The advertisement was inconsistent with the licensed indications of Lipitor. It was also alarmist and irresponsible.

When writing to Pfizer, the Authority asked it to respond in relation to Clauses 3.2, 7.2 and 7.10 of the Code.

RESPONSE

Pfizer noted that in the past, Lipitor advertisements had referred to the reduction in cholesterol in a broad spectrum of patients. In the context of increasing use of generic statins, Pfizer submitted that it was important to position Lipitor as a cholesterol lowering agent for particular patient groups rather than for everyone. The whole essence and concept behind this new advertisement was to position Lipitor as a cholesterol lowering agent for patients at high cardiovascular risk.

Pfizer addressed the complainant's four points as follows:

1 There was potential for readers to be misled about the role of Lipitor – Clause 7.2

Pfizer submitted that the advertisement raised awareness of Lipitor. The analogy (to the work of the emergency fire rescue services) drew a comparison with the decision made by a health professional when considering cholesterol lowering treatment of patients at very high risk of a cardiovascular event. High risk patients with established cardiovascular disease and/or diabetes might benefit from the lipid lowering which Lipitor afforded. Lipitor should always be prescribed as an adjunct to dietary and lifestyle changes. However, in very high risk patients, dietary and lifestyle changes alone would not be adequate measures to lower

cholesterol. The encounter between the prescriber and the high risk patient presented an important opportunity for the initiation of lipid lowering therapy and in some high risk patients there was a role for Lipitor.

2 The advertisement was inconsistent with the licensed indication of Lipitor – Clause 3.2

Pfizer submitted that the advertisement conveyed a very powerful and important message which was in line with the licensed indications of Lipitor. That message was about the importance of decision making when lowering cholesterol in patients at high risk of major cardiovascular events. There was a clearly identified role for Lipitor in reducing cholesterol in a high risk patient. The link between reducing cholesterol and lowering cardiovascular risk was well accepted. For example, the Cholesterol Treatment Trialists' meta-analysis suggested that a 1mmol/L reduction in LDL cholesterol could lead to a 21% reduction in major vascular events and a 12% reduction in all cause mortality (CTT Collaborators 2005).

3 The wording in the advertisement was inappropriate – Clause 7.10

Pfizer submitted that the advertisement represented appropriately the sense of urgency and seriousness surrounding the prescribing decision undertaken by a health professional when treating a high risk patient with elevated cholesterol. The words 'act quickly' and 'few minutes' related to the fact that when faced with such patients, it was incumbent on the prescriber to consider prescribing a statin and that this decision had to be made within the available time of a typical consultation. The phrase 'You don't often get a second chance to rescue someone' suggested that making the decision to reduce cholesterol in high risk patients was something not to be complacent about and that care should be taken in selecting the right statin for each patient. The word 'terrifying' was not used in isolation, but in a sentence, the sentiment of which related back to the analogy of drawing a comparison to decisions made by a health professional when considering cholesterol lowering treatment of patients at very high risk of cardiovascular events.

Finally, although hypercholesterolemia was indeed a chronic condition, Pfizer considered and clinical evidence suggested that once a patient was identified as being at high cardiovascular risk, the decision to prescribe a statin was a serious and urgent one.

4 The advertisement invited prescribers to disregard Section 4.4 of the Lipitor SPC which stated 'Liver function tests should be performed before the initiation of treatment and periodically thereafter' – Clause 7.10

Pfizer submitted that the advertisement did not invite prescribers to disregard Section 4.4 of the Lipitor SPC or their duties as a responsible prescriber. It would be wrong to assume that prescribing decisions which were made quickly, as most were whether managing acute or chronic illness, represented a less thorough and responsible approach on behalf of the prescriber. Pfizer upheld the ability and integrity of the medical profession in being able to consider the risks and benefits of the medicines they prescribed and to monitor treatment appropriately.

In summary, Pfizer submitted that advertising should never mislead or misinform, but argued that it could be creative. Pfizer had used the analogy of a fireman and his decision making in a risky situation to compare this to a prescriber managing a patient with hypercholesterolemia and at high cardiovascular risk. Lipitor might be an appropriate cholesterol lowering treatment in this situation. The fireman did not represent Lipitor. It was therefore not in breach of Clauses 3.2, 7.2 and 7.10.

PANEL RULING

The Panel noted Pfizer's submission about the purpose of the advertisement. Whilst the Panel accepted that there was a certain urgency attendant to lowering the cholesterol of patients at very high risk of a cardiovascular event it did not accept, as implied by the advertisement, that the degree of urgency was immediate and similar to that faced by a fireman in an emergency. For patients with raised cholesterol levels (other than type 2 diabetics) Lipitor was indicated only when diet or other non-pharmacological measures had failed. The SPC referred to the need to perform liver function tests before the initiation of therapy. Health professionals prescribing Lipitor would often have additional opportunities to tailor treatment for example by increasing the dose ie a 'second chance'. The SPC stated that adjustment of dose should be made at intervals of 4 weeks or more. The Panel considered that the advertisement was misleading as alleged. Breaches of Clauses 7.2 and 7.10 were ruled. These rulings were appealed by Pfizer. The Panel did not accept that the advertisement was inconsistent with the Lipitor SPC as alleged. It did not consider that it promoted Lipitor for an unlicensed indication ie that Lipitor was an acute/rescue treatment. No breach of Clause 3.2 was ruled. The complainant did not appeal this ruling.

APPEAL BY PFIZER

Pfizer noted that when taken in its entirety the advertisement stated: 'What's terrifying for them is everyday for me. I need to act quickly but decisions can never be rushed. You don't often get a second chance to rescue someone. For a few minutes, the family inside is more important than my own'. This wording sought to describe the role of the health professional in making decisions to treat patients.

Just as many would consider the role of a fireman was challenging, so would the role of a doctor be considered similarly; just as a fireman had to act quickly, so did a doctor. However, neither rushed a decision; both weighed the risks and benefits of a course of action. The advertisement represented the need for prescribers to decide to prescribe a statin without delay, but not with undue haste.

Pfizer submitted that the Panel's ruling was encouraging in that it accepted that there was a certain urgency attendant to lowering the cholesterol of patients at very high risk of a cardiovascular event. However, the advertisement did not imply an immediate emergency; it conveyed no more than the appropriate degree of urgency present in a doctor-patient consultation when addressing the need for treatment of high cholesterol levels in high risk patients. The advertisement creatively used an analogy (to the work of the emergency fire rescue services) to draw a comparison with the decision making process for a health professional when deciding to prescribe for a patient at high cardiovascular risk.

Pfizer submitted that the advertisement did not invite prescribers to disregard Section 4.4 of the Lipitor SPC or their duties as a responsible prescriber. The SPC stated 'Liver function tests should be performed before the initiation of treatment and periodically thereafter'. This advertisement portrayed the need for prescribers to decide to prescribe a statin without delay. Pfizer believed in the ability and integrity of the medical profession in carrying out the routine liver function tests after making this decision and issuing the statin prescription appropriately after receiving the test results. Therefore the advertisement, by highlighting a degree of urgency associated with the decision to prescribe Lipitor, could not be seen to mislead prescribers into not performing these tests. In addition, the degree of urgency represented in the advertisement had not invited prescribers to ignore diet or other non-pharmacological measures. In patients at very high risk of a cardiovascular event, it was likely that diet and non-pharmacological measures would be inadequate, hence the indication for the initiation of atorvastatin as an adjunct.

Pfizer submitted that a subjective view had been taken of what constituted a 'second chance'. Pfizer disagreed with the interpretation that a 'second chance' referred to the additional opportunities available to tailor Lipitor treatment by increasing the dose. In some patients at high risk of cardiovascular events, the opportunity to initiate Lipitor might not present itself again before the patient suffered a serious cardiovascular event. Hence, prescribers might not have a second chance to treat the high cholesterol levels of some of these very high risk patients and prevent them from having a cardiovascular event.

Finally, Pfizer noted that Lipitor was licensed for the reduction of cholesterol in 1997. Since then, it had been used widely by primary and secondary care physicians to treat hypercholesterolemia. Thus, from a practical viewpoint, the majority of doctors knew when and in whom Lipitor should be prescribed. It was very unlikely that this advertisement would mislead any prescribers in the UK and suggest any change to the established clinical practices associated with prescribing Lipitor.

In summary, Pfizer reiterated that advertising should never mislead or misinform, but argued that it could be creative in an established, widely used, mature medicine. Pfizer had used the analogy of a fireman and his decision making in a work situation to compare this to a prescriber managing a high risk patient with hypercholesterolemia. Lipitor might be an appropriate cholesterol lowering treatment in this situation.

For all the reasons given above, Pfizer submitted that the advertisement was not in breach of Clauses 7.2 and 7.10.

COMMENTS FROM THE COMPLAINANT

The complainant considered that Pfizer's argument that the advertisement simply aimed to highlight to doctors that their role was analogous to that of a fireman was not only patronising to both professions but also sought to obfuscate from the main issue which that this advertisement had only one function which was to promote the prescribing of Lipitor.

The complainant alleged that the depiction of a fireman, apparently stressed and in action and the associated wording clearly and deliberately set out to create an impression of 'immediate emergency'. If this was not the intention then why not consider depicting an alternative professional or indeed a fireman obviously shown not to be dealing with a life and death situation…such as giving members of the general public demonstrations on fire prevention and safety? Arguably, the latter was a more relevant situational analogy between doctors and the fire-service, with respect to the managing life-time risks of cardiovascular disease associated with raised cholesterol….but obviously not quite as alarmist or off-licence as Pfizer would prefer!

The complainant alleged that the advertisement did not state that the information was only to be considered with particular respect to patients with high cholesterol levels at very high risk of a cardiovascular event. Pfizer's appeal relied entirely on this qualification. Therefore, in the absence of a similar caveat in the advertisement one could reasonably assume that the claims could be attributed to all hypercholesterolaemic patients, even those with modestly elevated cholesterol levels and relatively low cardiovascular risk profile. The alarmist nature of the advertisement and the intentional focus on acute management of cardiovascular events was clearly not consistent

with the medicine's licensed indications or relevant to all patients with raised cholesterol.

The complainant also considered that, in the absence of any clarification that this advertisement was specific to patients with high cholesterol levels and at very high risk of a cardiovascular event, the wording 'second chance' promoted the message, as intended, that managing raised cholesterol was a therapeutic crisis and one which afforded no additional opportunities to consider treatment response/management and that not prescribing Lipitor was equivalent to signing a patient's death warrant. This wording was applicable to all patients, irrespective of the severity of their cardiovascular risk or degree of hypercholesterolaemia, and most definitely had not referred to missed opportunities to prescribe Lipitor and treat high cholesterol levels of some of these very high risk patients as suggested by Pfizer.

Intended or otherwise, the complainant considered that when taken in its entirety the advertisement clearly sought to communicate that Lipitor was indicated not only for the chronic management of elevated cholesterol but also for the management of acute cardiovascular events associated with hypercholesterolaemia.

Finally, given Pfizer's confidence that the majority of doctors knew when and in whom Lipitor should be prescribed the complainant questioned the need to continue advertising and promoting this medicine to an already well informed audience. This was precisely the cynical argumentation in support of misleading advertising that most healthcare now came to expect from companies like Pfizer; this not only served to irritate but also bring the industry into disrepute.

APPEAL BOARD RULING

The Appeal Board noted Pfizer's submission that the purpose of the advertisement was to re-position Lipitor as a treatment to lower cholesterol in patients at high cardiovascular risk. There was however no reference in the advertisement to high risk patients; it appeared to be relevant to all patients with hypercholesterolaemia.

The Appeal Board considered that the advertisement exaggerated the urgency to prescribe which was incompatible with advice given to prescribers in the Lipitor SPC. For patients with raised cholesterol levels (other than type 2 diabetics) Lipitor was indicated only when diet or other non-pharmacological measures had failed and the SPC also referred to the need to perform liver function tests before the initiation of therapy. The degree of urgency was not similar to that faced by a fireman in an emergency.

The Appeal Board considered that the advertisement was misleading as alleged and upheld the Panel's rulings of breaches of Clauses 7.2 and 7.10. The appeal was unsuccessful.

Complaint received **31 January 2008**

Case completed **15 May 2008**

ACTELION v ENCYSIVE

Pilot study with Thelin

Actelion Pharmaceuticals UK complained about a pilot clinical and cost effectiveness scheme run by Encysive (UK) whereby patients with pulmonary arterial hypertension (PAH) classified as WHO functional class III, and who were naïve to endothelin receptor antagonist (ETRA) therapy, could be treated with Thelin (sitaxentan).

The scheme was offered for up to 20 patients at each prescribing centre and would run for 6 months from the date of first prescription at that centre. The conditions of the scheme meant that the NHS would pay the treatment cost of only those patients deemed by the treating physician and patient to have responded to Thelin within the stipulated time frame of 24 weeks. If the patient discontinued due to a lack of efficacy or an adverse event, the cost of treatment up to that point would be refunded as a credit note to be used, within 12 months from the date of issue, against further purchases of Thelin.

Actelion alleged that the scheme represented an inducement to prescribe. The company was concerned that the central premise of prescribing, a combined assessment by the clinician based on the features of the patient, his or her needs and the safety and efficacy of the medicine, were undermined by the scheme. The credit note refund against future purchase of Thelin suggested that the only way the NHS could recoup the cost of failed treatment was to prescribe more Thelin; the scheme was thus self-perpetuating. Whilst there was no direct financial inducement for the prescriber, in the current financial climate of the NHS, cost savings were important for all prescribers, and therefore this scheme potentially constituted an indirect inducement to prescribe Thelin. Further, Actelion believed that a prescriber, with a credit note due to expire, would inevitably be pressured to use it and so prescribe Thelin, possibly inappropriately.

Actelion noted that the scheme was only for 20 patients or 6 months at each centre, whichever came first. As this was not a permanent way to guarantee outcomes for the NHS, the scheme could be seen as a way to establish pockets of Thelin patients across the country with limited savings to the NHS or risk to the company. The scheme was presented as a clinical and cost-effectiveness evaluation but there was limited clinical evaluation, which had no recognised standard criteria and was down to individual judgement. Additionally, there was no formal cost-effectiveness evaluation. Actelion alleged that the scheme was misleading in its presentation to potential NHS participants and its content.

Actelion accepted that these types of risk share or outcome guarantee schemes were not necessarily against the Code, each should be judged on its own merits and must demonstrate that there was no inducement to prescribe. Actelion did not suggest that there was any direct financial or other inducement to prescribe to the individual clinician. However, the refund and the length of time it was valid for might lead to an indirect inducement to individual clinicians to prescribe Thelin. The limited nature of this scheme (20 patients or 6 months) and the potentially misleading description further supported the notion that this scheme might be more about gaining prescriptions than saving the NHS money or performing a formal and robust clinical and cost-effectiveness evaluation of sitaxentan.

The detailed submissions from Encysive are given below.

Under the scheme at issue, a centre could initiate Thelin treatment in up to 20 patients (provided they had never previously been treated with either Thelin or Tracleer) over a 6 month period. Once therapy had started then the clinical endpoints (lack of efficacy and/or adverse events) used to determine discontinuation of treatment were entirely up to the discretion of the physician. The physician and patient determined the clinical endpoints. If clinical assessment led to the discontinuation of Thelin at any time within a 24 week evaluation period a credit note, covering the cost of Thelin used to date, would be issued. The credit note was valid for one year and could be used to offset the cost of Thelin for other patients prescribed the medicine.

The Panel considered that, as a matter of principle, it was not necessarily unacceptable to offer some sort of outcomes guarantee with a product; the acceptability of any scheme would depend on the individual arrangements.

The Panel noted that measures or trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the industry on 1 January 1993 were outside the scope of the Code. The Panel did not accept Encysive's submission that the pilot was exempt from the Code. Outcome guarantee schemes, were not in wide use by the industry on 1 January 1993. Further, the scheme in question related to more than financial arrangements.

The Panel did not agree with Encysive's submission that the pilot was neither conditional upon nor related to any commitment to purchase,

prescribe, administer or recommend any Encysive product. It was not a straightforward refund for failed therapy. The cost of failed therapy could only be recouped if more Thelin was prescribed. The Panel noted the submission that Encysive only provided information about its proposed refund to those at the commissioning level; the company did not tell the prescribers about the rebate. In this regard the Panel queried how the scheme could work given that the prescriber would be responsible for discontinuing therapy and thus starting the process to claim a rebate. Nonetheless, the Panel considered that policy makers, in receipt of credit notes against the future prescription of Thelin, would, at the very least, want to use them and thus recommend more Thelin to be prescribed. In that regard the Panel noted that Clause 18.1 stated that no gift, benefit in kind or pecuniary advantage shall be offered or given, *inter alia*, to administrative staff as an inducement to recommend any medicines, subject to the provisions of Clause 18.2.

The Panel considered that the terms of the pilot scheme were unacceptable. A breach of the Code was ruled which Encysive appealed.

During its consideration of this case the Panel was concerned the scheme was entitled 'A six month pilot clinical and effectiveness evaluation agreement for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO function functional class III who are naive to ETRA therapy'. In the Panel's view the scheme did not involve any meaningful clinical or cost effectiveness evaluation of Thelin given that it was clearly stated that the clinical endpoints used to determine success, or otherwise, of therapy were entirely up to the treating physician. It was, in effect, up to each prescriber to make their own mind up as to the clinical value of Thelin.

The Panel considered that the pilot would have the effect of promoting the prescription of Thelin. If treatment failed then the cost of that treatment could be offset only against future prescriptions of Thelin. In the Panel's view the pilot was unacceptable; it was not a *bona fide* evaluation as described and the arrangements were such that administrators would receive financial inducements that would lead them to recommend the further use of Thelin. The Panel decided in this regard to report Encysive to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Panel also required Encysive to suspend the pilot pending the final outcome of the case in accordance with Paragraph 7.1 of the Constitution and Procedure.

Upon appeal by Encysive, the Appeal Board was extremely concerned about the scheme. In particular it considered that the title 'A six month pilot clinical and cost effectiveness evaluation agreement …' suggested a degree of clinical rigour that appeared to be missing. In that regard the Appeal Board noted that there was no protocol, steering group, predetermined clinical endpoints etc associated with the scheme. In the Appeal Board's view the scheme was simply a financial arrangement between Encysive and the treatment centres. The Appeal Board considered that as a risk sharing scheme, the scheme at issue was not a model of good practice.

The Appeal Board noted that the complainant had alleged a breach of the Clause 18.1 of the Code. Clause 18.1 stated 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine …'. In that regard the Appeal Board noted that a credit note would be issued to cover the cost of the failed Thelin treatment. The credit note was valid for one year and could be used to offset the cost of Thelin treatment either in naïve patients or in those already on therapy. The credit note could be transferred to a centre other than the one to which it was issued. The Appeal Board noted that the credit note was issued to a treatment centre and so in that regard it was not a gift, benefit in kind or pecuniary advantage to any individual. On the narrow grounds of the complaint the Appeal Board ruled no breach of the Code. The appeal was thus successful.

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

Actelion Pharmaceuticals UK Ltd complained about a pilot clinical and cost effectiveness scheme run by Encysive (UK) Limited for Thelin (sitaxentan). Inter-company dialogue had failed to resolve the matter. Actelion marketed Tracleer (bosentan).

COMPLAINT

Actelion stated that the scheme was reported to be a six-month pilot clinical and cost effectiveness evaluation agreement for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class III who were naïve to endothelin receptor antagonist (ETRA) therapy. This pilot scheme was offered for up to 20 patients at each prescribing centre and would run for 6 months from the date of first prescription at that centre. The purpose of the scheme was suggested to be that the NHS would bear the cost of only those patients deemed by the treating physician and patient to have responded to Thelin within the stipulated time frame. If the patient discontinued due to a lack of efficacy or an adverse event, the cost of treatment up to that point would be refunded to the NHS in the form of a credit note to be used against further purchases of Thelin. This credit note would be valid for 12 months from the date of issue.

Actelion alleged that the scheme represented an inducement to prescribe in breach of Clause 18.1 of the Code.

Actelion's concerns were:

- The central premise of prescribing was that of a combined assessment by the clinician based on the features of the patient, his or her needs and the characteristics of the medicine (safety and efficacy date). Actelion considered that this scheme undermined this underlying best practice.
- The refund to the NHS in the form of a credit note against future purchases of Thelin suggested that the only way the NHS could recoup the cost of Thelin treatment failure was to prescribe more Thelin; the scheme was thus self-perpetuating. Whilst Actelion accepted that there was no direct financial inducement for the prescriber, in the current financial climate of the NHS, cost savings were important for all prescribers, and therefore this scheme potentially constituted an indirect inducement to prescribe Thelin.
- The credit note was valid only for 12 months from the date of issue. Should the prescriber not see a suitable patient for a number of months and have a credit note shortly due to expire, Actelion believed that there would inevitably be pressure to use this credit note and so prescribe Thelin. This would not only be an indirect inducement for this prescriber, but might lead to inappropriate prescribing.
- The scheme was only for 20 patients or 6 months at each centre, whichever came first. As this was not a permanent way to guarantee outcomes for the NHS, the scheme could reasonably be interpreted as an opportunity to establish pockets of Thelin patients across the country with limited savings to the NHS or risk to the company.
- The scheme was presented as a clinical and cost-effectiveness evaluation but there was limited clinical evaluation, which had no recognised standard criteria and was down to individual judgement. Additionally, there was no formal cost-effectiveness evaluation. Actelion alleged that the scheme was misleading in its presentation to potential NHS participants and its content.

Actelion accepted that these types of risk share or outcome guarantee schemes were not necessarily against the Code, each should be judged on its own merits and must demonstrate that there was no inducement to prescribe. Actelion did not suggest that there was any direct financial or other inducement to prescribe to the individual clinician. However, the refund and the length of time it was valid for might lead to an indirect inducement to individual clinicians to prescribe Thelin. The limited nature of this scheme (20 patients or 6 months) and the potentially misleading description further supported the notion that this scheme might be more about gaining prescriptions than saving the NHS money or performing a formal and robust clinical and cost-effectiveness evaluation of sitaxentan.

RESPONSE

1 Risk sharing schemes

Encysive submitted that risk sharing and outcome guarantee schemes were recognised by government and industry as a new way of working with the NHS to deliver better health outcomes for patients and improve the uptake of new medicines. They were therefore increasingly common in the UK. Examples were given.

2 Rationale for the pilot

Encysive devised the pilot scheme to comply with the Code and for consistency with both existing cases under the Code and outcome guarantee arrangements and for acceptability to the NHS.

In developing the pilot, the company consulted the national commissioning manager responsible for PAH within the national commissioning group (the national specialised commissioning group), which welcomed the proposals. The company also sought legal advice on the arrangements during their development and got informal advice on the acceptability of the scheme from both the Authority and the Medicines and Healthcare products Regulatory Agency (MHRA). Encysive submitted that the pilot complied fully with all applicable rules and was also acceptable to the NHS, prescribers and, ultimately, of benefit to patients.

Encysive considered that the pilot was purely financial in nature and, therefore, benefited from the trade practice exemption under the Code. Clause 18.1 of the Code excluded from its scope measures or trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. The Panel had previously considered the acceptability under the Code of a pilot study to assess the feasibility of an outcome guarantee for a statin therapy (Case AUTH/1109/11/00). The Panel noted that similar schemes that reimbursed health authorities might be implemented in the future and considered that, as a matter of principle, it was not necessarily unacceptable to offer some sort of outcome guarantee for a product. The Panel considered Clause 18.1 and determined that the pilot study was not in breach of this clause. It also suggested that the outcome guarantee scheme might benefit from the trade practice exemption and therefore fall outside the scope of the Code and the UK's medicine advertising rules. The scheme was reconsidered in 2006 (Cases AUTH/1807/3/06 and AUTH/1810/3/06) and the Panel accepted that it was not conditional upon or related to any commitment by the PCT to purchase, prescribe, administer or recommend any of the sponsoring company's products. The Panel again ruled no breach of Clause 18.1 of the Code.

On the basis of these decisions and the apparent

lack of challenges to subsequent schemes, Encysive considered that risk sharing or outcome guarantee schemes were similar to a discounting measure and should benefit from the trade practice exemption under the Code. However, the company also recognised that, unlike traditional discounting, risk sharing schemes and other joint working initiatives should be fair, transparent, based on sound and accepted clinical practice, provide additional non-financial benefits for the NHS, and benefit patients. Each of these elements was considered below.

2.1 Fairness

A key element to any outcome guarantee was that it must be meaningful, non-discriminatory and fair.

The pilot was available to all NHS institutions that treated PAH, so it was neither selective nor discriminatory. It was neither conditional upon, nor related to, any commitment to purchase, prescribe, administer or recommend any Encysive product nor was it a reward for past prescribing practices. Liaison between Encysive and payers was at the commissioning, rather than the prescribing level. Encysive's commissioning manager, rather than sales representatives, liaised directly with payers and the company's medical director addressed clinical queries.

Upon entering the pilot, the NHS took on the risk of investing scarce resources in Thelin. By underwriting the cost of failed treatment up to 24 weeks, Encysive helped the NHS apply its resources effectively.

Eligibility was assessed in accordance with Thelin's summary of product characteristics (SPC) and the decision to initiate Thelin treatment rested with the treating physician alone. The NHS bore the cost of only those patients the treating physician deemed to have responded to Thelin within 24 weeks, a period that was consistent with the response period identified in the SPC and that allowed a meaningful assessment of a patient's response.

There was also a fair and meaningful allocation of risk between the parties. The clinical endpoints used in the pilot as a basis for deciding whether to continue or discontinue Thelin were entirely at the discretion of the prescribing physician and the patient, an approach that was entirely appropriate bearing in mind the complexity of PAH and its management. Since the physician alone determined whether the response to Thelin was adequate, Encysive had no involvement in either the enrolment or outcomes decision making process. There could therefore be no argument that the allocation of risk was not meaningful or unfair.

This was a fair arrangement and, in Encysive's view, an example of a successful partnership between the NHS and the pharmaceutical industry.

2.2 Openness and transparency

Patient inclusion criteria and reimbursement under the pilot were transparent, approved by the NHS entities in question and set out in a commercial agreement (copy provided). All parties had a clear understanding of the pilot and its terms.

Encysive fully complied with the Data Protection Act 1998 and at no time before, during or after the pilot did it know or seek information likely to undermine, patient confidentiality.

2.3 Sound and accepted clinical practice

The pilot was based on sound and accepted clinical practice, a fact Encysive confirmed during consultation with key thought leaders for the treatment of PAH in the UK, including leading participants in the development of the Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland.

The recruitment of patients and treatment of PAH under the pilot were consistent with the Thelin SPC. Following inclusion, eligible patients were treated in accordance with existing local, national and international treatment guidelines on PAH and current clinical practice, including the British Cardiac Society guidelines: recommendations on the management of pulmonary hypertension in clinical practice (2001), the European Society of Cardiology guidelines on diagnosis and treatment of pulmonary arterial hypertension (2004) and the National Service Framework for Coronary Heart Disease (NSF for CHD).

Encysive therefore rejected Actelion's allegation that the pilot scheme undermined best practice.

2.4 Additional non-financial benefits

The pilot was intended to help PAH treatment centres comply with DoH guidance on pulmonary hypertension. The NSF for CHD (as amended by the specialised services definition) recommended medical therapy for treating pulmonary hypertension and many PCTs considered the treatment of PAH was an unmet need.

Encysive noted that the National Institute for Health and Clinical Excellence (NICE) was currently producing a multiple technology appraisal on medicines for PAH in adults, including Thelin. This was not expected to be published until April 2008. In the interim, therefore, the pilot would assist the NHS with the equitable distribution of finite funding for patients with PAH within the remit and framework of the NHS specialist commissioning services. The pilot should also improve patient access to medicines for PAH, while in no way being directive about any particular medicine.

2.5 Acceptable from the patient perspective

Patients would be treated according to treatment guidelines agreed with the prescriber. If anything, patients would receive better access to treatment for PAH under the pilot than would otherwise be funded by the NHS.

3 The rebate

Encysive noted that Actelion questioned the acceptability of a credit note as a form of rebate under the pilot. The pilot envisaged that a letter would be sent to the relevant payer if, under the terms of the pilot, the payer wanted to take advantage of the rebate. The letter offered the payer replacement stock within a 12 month period to be used at their discretion. Encysive provided information regarding the availability of the rebate only to the relevant payers; Encysive never communicated with prescribers on rebate issues.

Encysive considered this type of rebate was acceptable under the Code and similar to volume discounts or bonus stock offers, which were common in the industry and fell outside the scope of the Code as measures of trade practices related to prices, margins or discounts in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. Further, credit notes were generally accepted by the NHS as a method of rebate under risk-share schemes and they should not impose a disproportionate organisational burden on the NHS.

Encysive therefore refuted the suggestion that a credit note valid for 12 months was an inducement to prescribe. The pilot was not conditional upon or related to any commitment by the NHS or individual PAH centres or physicians to purchase, prescribe, administer or recommend any Encysive product nor to gain an interview. Eligibility for the pilot was assessed in accordance with the Thelin SPC. Patients only entered the pilot following the decision to prescribe and no health professional benefited either directly or indirectly under the pilot, so the credit note could not be considered a personal benefit. The credit notes were redeemable by the relevant NHS entity and the pilot was open to all NHS PAH prescribing centres.

The 12 month redemption limit was fair, reasonable and acceptable to the NHS entities that took part in the pilot. First, it was very likely that the payer would be asked to fund the treatment of another patient within a 12 month period. There were currently approximately 1,500 patients on targeted treatment for PAH and the vast majority were on Thelin or Tracleer. Most were treated in one of ten centres.

Encysive noted that when the pilot was conceived there was, and continued to be, a trend towards the centralisation of the commissioning of specialist therapies, further increasing the prospects that prescribing centres would receive a request within the relevant period. With this in mind, the credit note was designed to be transferable from individual PCTs to new [and existing] commissioning bodies.

Finally, as the name suggested, the pilot was a pilot scheme. When designing the scheme the 12 month period was considered to be realistic and appropriate. If, during the pilot, feedback had suggested that a 12 month period was insufficient, this would have been taken into account.

To reiterate, Encysive considered that the use of credit notes as a rebate was acceptable to the industry, the NHS and consistent with the spirit of the Code and previous rulings.

4 Other points raised by Actelion

Encysive noted that Actelion complained that the pilot was not a permanent scheme. This was so but Encysive made clear to the relevant NHS entities from the outset that this programme was a pilot. The industry commonly piloted major initiatives like this before considering a wider roll-out to ensure acceptability with all the relevant parties and to reconcile any problems that might occur during the pilot stage.

Encysive noted that Actelion suggested that the pilot was misleading because it was described as a 'clinical and cost-effectiveness evaluation'. There were obviously elements of independent clinical evaluations by an appropriate expert as defined in the pilot documentation. The appropriateness of a rebate was determined on the basis of that expert's assessment of cost-effectiveness. The pilot was also described as 'A six month pilot scheme for a risk and benefits share agreement for the treatment of patients with Pulmonary Arterial Hypertension (PAH) classified as WHO functional class III who are naïve to ETRA therapy'. As described above, the patient inclusion and exclusion criteria were transparent, based on sound and accepted clinical practice and the ultimate decision on whether or not to prescribe Thelin rested with the physician. Encysive did not consider that the description of the pilot was misleading.

PANEL RULING

The Panel noted that there were currently only two medicines available for the treatment of PAH – Encysive's product Thelin and Actelion's product Tracleer. [This point was corrected by Encysive in its appeal]. A month's treatment with Thelin cost £1,540 and a month's treatment with Tracleer cost £1,541.

Under the conditions of the pilot scheme at issue, a centre treating patients with PAH could initiate Thelin treatment in up to 20 patients over a 6 month period. Such patients had to have never previously been treated with either Thelin or Tracleer. Once therapy had started then the clinical endpoints (lack

of efficacy and/or adverse events) used to determine discontinuation of treatment were entirely up to the discretion of the physician according to the agreement. The slide presentation stated that the physician and patient determined the clinical endpoints. Treatment could be withdrawn any time within a 24 week evaluation period. If clinical assessment led to the discontinuation of Thelin within that time a credit note, covering the cost of Thelin used to date, would be issued. The credit note was valid for one year and could be used to offset the cost of Thelin for other patients prescribed the medicine.

The Panel noted that it had only considered one other similar scheme before (Case AUTH/1109/11/00 and Cases AUTH/1807/3/06 and AUTH/1810/3/06) and so there was very little in the way of precedent to refer to. One of the previous cases had involved a pilot study whereby a statin was guaranteed to achieve certain results in terms of cholesterol lowering in the study population and, failing the achievement of those targets, a financial rebate would be calculated at the end of the study. If the statin performed to target no rebate would be paid. In the pilot study although the rebate would be calculated, no payments would be made. In the other case the Panel had ruled no breach of the Code as the health professionals were not obliged to prescribe the product. The rebate was paid to the PCT for the general purpose of improving primary care services and not conditional upon use of products.

In the previous cases the Panel considered that, as a matter of principle, it was not necessarily unacceptable to offer some sort of outcomes guarantee with a product; the acceptability of any scheme would depend on the individual arrangements.

The Panel noted that measures or trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the industry on 1 January 1993 were outside the scope of the Code (Clause 1.2 of the Code). The Panel did not accept the submission from Encysive that the pilot was exempt from the Code. Outcome guarantee schemes, were not in wide use by the industry on 1 January 1993. Further, the scheme in question related to more than financial arrangements.

The Panel did not agree with Encysive's submission that the pilot was neither conditional upon nor related to any commitment to purchase, prescribe, administer or recommend any Encysive product. It was not a straightforward refund for failed therapy. The cost of failed therapy could only be recouped if more Thelin was prescribed for use. The Panel noted the submission that Encysive only provided information about its proposed refund to those at the commissioning level; the company did not tell the prescribers about the rebate. In this regard the Panel queried how the scheme could work given that the prescriber would be responsible for discontinuing therapy and thus starting the process to claim a rebate. Nonetheless, the Panel considered that policy makers, in receipt of credit notes against the future prescription of Thelin, would, at the very least, want to use them and thus recommend more Thelin to be prescribed. In that regard the Panel noted that Clause 18.1 stated that no gift, benefit in kind or pecuniary advantage shall be offered or given, *inter alia*, to administrative staff as an inducement to recommend any medicines, subject to the provisions of Clause 18.2.

The Panel considered that the terms of the pilot scheme were unacceptable. A breach of Clause 18.1 was ruled. This was appealed by Encysive.

During its consideration of this case the Panel was concerned the scheme was entitled 'A six month pilot clinical and effectiveness evaluation agreement for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO function functional class III who are naive to ETRA therapy'. In the Panel's view the scheme did not involve any meaningful clinical or cost effectiveness evaluation of Thelin given that it was clearly stated that the clinical endpoints used to determine success, or otherwise, of therapy were entirely up to the treating physician. It was, in effect, up to each prescriber to make their own mind up as to the clinical value of Thelin.

The Panel considered that the pilot would have the effect of promoting the prescription of Thelin. If treatment failed then the cost of that treatment could be offset only against future prescriptions of Thelin. In the Panel's view the pilot was unacceptable; it was not a *bona fide* evaluation as described and the arrangements were such that administrators would receive financial inducements that would lead them to recommend the further use of Thelin. The Panel decided in this regard to report Encysive to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Panel also required Encysive to suspend the pilot pending the final outcome of the case in accordance with Paragraph 7.1 of the Constitution and Procedure.

APPEAL BY ENCYSIVE

Encysive submitted that the scheme complied fully with the Code and was consistent with public policy and other risk share schemes approved by the DoH and NICE. Encysive submitted that the Panel's ruling had failed to take account of all the relevant evidence and public policy surrounding the scheme. The Panel appeared not to fully appreciate that the scheme was discussed with key opinion leaders in the management of PAH and negotiated with individual PAH centres at the commissioning level in an open and transparent manner. Any decision to prescribe or discontinue Thelin was entirely at the prescribing physician's discretion, without any

involvement or contact with Encysive. When PAH centres decided to take part in the scheme, communication occurred between hospital pharmacies and Encysive's cold chain distributor and between Encysive and the Specialist Commissioning Groups (SCGs) that commissioned PAH services. Further, the Panel did not fully appreciate the policy and rationale behind joint working arrangements of this type. Credit notes could be applied to patients who were already on Thelin and not just new patients. All of the participating PAH centres had a number of patients who were on Thelin. It would not be necessary, therefore, for physicians to just initiate treatment on new/naïve patients. Moreover, the credit note was transferable between the SCG payers within the NHS.

Encysive submitted that the Panel's ruling was not a consistent interpretation of the Code and case precedents. The underlying principle of the scheme was that Encysive was held accountable for the effectiveness of Thelin and if NHS resource was shown to be wasted then the company provided recompense in the form of a rebate. The rebate was allocated to the NHS as an organisation pursuant to a commercial agreement. No individual benefited financially or otherwise from the scheme. This was a fact that the Panel had previously considered important (Case AUTH/1109/11/00). Credit notes were widely accepted by the authorities as alternatives, and even preferable, to cash rebates. Encysive was dismayed that the Panel suggested that customers could be induced by this form of rebate. The Panel's current determination should require it to investigate and act against the other high profile risk share schemes that use, or offer, credit notes and replacement stock under their guarantees.

Encysive submitted that the Panel failed in its duty to apply the rules of natural justice as its ruling had no evidential basis: in order to demonstrate a breach of Clause 18.1 of the Code, it was necessary to show that a gift or benefit in kind had been offered to individual prescribers or administrative staff. The credit notes were for the benefit of the relevant payer, a key consideration of the Panel in previous cases. The Panel must also show an intention to induce recommendations of its products. The purpose of the scheme was to help alleviate the budgetary constraints under which SCGs typically operated. It was difficult to see how the Panel could sustain its suggestion that Encysive intended to induce recommendations since such interference with the doctor-patient relationship by administrative staff would constitute serious breaches of professional standards and ethical principles by both the administrative staff and prescribers.

Encysive submitted that the Panel's ruling was factually incorrect as it suggested that there were only two treatments for PAH available. This was incorrect. To the extent the Panel relied on this information, the ruling was ill-advised.

Encysive submitted that the Panel's ruling would hinder access to innovative therapies. NHS organisations routinely delayed funding decisions about new medicines until NICE guidance was available. This meant that patients were often denied access to modern medicines for months or years. The Panel's ruling could hinder patient access to innovative medicines. The reason that some medicines were available on the NHS was that a risk share scheme was in place. The Panel's ruling could hinder access to treatments available under risk share schemes. Encysive considered that the Panel's decision would have adverse consequences for current and future joint working initiatives with the NHS, patient access to new medicines and risk sharing schemes in particular.

The following sections contained Encysive's grounds for appeal in more detail.

1 The Panel's ruling failed to take account of all the available evidence and public policy surrounding the scheme

1.1 Summary of the scheme

Encysive noted that the main principles of the scheme were set out in its response. However, the Panel had queried how the scheme actually worked given that the prescriber would be responsible for discontinuing therapy and thus starting the process to claim a rebate. This query suggested that the Panel ruled on the scheme without full knowledge or understanding of how it actually worked. Although Encysive was more than happy to elaborate on points that the Panel did not fully understand, it was not given an opportunity to do so prior to the ruling.

Encysive submitted that the scheme was a joint working agreement between Encysive and the NHS, in particular the SCGs involved in the funding and approval process for patients needing targeted PAH therapy. The National Specialist Commissioning Advisory Group (NSCAG) transferred to the NHS in April 2007 and was now known as the Specialist Commissioning Group. Under the working arrangements, Encysive and the relevant NHS entity agreed to share the risks and benefits associated with the administration of Thelin. These types of joint working arrangements were relatively new and had become known as risk share or outcome guarantee schemes.

Encysive submitted that its scheme involved the company guaranteeing the effectiveness of Thelin over a 24 week treatment period. If this did not occur, Encysive provided the NHS entity participating in the scheme with a credit note. The ultimate decision as to whether or not to prescribe Thelin rested with physicians who were free to prescribe whichever treatment for PAH they wished. The underlying principle was that Encysive was accountable for the effectiveness of Thelin over a 24 week period and, rather than waste the financial resource of the cost of the medicine, Encysive

agreed to recompense the NHS. This ensured that the allocation of this financial outlay was made available for future use. Disseminating new medicines under the terms of such a guarantee provided reassurance to both parties; the company was more likely to get its medicine to those who needed it most, and the NHS had a reassurance of return on investment. The details of the scheme, including the patient inclusion criteria and rebate, were previously provided.

Encysive submitted that to answer the Panel's specific query about the operation of the scheme, it pointed out that the response did not, as the Panel suggested, state that the prescribers would be ignorant of the existence of the scheme and the manner in which it operated. It simply made clear that liaison between the company and payers in respect of the scheme was an on-going process and occurred primarily at the SCG level.

Encysive submitted that it involved key opinion leader prescribers in the PAH field and SCG managers responsible for PAH when developing the scheme. The scheme was offered to all PAH centres and it was for them to decide whether or not to sign up. All participating centres had already included Thelin on their formulary list. If a PAH centre was interested in the scheme, Encysive's commissioning and policy manager, a non-marketing role within the company, talked to the SCGs about the possibility of offering the scheme to that PAH centre and also visited the centre to explain the scheme using the presentation previously provided. The decision whether to prescribe Thelin then rested with the prescriber. The physician or a nurse completed the relevant paperwork which was then faxed to the cold chain distributor.

Encysive submitted that the hospital pharmacist would also be told that a patient had been included in the scheme and would fax the relevant paperwork to Encysive's cold chain distributor which distributed one month's supply of product to the hospital for that patient and the pharmacist must re-order monthly. The hospital/PCT or SCG were invoiced directly.

Encysive submitted that if a physician withdrew a scheme patient from Thelin therapy, the hospital pharmacy informed the cold chain distributor which then informed the company. The company then sent a credit note to the relevant payer. This credit note could be applied against any patient on Thelin therapy, including patients already using the product but who were not in the scheme, and had been designed to accommodate the new NHS pooled budgets that were now emerging for the PAH funding processes and so was transferable between SCGs.

Encysive submitted that the Panel appeared to have misunderstood a number of important features of the scheme:

- The scheme was discussed and agreed at SCG level.
- The SPC for Thelin made it clear that therapy 'should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension'. Treatment was therefore initiated by a very small number of highly specialised physicians at each PAH centre participating in the scheme, who met eligible patients as per their normal practice and decided whether Thelin was an appropriate treatment to prescribe.
- Once the physician had decided to prescribe Thelin under the scheme liaison was between the centre's pharmacy/nurse and Encysive's cold chain distributor.
- When patients were withdrawn, the physician played no role in requesting or receipt of the credit note.

1.2 The title and operation of the scheme

Encysive noted that the Panel queried the appropriateness of the title of the scheme, which in its ruling was incorrect, the correct title was: 'A six month pilot clinical and effectiveness evaluation agreement for the treatment of patients with Pulmonary Arterial Hypertension (PAH) classified as WHO function functional class III who are naïve to ETRA therapy'. The Panel stated the scheme was not a *bone fide* evaluation of Thelin because the clinical end-points were at the discretion of the physician and the patient. Encysive disagreed.

Encysive noted that the title to the scheme was actually decided upon following a consultation with one of the SCG managers prior to rolling out the scheme. The SCG manager said that the term 'risk share' (the original title of the scheme) suggested that the scheme would be an administrative burden. As part of the joint working arrangements, Encysive considered that it was acceptable for the SCGs to have an input into the title of the scheme.

Encysive noted that the Panel's ruling also stated that it was up to each prescriber to make their own mind up about the clinical value of Thelin. The Panel thought that this would provide no meaningful evaluation'. Encysive disagreed, the Panel had placed too much emphasis on the title without first learning the full facts of the scheme. Encysive did not want to impose treatment endpoints for several reasons. PAH was an extremely complex condition that manifested itself in many different ways. The way in which patients responded therefore also differed and was a matter for interpretation by an expert and the patient themselves. Rather than define limited endpoints and response criteria, Encysive considered it appropriate to give physicians the discretion to assess clinical response. In some patients, success might be defined by no further, or a slower rate of, deterioration in their condition. In others, it might be defined as an increased capacity to exercise eg their ability to walk might improve.

Therefore, in Encysive's view, and the view of the SCG managers and key opinion leaders, the title

was neither misleading nor inappropriate. A scheme whereby the value of the product subject to the scheme was determined by prescribers and patients could provide meaningful data. Encysive would, nevertheless, be happy to amend the title of the scheme to, for example, Risk Share or Outcome Guarantee Scheme if that was considered more appropriate.

1.3 Public policy

Encysive submitted that the Panel did not take proper account of the public policy that surrounded joint working initiatives such as this. The NHS was rapidly changing and the DoH encouraged NHS organisations and staff to consider partnership opportunities with the pharmaceutical industry to meet the needs of patients and prescribers in a cost-effective manner. Indeed, the proposals under the draft Code 2008 stated that 'joint working with health authorities and trusts and the like is permitted if carried out in a manner compatible with the Code'.

Joint working was distinctly different from 'sponsorship' whereby pharmaceutical companies simply funded specific events or work programmes. In joint working, goals were agreed jointly by the NHS organisation and company, in the interest of patients, and shared throughout the project. A joint working agreement was drawn up and management arrangements conducted with participation from both parties in an open and transparent manner. For many organisations, this was a new way of working. The DoH's joint working toolkit actually stated that joint working required a different mindset from sponsorship and a collaborative approach. The scheme should be reviewed in this light.

Encysive submitted that the NHS, government and industry had adopted a 'common agenda' to improve patient outcomes through high quality and cost effective treatment and management. The DoH and the ABPI agreed that the common agenda could be achieved through working together to ensure that patients got optimal care, including appropriate use of cost-effective innovative medicines, with support to help them maximise the benefits of treatment.

Encysive noted that the DoH's joint working toolkit stated that this could be achieved through services designed to ensure, amongst others: identification of appropriate patients; optimal numbers of appropriate patients received treatment; appropriate use of innovative medicines that were cost effective for the NHS; measurable improvements in outcomes and a positive patient experience.

Encysive also noted the DoH's Long-Term Leadership Strategy for medicines which stated that NHS payers would increasingly require the demonstration of relative and cost-effectiveness to allow widespread use of new medicines in patients. However, there would be some medicines, like Thelin, and many other orphan medicines, where value could not be demonstrated at launch but for which collection of additional data would provide a good chance of proving value. The strategy acknowledged this and stated that without some give by both industry and government, there was a possibility that these medicines would not be used in the NHS. It specifically referred to the concept of risk sharing at paragraph 6.33:

'A compromise needs to be found that allows a degree of risk-sharing to ensure that the government does not pay for medicines that do not work but that equally, patients get access to medicines that may help them. **These important issues need to be discussed and a solution agreed that meets the needs of payers, patients and industry'** (emphasis added).

Encysive submitted that this position was also made clear in the Office of Fair Trading (OFT) Market Study into the Pharmaceutical Price Regulation Scheme (PPRS), which was issued around the same time as the long-term strategy report. It proposed that manufacturers offer risk sharing agreements where there was a lack of clarity about a value based price at launch and referred to two examples. In particular, it stated: 'we believe that risk sharing is a potentially promising approach for the future for drugs where there is a plausible but unproven value proposition and there are reasonable prospects of data being available in the medium term to make a more thorough determination'. It was clear, therefore, that the NHS was required to identify risk sharing opportunities so that patients did not miss out on effective treatment. The scheme at issue was one such initiative. It was developed based on the underlying public policy considerations above, approved by the NHS entities in question and set out in a commercial agreement. All parties clearly understood the scheme and its terms. The SCG managers consulted about the scheme acknowledged that it assisted their organisations with the equitable distribution of finite funding for PAH patients within the remit and framework of the NHS specialist commissioning services. The scheme should also improve patient access to medicines for PAH, as described above.

2 The Panel's ruling was not a consistent interpretation of the Code and case precedents

Encysive noted that the Panel ruled that the arrangements of the scheme were unacceptable and in breach of Clause 18.1 of the Code. The rationale, the Panel said, was that policy makers, in receipt of credit notes against the future prescription of Thelin, would, at the very least, want to use them and thus recommend more Thelin to be prescribed. The Panel also ruled that outcome guarantee schemes did not benefit from the trade practice exemption under Clause 1.2 of the Code.

Encysive disagreed with this analysis and submitted that it was based on a misinterpretation of the Code and was inconsistent with previous rulings and other high profile risk share schemes.

2.1 Clause 18.1 of the Code

Clause 18.1 of the Code stated 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine, subject to the provisions of Clause 18.2.' Encysive had not offered any administrative staff a gift, benefit in kind or pecuniary advantage. It had offered the NHS a rebate in the form of a credit note. The rebate did not attach itself to one particular SCG but was transferable between SCGs within the 12 month timeframe. It was not possible to 'induce' an organisation as a whole. In fact, the Oxford English Dictionary defined the verb 'induce' as:

'To lead (**a person**), by persuasion or some influence or motive that acts upon the will, to (into, unto) some action, condition, belief, etc.; to lead on, move, influence, prevail upon (any one) to do something' (emphasis added).

Further, Encysive submitted that a rebate offered to the NHS pursuant to a commercial contract was neither an inducement nor a 'gift, benefit in kind or pecuniary advantage' to a prescriber or administrative staff. It was effectively a cash-equivalent discount allocated to the NHS where the product failed to meet the terms of the company's guarantee. The MHRA Blue Guide recognised 'equivalent business discount schemes' as alternatives to cash rebates. The rebate was not conditional upon the recruitment of new patients as Thelin was already prescribed by each PAH centre that had signed up to the scheme and so existing patients could also benefit. The scheme was conditional in the sense that, where a prescriber chose to prescribe Thelin, the company would guarantee the effectiveness of Thelin pursuant to the terms of the scheme.

Encysive submitted that in addition, there was no voluntary element under terms of the scheme as one would expect when offering or providing a gift. Rather, a credit note supplied under commercial terms such as these was good consideration, as that term was contractually understood, for the NHS agreeing to reimburse Thelin. Consideration was something of value that was necessary for parties to enter into a legally-binding contract. Under the scheme, the NHS was not volunteering to accept the guarantee/rebate (as it would if it were a gift), rather it entered into a legally-binding agreement with Encysive whereby it took on the risk of investing its resources into making Thelin available on the NHS. Such rebates could not, therefore, be considered a gift, benefit in kind or pecuniary advantage. Encysive also referred to the OFT PPRS report, which suggested that risk sharing was merely a mechanism to smooth prices, as opposed to a gift or benefit in kind.

Encysive noted that the supplementary information to Clause 18 followed this reasoning and suggested that a gift, benefit in kind or pecuniary advantage must be a personal benefit. It gave the example of gift vouchers for high street stores.

Encysive noted that when the Panel had previously ruled on the acceptability of a pilot scheme (Case AUTH/1109/11/00), it raised the possibility that the scheme could benefit from the trade practice exemption. In that case, the Panel did not discount the possibility that risk sharing schemes would fall outside the scope of the Code. It was troubling and inconsistent, therefore, for the Panel to rule nearly seven years on that such schemes did not benefit from the trade practice exemption. Encysive further noted that the Panel stated that if any actual rebates had been paid, they would not be considered a gift. This was because the payments would have been payable to a health authority and not to an individual physician. The Panel stated: 'With the pilot study in question, the Panel noted that if payments had been made, they would have been made to the health authority and not to the GPs or the PCG. **No individual health professionals would have benefited either directly or indirectly'** (emphasis added).

Therefore, Encysive submitted that that no gift, benefit in kind or pecuniary advantage (as those terms were discussed above) was offered to any individual health professional or administrative staff to induce a prescription of Thelin. In actual fact, the NHS as a whole received a rebate (as the credit note was transferable) where Thelin did not meet the terms of its guarantee. Any form of rebate (credit notes, replacement stock, cash, future discounting, etc.) supplied under commercial terms such as these was good 'consideration', as that term was contractually understood, for the NHS agreeing to reimburse Thelin. As such, the NHS had not volunteered to accept the rebate but agreed to invest scarce resources by reimbursing the product. Such rebates could not, therefore, be considered a gift, benefit in kind or pecuniary advantage.

2.2 Credit notes as rebates

Encysive disagreed with the Panel's view that the rebate of a credit note against replacement stock of Thelin would at the very least lead to a recommendation that Thelin should be prescribed. Encysive considered that the use of credit notes/replacement stock was acceptable under the Code and similar to bonus stock offers, which were common in the industry and fell outside the scope of the Code as measures or trade practices related to prices, margins or discounts in regular use by a significant proportion of the industry on 1 January 1993. Importantly, credit notes were recognised by the DoH, NICE and the SCGs with whom Encysive entered into joint working arrangements with as acceptable alternatives to cash rebates. In particular,

the use of replacement stock and credit notes in risk share schemes had previously been permitted by the DoH and NICE in another scheme as acceptable to the NHS. During the development of that scheme, the DoH commented on the acceptability of credit notes (with a one month time limit) and replacement stock as a form of rebate under the scheme. It stated: 'We note that [the company's] proposal involves supplying credit notes or replacement stock in the event of patients not responding to [the medicine] because their understanding is that this is easier for provider units to administer. **We are content with this approach** but are equally happy with a cash payment as long as the process remains easy for the NHS to manage locally' (emphasis added).

Encysive submitted that the understanding referred to in this extract was based on a survey carried out by the scheme's sponsor with NHS administrative staff in 10 hospitals as to the acceptability of different forms of rebate. Given the option of a credit note or cash refund, the NHS clearly preferred for credit notes (8/10) as these were easier to track and administrate than cheque refunds. They also helped ensure that the relevant units or functions within the NHS retained their allocated funds, rather than risking their allocation elsewhere within the service. This was particularly important in the specialist commissioning context, where budgets were often hard-fought and tight, and where patients relied on a small number of often costly therapies. Two hospitals preferred replacement stock and none stated a preference for a cash refund. The DoH's letter also confirmed that credit/notes replacement stock benefited the local health economy: 'The company distributes [the medicine] directly to the NHS, so rebates or replacement stock can be given back to the same unit that placed the initial order, **ensuring that the local health economy receives the benefit of the scheme'** (emphasis added).

Encysive submitted that during the development of its scheme, it relied on the above survey and the comments from the DoH as to the acceptability of credit notes for risk share schemes. Encysive also consulted with the SCG Manager responsible for PAH and, as evidenced by the agreement, the credit notes were acceptable. There was little practical difference between the scheme referred to above and the Thelin risk share scheme. In both cases, the terms of the outcome guarantee and the form of the rebate were negotiated at some length and agreed by the DoH.

2.3 Commercial aspects

Encysive submitted that the directors of the company had a statutory duty to exercise reasonable care and skill in running the company. This included monitoring business cash flow and accounts. Cash flow was important to all companies, and particularly smaller ones such as Encysive, because it enabled them to pay their debts as they fell due and so avoid any potential insolvency risk. For this reason, credit notes or replacement stock would usually be the preferred option for a well run company.

Encysive noted the Panel's ruling referred to Cases AUTH/1807/2/06 and AUTH/1810/3/06. In the scheme considered then cash rebates were paid to the PCTs rather than individual GP practices. The rebates were for the general purpose of improving primary care services. The Panel found no breach of the Code. However, that cash rebates of this kind could, in fact, be less attractive to the NHS because such payments could be allocated elsewhere, for example, spent on resurfacing the hospital car park rather than going on patient therapies. This was supported by the statements from the DoH and the survey cited above.

2.4 Pilot scheme

Encysive noted that the scheme was in its pilot stage. It was common in the industry to pilot major initiatives like this before considering a wider roll-out to ensure acceptability with all the relevant parties and to reconcile any problems that might occur during the pilot stage. As with any pilot, if feedback suggested that a cash rebate would be preferred then that was something Encysive would fully consider going forward. However, provided this form of rebate was acceptable to the NHS, which it clearly was, then Encysive submitted that it would be an unreasonable precedent to uphold the Panel's ruling. It would also impose on the PMCPA a positive duty to investigate the other risk share schemes mentioned that used, or offered, credit notes and replacement stock under their guarantees. Such a move would be greeted with dismay by companies complying with the Code, the DoH, NICE, the NHS and many of the patients that benefited from treatment on that basis.

2.5 The conduct of SCG managers, administrative staff and senior physicians

Encysive noted that the Panel had questioned the conduct of the SCG managers, administrative staff in receipt of credit notes for Thelin and, ultimately the senior specialist physicians at the PAH centres involved in the scheme. The Panel's ruling alleged that they would, at the very least, want to use them and thus recommend more Thelin to be prescribed and suggested that credit notes were financial inducements. Encysive was concerned about this allegation and considered the role of the SCG managers as essential in helping patients access some very specialised services. Indeed, the Government's vision for World Class Commissioning, published in December 2007, described the role of commissioners as 'working collaboratively with partners ... to stimulate innovation, efficiency and better service design, increasing the impact of the services they commission to optimise health gains and reductions in health inequalities'. The Panel's ruling suggested that such managers behaved in a corrupt manner by accepting financial inducements. This was in breach of NHS ethical standards that NHS

employees must adhere to when dealing with commercial sponsorship. When entering into joint working arrangements, Encysive trusted that NHS staff and physicians would adhere to NHS ethical guidelines, just as the NHS organisations trusted that the company and its employees would comply with the Code. In particular, the NHS ethical guidance stated that staff working in the NHS were expected, *inter alia*, to: not misuse their official position or information acquired in the course of their official duties, to further their private interests or those of others; ensure professional registration (if applicable) and/or status were not used in the promotion of commercial products or services and to neither agree to practice under any conditions which compromised professional independence or judgement, nor impose such conditions on other professionals. This last point was particularly relevant as it clearly stated that NHS staff must not impose conditions that could compromise professional judgment, ie under a commercial sponsorship arrangement, NHS administrative staff could not recommend to prescribers that they prescribe more Thelin.

Encysive noted that as referred to in the public policy section above, joint working was based on an open and transparent relationship. Mutual trust was recognised by the DoH and the ABPI as fundamental if joint working initiatives were to be successful. Therefore, Encysive trusted that the SCG managers abided by the NHS ethical standards. Similarly, the SCG managers and physicians trusted that Encysive and its employees would abide by the Code and the law. This was evidenced by Encysive's willingness to accept the jurisdiction of the PMCPA following this complaint.

Encysive submitted that the Panel's ruling also suggested that the use of credit notes as a rebate was an indirect inducement to prescribers. Prescribers were typically staff working in the NHS and were subject to the ethical guidelines referred to above. However, physicians were also subject to GMC Good Medical Practice Guidelines 2006, which stated that doctors must act in their patients' best interests when providing treatment. They must not ask for or accept any inducement, gift or hospitality which might affect or be seen to affect their judgment. It added that financial or commercial interests in healthcare, pharmaceutical or other biomedical companies must not affect prescribing or treatment and that these interests must be declared to patients or the healthcare purchaser if there was a possibility that they were relevant. Therefore, it was clear that there were appropriate checks and balances in place to prevent a physician from actually accepting an indirect financial inducement.

The physicians in question were members of a very small number of highly specialist, often eminent, experts in the treatment of PAH. It was difficult to accept that the professional integrity and ethical principles of individuals such as these could be compromised in the manner that the Panel suggested.

Encysive noted that a letter attached from a professor of respiratory medicine stated that he was comfortable with the manner in which the scheme was run. A statement from the Director of the PMCPA, when this GMC guidance was published, suggested that it was up to both parties to maintain ethical integrity. She stated: 'It is essential that doctor's relationships with pharmaceutical companies are professional and transparent at all times. It is up to both parties to ensure that this is so and that the interests of patients are put first.'

Encysive considered that it, the SCG managers, the NHS administrative staff and physicians had maintained the highest ethical standards in running this scheme.

3 The Panel failed in its duty to apply the rules of natural justice as its ruling had no evidential basis

Encysive submitted that the Panel was under a duty to ensure that it applied the rules of natural justice when adjudicating on cases before it. To this end, Encysive considered that the Panel's ruling was procedurally unfair because it completely lacked precedence/evidence. The Panel disagreed with Encysive's submission that the scheme was neither conditional upon nor related to any commitment to purchase, prescribe, administer or recommend any Encysive product based on the fact that the rebate was in the form of a credit note (which had little practical difference to the other scheme discussed above) and allegations it made that policy makers would want to use the credit note as a financial inducement to persuade physicians to prescribe more Thelin. There was no evidence that this was the case. The fact that NHS staff must comply with NHS ethical standards and, in the case of health professionals, GMC or other professional standards, meant that on the balance of probability, NHS staff would not use the credit notes as a financial inducement. When public authorities made a decision or ruling that had no evidential basis, then the decision must be regarded as irrational.

Further, Encysive submitted that the complete lack of evidence went against the well-established principle that persons, including companies, should not be punished in the absence of some conduct or state of affairs that justified liability attaching to a person. This was encapsulated in the general principle that criminal liability required both an unlawful act and an unlawful intention. This maxim was appropriate to apply here as Clause 18.1 of the Code reflected Regulation 21(1) of the Medicines (Advertising) Regulations 1994, as amended. Any person (including a company as a legal person) in breach of Regulation 21(1) was guilty of an offence. In order to prove the offence, it was necessary to prove that a gift or inducement was actually offered or given to a health professional or administrative staff to induce a prescription. The Panel had not evidenced either element.

Encysive did not intend or consider using the scheme to induce prescriptions or recommendations of its products. Encysive hoped that the scheme would simply alleviate some of the NHS's financial or budgetary constraints, thus allowing physicians more freedom to prescribe as they saw fit. Encysive could not have predicted, as the Panel appeared to have done, that these circumstances would at the very least result in behaviour that was unethical and contrary to NHS and GMC rules.

Encysive submitted that the Panel appeared to have a hypothetical and unlikely set of circumstances to find the company in breach. In doing so, it ignored the fact that the scheme involved a commercial relationship between Encysive and the NHS. No inducement was offered to any administrative staff or prescribers, the act required for a breach of Clause 18.1. It also ignored the fact that the rules and ethical principles underpinning the NHS and the practice of medicine precluded the recommendation that the Panel suggested was inevitable. It was therefore difficult to understand how the Panel could have discharged its burden of proving any intention on the part of Encysive.

Encysive submitted that while it was true that the directors of a company owed a duty to its shareholders, both the ABPI and the DoH recognised that companies working in partnership with the NHS gained shareholder value by researching and developing innovative medicines that met clinical need, optimised the use of its medicines in appropriate patients and encouraged more proactive treatment and management of patients. It was important that Encysive developed joint working opportunities to enhance its understanding of the NHS service reconfiguration process and to increase its credibility as a genuine partner in providing care for PAH patients. Encysive submitted that, therefore, that there was no evidence with which to find it in breach of Clause 18.1. As the Panel had observed in the previous cases the scheme did not involve the offer of any inducements to prescribers or administrative staff. Even if this was put aside, the ethical standards expected of NHS staff and GMC-registered physicians provided a robust check against the alleged inappropriate and unethical conduct. The Appeal Board must, therefore, overrule the Panel's decision.

Encysive submitted that it was most concerned about the Panel's ruling in this regard. It suggested many common commercial arrangements between pharmaceutical companies and the NHS were intended at the very least to induce administrative staff to recommend prescription of its products, contrary to Clause 18.1 of the Code. This had cast doubt on the legitimacy of many joint working initiatives and portrayed the industry, the NHS and the medical profession in a poor light

4 The Panel's ruling contained mistakes of fact and therefore the ruling was ill-advised

Encysive submitted that the Panel's ruling stated that there were only two medicines available for the treatment of PAH; Thelin and Actelion's product Tracleer. This was not correct. Treatment options for patients with the disease had evolved to help prolong their survival and improve their quality of life. Conventional treatment for patients with primary and secondary PAH include calcium-channel blockers, anticoagulants, diuretics and oxygen. In addition, oral endothelin-1 receptor antagonists (sitaxentan sodium, bosentan), an intravenous prostacyclin (epoprostenol), an inhaled prostacyclin (iloprost), a subcutaneous prostacyclin (treprostinil) and a phosphodiesterase-5 inhibitor (sildenafil) had also been licensed for the treatment of PAH in various European countries. Of these, Thelin, Tracleer, iloprost (Ventavis) and sildenafil (Revatio) had been authorised through the European centralised procedure. NICE was currently conducting a technology appraisal of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for the treatment of PAH in adults. It was a mistake of fact, therefore, to suggest that there were only two available treatments for PAH. To the extent that the Panel relied on this information in forming its opinion, then the Appeal Board must consider the ruling ill-advised.

5 The Panel's ruling would hinder access to innovative medicines

Encysive submitted that in consultation with the SCGs, it developed the scheme so that appropriate patients could access its treatment in a cost-effective manner. As discussed, the benefit for the SCGs was that the scheme would assist the NHS with the equitable distribution of finite funding for PAH patients. The transferable nature of the credit note meant that the rebate was not restricted to one particular centre but could be used to treat PAH patients in other parts of the country. The scheme therefore helped improve patient access to PAH medicines, while in no way being directive about any particular medicine. Although PAH targeted monotherapy was generally accepted for funding, if the scheme was considered to be in breach of the Code, then there was a risk that patients would find it difficult to access other innovative and costly treatments now and in the future.

6 Summary

Encysive considered that the scheme was a successful example of an open and transparent joint arrangement with the NHS. By entering into a risk sharing arrangement that was acceptable to all the parties involved, Encysive was held accountable for the effectiveness of Thelin. If an NHS resource was shown to be wasted then the company paid the NHS back with a credit note against replacement stock that could be used throughout the country for existing patients taking Thelin. Disseminating new medicines, and in particular medicines with orphan status, under the terms of such a guarantee provided reassurance to both parties; the company was more likely to get its medicine to those who needed it most, and the NHS had a reassurance of return on investment within a 24 week evaluation

period. This was accepted by the SCG managers who agreed to the scheme as a rational and professional way of managing the entry of new, expensive medicines, such as Thelin, into the NHS. The scheme complied with the Code and was consistent with public policy and other risk share schemes approved by the DoH and the NICE.

COMMENTS FROM ACTELION

Actelion noted that Encysive had commented on a number of previous examples of 'risk share' between the pharmaceutical industry and the NHS. Actelion alleged that there were significant differences between the previous cases and the current case, therefore this case should be considered on its individual merits and the reasonable perceptions associated with it.

Actelion alleged that the Encysive scheme still fell within Regulation 21 of the Advertising Regulations, was promotional, and, by incentivising the NHS centre, contravened Clause 18.1 of the Code.

Actelion submitted that a contextual feature of paramount interest was the relative market place of the licensed endothelin receptor antagonists (ERAs); bosentan (Tracleer) and sitaxsentan (Thelin). Tracleer was launched in May 2002, and at the end of 2007 had over 1,000 patients on commercial therapy within the UK/Ireland market. Thelin was authorised by the EMEA in August 2006 and at the end of 2007 (when the scheme in question was being proposed to the specialist centres) Actelion estimated that there were about 40 - 50 patients on commercial supply throughout the same territory. While Encysive could provide more accurate numbers, it was unlikely that any centre involved in the scheme had, in late 2007, even 10 commercially treated patients. This supported Actelion's underlying view that the scheme was designed to accelerate the development of pockets of Thelin prescribing in these centres. Actelion noted Encysive's submission that the credit note could be applied to a patient currently already on Thelin, however the low initial patient numbers at the treating centres would limit the practical application of this option.

Actelion noted that Encysive had suggested that the scheme was developed in consultation with clinical key opinion leaders in PAH and with payers. This did not diminish the company's responsibility for compliance with the Code.

Actelion noted that the professor of respiratory medicine who headed one of the treating centres, had stated that he was completely comfortable with the manner in which the scheme is run. The implication within these various sections was that the clinicians in the PAH centres and the various payers were overall happy with the scheme. Actelion alleged however that Encysive had not fully represented the views of the PAH specialist centres. Actelion had no accurate knowledge regarding which centres the scheme was presented to, the proportion which refused participation and why. At least one of the six adult designated centres did not consider the scheme to be appropriate. Staff at one hospital had told Actelion that they were unhappy with the proposal and did not agree with the principles of the scheme and felt that it put undue pressure on prescribing habits and in order to get a more formal view they discussed the matter with the legal and corporate team within the trust and were advised they should not become involved with it in any way.

Actelion noted that Encysive had made speculative statements regarding the potential negative impact on uptake of innovative treatments, should the Panel's ruling be upheld. Actelion had approached the PMCPA on this specific, *individual* matter, which the PMPCA had reviewed as such. Risk share agreements could be initiated without contravening the Code, therefore there was no justification for Encysive's position.

Actelion alleged that the appeal from Encysive did not alleviate its concerns that this scheme had been misrepresented as a clinical and cost-effectiveness evaluation. There was a lack of common clinical or economic endpoints, and it was clear that individual clinician judgment was all that was needed. It was therefore not possible to make a robust evaluation of clinical or cost-effectiveness. While Encysive stated that the Panel placed too much emphasis on the title, Actelion disagreed, and alleged that the title was a key element in the impression given to customers regarding the scheme. Actelion doubted the extent of material clinical input and endorsement into developing the scheme.

ENCYSIVE'S COMMENTS ON THE REPORT FROM THE PANEL

Encysive acknowledged that it had commented at length as part of the appeal process. It had designed its pilot scheme to comply fully with the Code. In doing so it had taken legal advice and the matter had been discussed with the MHRA and the ABPI.

APPEAL BOARD RULING

The Appeal Board was extremely concerned about the scheme. In particular it considered that the title 'A six month pilot clinical and cost effectiveness evaluation agreement …' suggested a degree of clinical rigour that appeared to be missing. In that regard the Appeal Board noted that there was no protocol, steering group, predetermined clinical endpoints etc associated with the scheme. In the Appeal Board's view the scheme was simply a financial arrangement between Encysive and the treatment centres. The Appeal Board considered that as a risk sharing scheme, the scheme at issue was not a model of good practice. With regard to the other schemes referred to by Encysive the Appeal Board noted that it had not considered any

complaints about these schemes and it appeared that they were different to the Encysive scheme.

The Appeal Board noted that the complainant had alleged a breach of Clause 18.1 of the Code. Clause 18.1 stated 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine …'. In that regard the Appeal Board noted that a credit note would be issued to cover the cost of the failed Thelin treatment. The credit note was valid for one year and could be used to offset the cost of Thelin treatment either in naïve patients or in those already on therapy. The credit note could be transferred to a centre other than the one to which it was issued. The Appeal Board noted that the credit note was issued to a treatment centre and so in that regard it was not a gift, benefit in kind or pecuniary advantage to any individual. On the narrow grounds of the complaint the Appeal Board ruled no breach of Clause 18.1. The appeal was thus successful.

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

Complaint received	**5 February 2008**
Case completed	**23 April 2008**

TEVA v TRINITY-CHIESI

Clinical support service

Teva complained about a Clinic Support Service (CSS) with particular reference to two CSS pharmacist forms dated 2 and 24 October 2007 respectively used by Trinity-Chiesi. These CSS pharmacist forms were the basis of Teva's concern; Teva submitted that they represented the CSS service as a whole.

Each form had been signed by a pharmacist, a member of the Trinity-Chiesi CSS team. The forms were headed 'For the attention of the pharmacist' and told the reader that having assisted the named GP practice with issues relating to prescribing, there was likely to be an increased use of Clenil Modulite (CFC-free beclometasone dipropionate BDP) in place of CFC BDP. The form was an advisory note to help pharmacists plan stock levels of the various products concerned. Each form advised of a 'Likely INCREASED use of' Clenil Modulite and in addition the form dated 24 October also advised of an increased use of CFC-free inhalers. The form dated 2 October advised of a 'Possibly REDUCED use of', 'Beclometasone, Beclazone, Becotide and Becloforte pmdi' whilst the form dated 24 October referred simply to 'Beclometasone CFC-containing pmdi's [sic]'. Teva's product Qvar was a CFC-free BDP inhaler for asthma.

Teva noted that there was nothing on the forms at issue to indicate what work had been carried out at the GP practice, whether the work was endorsed by the GP or whether the changes noted on the form had been agreed with the GP. The pharmacist could have simply written the form themselves to ensure that the listed products were switched to Clenil. Teva noted that the Code stated that 'sponsored healthcare professionals should not be involved in the promotion of specific products'. It also stated that 'registration status should not be used in the promotion of commercial products or services'. The forms started with the words 'Dear colleague' and described the sender as 'a fellow pharmacist' who had been 'assisting the above practice with certain issues relating to prescribing'. Teva concluded that the lack of customer endorsement of any agreed actions on the forms was clear evidence of a breach of the Code and of an assisted switch to Clenil Modulite. In addition the phrase 'as a fellow pharmacist' abused the position of the Trinity-Chiesi pharmacist and was likely to contravene professional guidance issued by the Royal Pharmaceutical Society of Great Britain (RPSGB).

The Code also stated that 'a genuine therapeutic review should include a comprehensive range of relevant treatment choices, including non-medicinal choices, for the health professional and should not be limited to the medicines of the sponsoring pharmaceutical company'.

It was not clear that therapeutic review had taken place ensuring the patient received optimal treatment following a clinical assessment taking into account their specific individual disease. Both of the CSS pharmacist forms stated that there would now be a 'possible reduced use of ' CFC BDP and a 'likely increased use of ' Clenil Modulite CFC free inhalers. This therefore stated the use of the Trinity-Chiesi product as the likely change to prescribing and indicated that the service as a whole was limited to the medicines of the sponsoring company only. This was therefore clear evidence of a breach.

In Teva's opinion, these two clear breaches were enough to also lead to subsequent further breaches, including a breach of Clause 2.

The Panel noted that Teva had made its complaint solely on the basis of the two forms at issue. The Panel noted Teva's concern that sponsored health professionals should not be involved in the promotion of specific products and that registration status should not be used in the promotion of commercial products or services. The pharmacists that formed Trinity-Chiesi's CSS team were not sponsored health professionals – they were employees of the company. The Panel considered that the forms at issue were not sufficiently clear about the role of the pharmacists employed by Trinity-Chiesi. Community pharmacists reading the form would not necessarily consider an employee of a pharmaceutical company – albeit that employee was a pharmacist – as a colleague. The Panel did not consider that the lack of customer endorsement on the forms at issue of any agreed actions provided clear evidence that Trinity-Chiesi's service was a switch to Clenil Modulite which would be a breach of the Code rather than a therapeutic review. On the very narrow basis of the complaint made, the Panel ruled no breach.

The Panel noted that the forms referred to by Teva were just one part of the overall service offering. Only two forms had been provided by Teva. The Panel considered that, on the basis of the two forms before it, there was no evidence to show that the service as a whole was limited to Trinity-Chiesi's products. The Panel did not consider that it had a complaint about the clinical support service as a whole. No breach was ruled.

The forms at issue did not demonstrate that an inducement to prescribe, supply administer, recommend, buy or sell any medicine has been

offered or given. Thus the Panel ruled no breach in that regard. Given the circumstances there was no breach of Clause 2.

Teva UK Limited complained about a Clinic Support Service (CSS) with particular reference to two CSS pharmacist forms (ref TRCSS20040235) dated 2 and 24 October 2007 respectively used by Trinity-Chiesi Pharmaceuticals Ltd. These CSS pharmacist forms were the basis of Teva's concern; Teva submitted that they represented the CSS service as a whole.

Each form had been signed by a pharmacist, a member of the Trinity-Chiesi CSS team. The forms were headed 'For the attention of the pharmacist' and told the reader that having assisted the named GP practice with issues relating to prescribing, there was likely to be an increased use of Clenil Modulite (CFC-free beclometasone dipropionate BDP) in place of CFC BDP products. The form was sent to the pharmacist as an advisory note to help with stocking the various products concerned.
The section of each of the forms headed 'Likely INCREASED use of' had 'Clenil Modulite' written in it and in addition the form dated 24 October also stated 'CFC-Free inhalers'. The forms also had a section headed 'Possibly REDUCED use of'. On the form dated 2 October this section was completed with 'Beclometasone Beclazone, Becotide and Becloforte pmdi'. On the form dated 24 October this section was completed with 'Beclometasone CFC-containing pmdi's [sic]'. Teva's product Qvar was a CFC-free BDP inhaler for asthma.

COMPLAINT

Teva noted that there was no customer signature or endorsement of the actions on either form and so no evidence as to whether the pharmacist had been working with GPs or had simply written the form themselves to ensure that the listed products were switched to Clenil. This was misleading to say the very least as it did not state what this work was and also did not indicate whether any changes had been agreed with the relevant GPs.

Furthermore, the forms did not appear to have a slot allocated to a customer signature. This significant omission had a number of implications and led Teva to the following two major conclusions related to the CSS service as a whole.

1 Clause 18.4 (vi) of the supplementary information to the Code stated that 'sponsored healthcare professionals should not be involved in the promotion of specific products'. It also stated that 'registration status should not be used in the promotion of commercial products or services'.

  This form started with the words 'Dear colleague' and described the sender as 'a fellow pharmacist', who had been 'assisting the above practice with certain issues relating to prescribing'. Given the lack of customer endorsement of any agreed actions on this form then Teva concluded that this form was clear evidence of a breach of the Code and evidence of an assisted switch to Clenil Modulite. In addition the phrase 'as a fellow pharmacist' abused the position of the Trinity-Chiesi pharmacist and in Teva's view was likely to contravene professional guidance issued by the Royal Pharmaceutical Society of Great Britain (RPSGB). In Teva's view, this was clear evidence of a breach of Clause 18.4.

2 The supplementary information to Clause 18.4 also stated that 'a genuine therapeutic review should include a comprehensive range of relevant treatment choices, including non-medicinal choices, for the health professional and should not be limited to the medicines of the sponsoring pharmaceutical company'.

  It was not clear that a therapeutic review had taken place ensuring the patient received optimal treatment following a clinical assessment taking into account their specific individual disease. Both of the CSS pharmacist forms stated that there would now be a 'possible reduced use of ' CFC BDP and a 'likely increased use of ' Clenil Modulite CFC free inhalers. This therefore stated the use of the Trinity-Chiesi product as the likely change to prescribing and indicated that the service as a whole was limited to the medicines of the sponsoring company only. This was therefore clear evidence of a breach of Clause 18.4. In Teva's opinion, these two clear breaches of the Code were enough to also lead to subsequent further breaches of Clauses 2, 9.1 and 18.1.

RESPONSE

Trinity-Chiesi explained that the form at issue was used by its clinical support team to inform the local community pharmacists of the outcomes of the CSS which had been carried out in their local surgery and which might directly affect them and the service they provided. The form helped to ensure that the appropriate medicine was available and consistent patient information was provided from all members of the primary healthcare team. All pharmacists were accountable for the quality and standards of the services they provided and for their individual professional practice and the forms formed part of the clinical governance used by the CSS pharmacists to maintain and improve the quality of their professional practice.

The forms were in effect letters advising the community pharmacist of the likely outcome of the CSS which had been carried out within the surgery as authorised by the necessary GP/GPs. This letter did not require a customer signature as no action was required by the community pharmacist, it was purely an advisory letter between two health professionals. The letter did not contain or imply any promotion of commercial products or services.

As the letter was from a pharmacist to a fellow pharmacist within community pharmacy the terms 'Colleague' and 'fellow pharmacist' were valid, aided effective communication and did not represent any breach of the Code. The use of the term 'fellow pharmacist' was a professional courtesy and clearly did not abuse any position. This form was introduced to ensure the pharmacists complied fully with the RPSGB Medicines, Ethics and Practice guidelines and Teva's suggestion of a contravention of these guidelines was unsubstantiated and not valid. Furthermore, as the letter referred to the CSS which had been duly authorised by the GP and completed within the surgery, the term 'assisting the above practice with certain issues relating to prescribing' was used to explain those outcomes of the CSS which would be seen by the community pharmacist.

Trinity-Chiesi submitted that its CSS service complied with the guidelines set out in the supplementary information to Clause 18.4:

> 'A therapeutic review is different to a switch service. A therapeutic review service which aims to ensure that patients receive optimal treatment following a clinical assessment is a legitimate activity for a pharmaceutical company to support and/or assist. The results of such clinical assessments might require, among other things, possible changes of treatment including changes of dose or medication or cessation of treatment. A genuine therapeutic review should include a comprehensive range of relevant treatment choices, including non-medicinal choices, for the health professional and should not be limited to the medicines of the sponsoring pharmaceutical company. The arrangements for therapeutic review must enhance patient care, or benefit the NHS and maintain patient care, and must otherwise be in accordance with Clause 18.4 and the supplementary information on the provision of medical and educational goods and services. The decision to change or commence treatment must be made for each individual patient by the prescriber and every decision to change an individual patient's treatment must be documented with evidence that it was made on rational grounds.'

The form at issue in isolation communicated any changes of medicine made for patients by the prescriber and each change would have been duly documented that it was made on rational grounds and would have been duly authorised and signed by the prescriber. The clinical assessments made by the pharmacist during the provision of the service would include interactions, over/under ordering of medicines, duplicate therapies, compliance issues, dosages, strengths, licensed indications, quantities issued and inequivalence of quantities, clinical investigations - tests overdue or not recorded, side effects and strength optimisation. Any of the clinical outcomes which occurred as a result of these assessments, such as cessation of treatment or change of dose would be detailed on a medication query form and discussed directly with the authorising GP. Such outcomes would obviously not be detailed on the form at issue and Teva's assumption that this would be the case was incorrect.

Trinity-Chiesi noted that Teva's complaint was almost identical to inter-company correspondence dated 21 December 2007 save the additional statement 'What is not clear is whether any therapeutic review has taken place ensuring the patient receives optimal treatment following a clinical assessment, taking into account their specific individual disease…'.

The CSS was provided by registered pharmacists who, under written instructions from the authorising GP, accessed individual patient records and carried out a full clinical assessment of each patient's therapy before any therapeutic review took place. The clinical assessments made by the pharmacist, as the recognised professional expert on medicines, included assessments checks of:

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

Any of the clinical queries or recommendations arising from these assessments, would be detailed on a medication query form and discussed and resolved directly with the authorising GP.

From its detailed response above Trinity-Chiesi did not agree that the concerns raised by Teva were in breach of Clauses 2, 9.1, 18.1 or 18.4.

In addition to responding to the complaint, Trinity-Chiesi considered that in this case the correct complaint procedure had not been followed by Teva and that inter-company dialogue was not complete. Details were provided.

PANEL RULING

The Director decided that taking all circumstances into account that inter-company dialogue satisfied Paragraph 5.2 of the Constitution and Procedure and the complaint should proceed.

The Panel noted that Teva had made its complaint

solely on the basis of the two forms at issue. The Panel noted Teva's concern that sponsored health professionals should not be involved in the promotion of specific products and that registration status should not be used in the promotion of commercial products or services. The pharmacists that formed Trinity-Chiesi's CSS team were not sponsored health professionals – they were employees of the company. The Panel considered that the forms at issue were not sufficiently clear about the role of the pharmacists employed by Trinity-Chiesi. Community pharmacists reading the form would not necessarily consider an employee of a pharmaceutical company – albeit that employee was a pharmacist – as a colleague. The Panel did not consider that the lack of customer endorsement on the forms at issue of any agreed actions provided clear evidence that Trinity-Chiesi's service was a switch to Clenil Modulite which would be a breach of Clause 18.4 rather than a therapeutic review. On the very narrow basis of the complaint made, the Panel ruled no breach of Clause 18.4.

The Panel noted that the forms referred to by Teva were just one part of the overall service offering. Only two forms had been provided by Teva. The Panel considered that, on the basis of the two forms before it, there was no evidence to show that the service as a whole was limited to Trinity-Chiesi's products. As noted above the Panel did not consider that it had a complaint about the clinical support service as a whole. No breach of Clause 18.4 was ruled.

Bearing in mind its ruling of no breach of Clause 18.4, the Panel did not consider there was a breach of Clause 18.1. The forms at issue did not demonstrate that an inducement to prescribe, supply administer, recommend, buy or sell any medicine has been offered or given. Thus the Panel ruled no breach of Clause 18.1. Given the circumstances there was no breach of Clauses 2 and 9.1.

Complaint received **14 February 2008**

Case completed **22 April 2008**

EX-EMPLOYEE and MEDIA/DIRECTOR v ROCHE

Supply of Xenical and support for a slimming clinic

In Case AUTH/2099/2/08, a former Roche employee complained about the supply of Xenical (orlistat) to a bogus health professional and the funding of a clinic by Roche.

The Panel noted that the complainant had referred to an article in the Financial Times which alleged that Roche had sold large quantities of Xenical to the operator of a chain of private UK diet clinics, in spite of suspicion at one stage that the product was being sold illegally, and agreed to provide him with £55,000 for the purchase of another diet clinic. In accordance with established practice the matter was taken up as a complaint under the Code (Case AUTH/2100/2/08).

In Case AUTH/2099/2/08, with regard to the supply of Xenical, the Panel was extremely concerned about the circumstances which had led to a prescription only medicine in effect being supplied to a person who was not a health professional and by that person to patients. The Panel noted Roche's submission that it had validated the General Medical Council (GMC) number of the doctor named on the new account proposal form. The Panel considered that companies needed to be particularly careful about the supply of medicines to private clinics. It noted that Roche had made enquiries about the doctor but not about the owner who claimed he was a pharmacist, but was not. The FT article referred to a report written by a member of Roche's staff posing as a new client in May 2003 which described how [the owner] '… personally sold him Xenical …' and that 'To a lay person he would have passed as a doctor'. The Panel considered that Roche had not paid sufficient attention to ensuring that the supply of its product to the private clinic was appropriate. Thus the Panel ruled a breach of the Code. The Panel considered that the arrangements brought discredit upon the pharmaceutical industry and a breach of Clause 2 of the Code was ruled. Upon appeal by Roche, the Appeal Board noted that the company should have strongly suspected that the manner in which Xenical was prescribed at the clinic was inappropriate and possibly prejudicial to patient safety. The Panel's rulings were upheld.

The Panel noted that Roche had agreed to sponsor the purchase of another diet clinic. Payment was to be in two parts, £20,000 payable in August 2004 and £35,000 in January 2005. According to Roche only £20,000 had been paid. The second payment had been halted following contact by the Medicines and Healthcare products Regulatory Agency (MHRA).

Roche had agreed to pay the money in August 2004. This meant that the applicable Code was the 2003 Code.

The supplementary information to the 2003 Code stated that medical and educational goods and services could be provided if they enhanced patient care or benefited the NHS. The provision of such goods and services must not be done in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine.

It was difficult to see how providing £55,000 to an individual to purchase a private diet clinic was a medical and educational good or service that would enhance patient care or benefit the NHS as required by the Code. Thus the Panel ruled a breach of the 2003 Code. The Panel did not consider that Roche had maintained high standards in relation to its agreement to provide an individual with £55,000. A breach of the Code was ruled. The Panel considered that the arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

In Case AUTH/2100/2/08, with regard to the supply of Xenical, the Panel was extremely concerned about the circumstances which had led to a prescription only medicine in effect being supplied to a person who was not a health professional and by that person to patients. The Panel noted Roche's submission that it had validated the GMC number of the doctor named on the new account proposal form.

The Panel noted that the contract did not stipulate that the professional status of the signatory be included. Roche had not confirmed the professional status of the clinic owner whom it submitted had posed as a pharmacist. The Panel considered that in effect Roche had sold a prescription only medicine to a member of the public. The Panel was extremely concerned about the arrangements, particularly given that someone from Roche had visited the diet clinic in May 2003 and had been seen by the owner. The report of that visit noted that to the lay person the owner would have passed as a doctor as he 'had the bag and sphygmomanometer etc to almost prove it'. The document used the term 'prescribed' and reported that the owner was clearly not a fan of Xenical. The Panel considered that companies needed to be particularly careful about the supply of medicines to private clinics. It noted that Roche had made enquiries about the doctor but not about the owner who claimed to be a pharmacist. The clinic visit report in May 2003 from the Roche employee should have led to further action on Roche's part and the company to question supply

of Xenical to the clinic in 2004. The Panel considered that Roche had not paid sufficient attention to ensuring that the supply of its product to the private clinic in question was appropriate. Thus the Panel ruled a breach of the Code. The Panel considered that the arrangements brought discredit upon the pharmaceutical industry and a breach of Clause 2 of the Code was ruled. Upon appeal by Roche the Appeal Board noted that the company should have strongly suspected that the manner in which Xenical was prescribed at the clinic was inappropriate and possibly prejudicial to patient safety. The Panel's rulings were upheld.

The Panel noted that Roche had agreed to sponsor the purchase of a further clinic. Payment was to be in two parts, £20,000 payable in August 2004 and £35,000 in January 2005. According to Roche only £20,000 had been paid. The second payment had been halted following contact by the MHRA. A document prepared by a Roche employee headed 'Private Clinic Funding Proposal' was undated. It stated that if Roche agreed to the proposal it was hoped to complete purchase of the diet clinic before the end of June 2003. The Private Clinic Funding Proposal also included sales analysis data for 2003 and 2004 showing the return on a £55,000 investment. The Private Clinic Funding Proposal referred to the diet clinics as 'a real Xenical success story'. The owner was reported as having put enormous efforts into establishing Xenical across his group of clinics as the medicine of choice for safe and effective long-term weight loss.

The Panel considered that the proposed payment of £55,000 for the clinic was linked to the use of Xenical. The proposal had been made on the basis that Xenical would become the medicine of choice at the clinic. The Private Clinic Funding Proposal stated that the current treatment guideline at the clinic was not to use Xenical. The proposal produced by the Roche employee focussed only on the increased use of Xenical. There was nothing in the proposal to suggest that Roche had considered whether or not this was a medical or educational good or service. There was no evidence to show that Roche considered the proposal in relation to anything other than the potential increased use of Xenical. It was difficult to see how providing £55,000 to an individual to purchase a private diet clinic was a medical and educational good or service that would enhance patient care or benefit the NHS as required by the Code. Thus the Panel ruled a breach of the Code.

The Panel did not consider that Roche had maintained high standards in relation to its agreement to provide an individual with £55,000. A breach of the Code was ruled. The Panel considered that the arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel also considered that in both cases the circumstances warranted consideration by the Appeal Board in relation to the possibility of additional sanctions. Thus the Panel reported Roche to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board noted that the report from the Panel concerned both the supply of Xenical and the funding of the clinic. The Appeal Board was extremely concerned about these cases, particularly with reference to Roche's disregard for patient care. The payment for the purchase of the clinic was clearly linked to the prescribing of Xenical and thus totally unacceptable. The Appeal Board decided that Roche would be publicly reprimanded and reported to the ABPI Board of Management with the recommendation that the company be suspended from membership of the ABPI.

The ABPI Board noted that Roche had been ruled in breach of the Code including Clause 2. It also noted that Roche had been audited three times and a fourth audit was arranged for September in relation to another unrelated case.

The ABPI Board noted Roche's submission that the MHRA had not suggested any wrong-doing by Roche. However, it believed that funding of the clinic, and Roche not taking any action in relation to the supply of Xenical to the clinic following the visit by the Roche employee posing as a new patient in 2003, were very serious matters.

The ABPI Board agreed that Roche would be suspended from membership of the ABPI for a period of six months commencing 14 July 2008 with re-entry conditional upon the audit which the company was to undergo in September proving satisfactory to the Board.

CASE AUTH/2099/2/08

A former employee of Roche Products Limited complained about the supply of Xenical (orlistat) to a bogus health professional and the funding of a clinic by Roche.

COMPLAINT

The complainant stated that in early 2005, two senior colleagues told her that Roche had been involved with funding and supplying medicines to a bogus doctor who had been providing slimming medicines – including Xenical – to patients at a 'clinic' held on the site of a 'tanning and toning' beauty parlour. They told the complainant this because they had received a telephone call from the Medicines and Healthcare products Regulatory Agency (MHRA) notifying them of a visit by an MHRA enforcement officer in relation to this bogus doctor. The MHRA had been informed about the bogus doctor because one of the patients who attended the 'clinic' had suffered an epileptic fit. The neurologist who treated the patient subsequently reported the incident to the MHRA.

The complainant telephoned her manager in Switzerland later the same day, and told him what she had learned. Eight working days later, her employment was terminated and she was escorted from the Welwyn premises.

Given the circumstances of her dismissal, the complainant lodged a claim of unfair dismissal with the Employment Tribunal Service. At the end of the hearing the complainant was awarded unfair dismissal and reinstatement (which Roche refused to comply with).

The complainant alleged that throughout the tribunal hearing, various intimidating tactics were used by Roche. In the first instance it claimed that the reason for the complainant's dismissal was gross professional misconduct, an accusation that it withdrew on day one of the hearing and changed to 'some other substantial reason'. In addition, Roche brought in witnesses including an enforcement officer from the MHRA who the complainant had previously met at the MHRA to inform him and his colleagues of Roche's activities regarding the funding of the bogus doctor and the slimming clinic.

The complainant also alleged that Roche also gave a statement to the BMJ that portrayed the complainant as 'a concerted troublemaker, addicted to rowing with senior colleagues and unable to obey orders from above'. The complainant submitted that evidence produced at the tribunal hearing could substantiate none of this, and previous appraisals and employment references described the exact opposite.

In the meantime, the complainant had been informed by an unofficial but reliable source, that whilst the bogus doctor had been charged, tried (entering a guilty plea) and was about to be sentenced, no action had been taken against Roche which in her opinion had knowingly aided and abetted him.

In its defence, Roche claimed that it thought the bogus doctor was a pharmacist – which he was not – and so considered that it 'did nothing wrong' in supplying him with Xenical and observing him at first hand supplying this medicine to patients. The complainant was completely astounded by this and had letters from the Department of Health (DoH) confirming that no legal action was to be taken against Roche. The complainant therefore lodged a complaint against Roche for contravening the Code regarding the supply of Xenical to a bogus doctor and the funding of the slimming clinic.

The complainant provided a copy of an article from The Financial Times (FT) 12 February written by Andrew Jack [This became the subject of Case AUTH/2100/2/08]. The complainant stated that the FT article detailed Roche's activities with Xenical. The complainant offered to provide more information and details. When asked by the Authority to supply any material in writing to be considered none was provided.

When writing to Roche, the Authority asked it to respond in relation to Clauses 2, 9.1, 17 and 18 of the Code.

RESPONSE

Roche stated that the background to this complaint was complex and spanned the last five years.

- Roche and other pharmaceutical manufacturers were the victims of criminal activity relating to a group of private diet clinics.
- From March 2005 Roche supported the MHRA at all levels to provide information and intelligence for it to build a criminal case against two individuals. One had posed as a pharmacist and treated patients for obesity, including the provision of prescription medicines.
- It later transpired that the latter was employed by another pharmaceutical company as a medical sales representative and the other was his previous line manager selling their company's anti-obesity treatment.
- The case was heard in court (November 2007) and both defendants pleaded guilty (one to five offences and the other to one offence against the Medicines Act) and awaited sentencing.
- Over the course of its investigation the MHRA had seen all related Roche internal documents and had cleared Roche of any wrong-doing in relation to this complex case. In fact the MHRA had thanked Roche for its co-operation and support to help it prosecute these individuals.
- Similarly, Roche had been engaged in an employment tribunal with the complainant for the last 3 years who claimed her dismissal from the company was a result of whistle blowing when questions about the diet clinic came to light – something which Roche strongly refuted. The employment tribunal found that as Roche did not follow the correct dismissal process the complainant was unfairly dismissed. Roche acknowledged the unfair dismissal, however this was not for whistle blowing. The claimant's whistle blowing claim was therefore not upheld. The employment tribunal was still ongoing as the claimant had appealed this ruling.
- The claimant had similarly approached the MHRA during the course of her tribunal claim, the MHRA did not take any action against Roche as a result of that approach, as the claimant did not raise any new issues.
- Thus this was a very complex situation of which detailed information had already been heard by a criminal court of law, an employment tribunal, and full documentation had been reviewed by the MHRA.

Roche would not respond to matters that related to the complainant's dismissal or the employment tribunal. Roche therefore responded to the complainant's specific comment around raising a formal complaint for 'contravening the Code regarding the supply of Xenical to a bogus doctor and the funding of a Slimming Clinic', which Roche

discussed in relation to Clauses 2, 9.1, 17 and 18.

Roche explained that from 2002 it took the first step into a new market place – that of private slimming clinics. Roche was in contact with a private slimming clinic which it understood was owned by a pharmacist who was supported by a doctor. Roche had met the doctor and the owner on a regular basis, though the latter clearly drove the initiative.

The clinic requested Roche supplied it directly with Xenical and in line with standard procedure, Roche validated the General Medical Council (GMC) number of the doctor. Roche was able to confirm the legitimacy of the doctor and it therefore authorised direct distribution of stock. This was the standard procedure for such an arrangement and all information and facts in relation to the clinic appeared to be accurate. There was a health professional qualified to prescribe Xenical working at the clinic, which was verified and clearly the doctor was legitimate and therefore Roche submitted that a breach of Clause 17 was not justified.

Roche assumed that the complainant was referring to discussions Roche had with the owner in relation to a slimming clinic located elsewhere and Roche responded on that basis.

As part of Roche's ongoing discussions with the first clinic, the owner positioned himself as owning several other clinics in the UK, and that he proposed to set up another clinic which was otherwise about to close. He approached Roche in 2004 for funds to support the setup costs. Before it made any such decision Roche analysed internally whether such an investment would be in its longer term interests, and in this instance it concluded that it would. In addition it would benefit the local patients who had used the clinic and others who would do so in future. Roche therefore agreed to sponsor the clinic for £55,000 with two payments spread over six months, as evidenced by confirmation from the owner of the first clinic and the invoice. This funding was not linked to the clinic's prescribing of Xenical. The funding was part paid - Roche paid the first instalment of £20,000 but the final payment of £35,000 was stopped when it was contacted by the MHRA and suspicions were raised about the owner's legitimacy.

In March 2005 the Enforcement Division of the MHRA advised Roche that it was investigating allegations of criminal activity at a diet clinic supplied by Roche and other pharmaceutical companies. The MHRA asked Roche to continue supplying the clinics with Xenical whilst its investigation was ongoing and it co-operated fully with the request and with the investigation. Roche believed that in working with the MHRA it had maintained the high standards of the industry and it refuted a breach of Clause 9.1.

Roche was a victim of criminal activity in this case and had worked with the MHRA to ensure that there was sufficient evidence to convict the individual involved. Roche argued that as such it had maintained high standards (Clause 9.1).

Roche noted that it had withdrawn from the private slimming market, and had stopped direct supply of Xenical to any diet clinic.

Funding of the further clinic would fall under Clause 18 Medical and Educational Goods and Services in the 2003 Code. Roche was approached by the owner of the original clinic to provide sponsorship and, recognising the benefit to patients in the proposed new location, agreed. As such, Roche refuted that this was a breach of Clause 18, as the sponsorship was not linked to the prescribing of its product.

As victims of criminal activity, Roche did not consider its actions discredited the industry (Clause 2) and that high standards had been maintained (Clause 9.1). Roche had worked with the MHRA to assist it with its actions in relation to the criminal behaviour and the MHRA which had investigated Roche for any improper behaviour had no further concerns.

PANEL RULING

The Panel noted Roche's submission that the MHRA had seen all related Roche internal documents and had cleared the company of any wrong-doing. The Panel noted Roche's submission that it was a victim of criminal activity. The Panel's role was to consider the matter in relation to the Code which was not the role of the MHRA.

The Panel noted that the activities had taken place in 2003 and 2004. The applicable Codes would be the 2001 Code and the 2003 Code. With regard to Clause 2, there was no difference between the requirements in the 2001 and 2003 Codes. Clause 9.1 in both the 2001 Code and 2003 Codes required that high standards be maintained. Other wording in Clause 9.1 of the 2001 Code had become Clause 9.2 in the 2003 Code. Taking all these factors into account, the Panel decided it would make its rulings in relation to the 2003 Code using the Constitution and Procedure in the 2006 Code.

The Panel was concerned that Roche had supplied less information in relation to this case than it had in Case AUTH/2100/2/08 which concerned the article published in the FT, 12 February 2008.

The Panel noted that Roche had been asked to respond in relation to a number of clauses of the Code, including Clause 17. On reviewing Roche's response the Panel did not consider that Clause 17 of the 2003 Code was relevant to the activities in question and thus that clause was not considered. The complainant's allegations related to the supply of Xenical to a bogus doctor and the funding of a clinic.

The Panel noted that the complainant had referred to the article in the FT. The article alleged that Roche had sold large quantities of Xenical to the operator of a chain of private UK diet clinics in spite of suspicion at one stage that the product was being sold on the 'grey market'. Roche had agreed to provide £55,000 for the purchase of another diet clinic.

With regard to the supply of Xenical, the Panel was extremely concerned about the circumstances which had led to a prescription only medicine in effect being supplied to a person who was not a health professional and by that person to patients. The Panel noted Roche's submission that it had validated the GMC number of the doctor named on the new account proposal form. The Panel considered that companies needed to be particularly careful about the supply of medicines to private clinics. It noted that Roche had made enquiries about the doctor but not about the owner who claimed he was a pharmacist. The FT article referred to a report written by a member of Roche's staff posing as a new client in May 2003 which described how the latter '… personally sold him Xenical …' and that 'To a lay person he would have passed as a doctor'. The Panel considered that Roche had not paid sufficient attention to ensuring that the supply of its product to the private clinic was appropriate. Thus the Panel ruled a breach of Clause 9.1. The Panel considered that the arrangements brought discredit upon the pharmaceutical industry and a breach of Clause 2 was ruled.

The Panel noted that Roche had agreed to sponsor the further clinic. According to documents (on clinic headed paper) from the owner payment was to be in two parts, £20,000 payable in August 2004 and £35,000 in January 2005. According to Roche only £20,000 had been paid. The second payment had been halted following contact by the MHRA.

The Panel noted that Roche had agreed to pay the money in August 2004. This meant that the applicable Code was the 2003 Code.

The supplementary information to Clause 18.1 of the 2003 Code stated that medical and educational goods and services could be provided if they enhanced patient care or benefited the NHS. The provision of such goods and services must not be done in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine.

It was difficult to see how providing £55,000 to an individual to purchase a private diet clinic was a medical and educational good or service that would enhance patient care or benefit the NHS as required by the Code. Thus the Panel ruled a breach of Clause 18.1 of the 2003 Code. The Panel did not consider that Roche had maintained high standards in relation to its agreement to provide an individual with £55,000. A breach of Clause 9.1 was also ruled. The Panel considered that the arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel also considered that the circumstances warranted consideration by the Code of Practice Appeal Board in relation to the possibility of additional sanctions. Thus the Panel decided to report Roche to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY ROCHE

Roche noted that Clause 1 of the 2006 Code, set out the scope of the Code. Clause 1.2 stated that 'The term "promotion" means any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines'. Roche submitted that the commercial supply of medicine was not a promotional activity and therefore it did not fall under the scope of the Code. Commercial supply fell under the scope of the MHRA and specifically under the scope of the 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors' - the orange guide.

Although Roche considered the commercial supply of medicines fell outside the scope of the Code it demonstrated the robust processes and checks it carried out prior to supply of Xenical to the original clinic.

Roche noted that the Panel was extremely concerned about the circumstances which had led to a prescription only medicine in effect being supplied to a person who was not a health professional and by that person to patients. Roche as a wholesale dealer complied with UK legislation on wholesale distribution as stated in 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors' compiled by the Inspection and Standards Division of the MHRA, Chapter 9, Section 9.

Within the UK Roche supplied to other wholesale dealers who held valid licences as issued by the MHRA, hospital pharmacies, having checked their validity in the hospital yearbook, retail pharmacies where they were registered with the Royal Pharmaceutical Society of Great Britain (RPSGB), and clinics and dispensing doctors, under the supervision of a GP, having checked their status with the General Medical Council via their GMC certificate.

Roche submitted that it had presented its own internal 'Guidelines for Opening New Accounts and Bona fide checks' to an MHRA inspector at an importation audit carried out in January 2007. This was a standard audit by the MHRA and was not related to the diet clinics or any other event. The auditor's only recommendation was that Roche create a GMP relevant Standard Operating

Procedure and this was actioned and last reviewed on 2 April 2007.

When selling prescription only medicines Roche and other pharmaceutical companies sold to the organisation, not an individual, and ensured that either the organisation had an approved licence to supply prescription only medicines or alternatively had a responsible person attached to that organisation who could lawfully administer the prescription only medicines.

- For wholesalers Roche sold directly to a wholesaler branch which was under the supervision of the Responsible Person. In practice the owner of the wholesaler was not the Responsible Person and the ordering was generally carried out by a buyer or replenishment coordinator.
- Roche sold directly to retail pharmacists and it would check that they were registered with the RPSGB, however the ordering from that retail pharmacist could be performed by a locum, or general pharmacy staff rather than the registered pharmacist who took ultimate responsibility for product ordering, storage and dispensing. The pharmacy owner was not necessarily the registered pharmacist or Responsible Person but they had a duty to nominate a Registered Pharmacist as their superintendent.
- In supplying GPs or dispensing doctors, Roche sold to the organisation, not the individual. Roche ensured that that there was a GP with a valid GMC certificate at the delivery address to take full liability for the procurement, storage and dispensing of product. This approach was in line with other wholesaler dealers and complied with current legislation, and was the approach taken in supply of Xenical to the diet clinic.

Therefore Roche submitted that it was in line with standard practice of other wholesaler dealers, and it had fully adhered to the legal requirements as set out by the MHRA in supply of medicine and validated by the MHRA audit, previously discussed, in January 2007. The fact one of the parties provided a prescription only medicine to patients was his responsibility and that was why he was successfully prosecuted by the MHRA, which Roche had fully supported from the outset.

Roche considered that if the Appeal Board upheld the Panel's rulings of breaches of Clauses 2 and 9.1 in Cases AUTH/2099/2/08 and AUTH/2100/2/08, there would be significant implications on how current UK legislation for wholesaler distribution was interpreted and applied, and on how the entire pharmaceutical industry and wholesalers conducted business.

Roche disagreed with the Panel's view that the company had not paid sufficient attention to ensuring that the supply of its products to the private clinic was appropriate.

With specific regard to the group of slimming centres Roche sold Xenical to one slimming clinic and carried out the following detailed review to check the validity of the centre:

- A Roche medical representative visited the slimming centre to meet the lead doctor and business owner and to see the clinic and how it operated. A report was produced detailing:
  - The centre's addresses and telephone numbers
  - Treatment protocol and guidelines
  - Doctors' names at each location
  - Opening times for each centre
- When the account opening form was completed and returned to Roche it established that the doctor who met the medical representative at the field visit had provided his GMC number and this went through the Roche standard procedure for opening new accounts with the doctor's name and number being checked through the GMC website. In addition other checks were completed such as the financial security of the organisation.
- Advertisements in local newspapers showed that the slimming centres were active in the local market.
- The clinic also advertised within the local GP surgery appointment cards highlighting links with general practice.
- Once the account was opened the medical representative visited the account and met the doctor and business owner.
- Roche monitored the sales of Xenical in total and by individual purchaser. At the peak of its sales to the entire private sector the quantity of Xenical sold to all private clinics was 5.5%.
- Once Roche realised that the quantity being purchased through the group of clinics was higher than expected for the private sector then a member of the market analyst team visited the centre and other larger buying centres to validate their models and patient numbers. In addition to this the analyst also measured sales in the surrounding areas to see whether Roche were experiencing a corresponding fall in volume to standard wholesalers. This was to provide additional assurance with regard to supply of Xenical.
- Roche limited the amount of stock that the diet centre could order, whilst its investigation was underway. The cap on the sales quantity was still in place when the MHRA enforcement team visited.

Roche also sent a member of staff to the clinic to act as a new patient in order to provide additional assurance that the Xenical supplied to the group was being dispensed and the group was not acting as a wholesaler and supplying the packs to other chemists/wholesalers.

In this regard Roche submitted that a significant amount of time was taken in investigating the sales to the clinic to ensure the validity of the sales through this group. In addition as far as Roche was

aware at least one other pharmaceutical company had seen that this group was legitimate and had also supplied a prescription only medicine.

In summary, Roche submitted that the commercial supply of medicines did not constitute promotion as defined in Clause 1.2 and therefore considered its commercial supply of Xenical to the diet clinic to be outside of the Code. If the Appeal Board took the view that the Code did apply then Roche challenged the findings that it was in breach of Clauses 9.1 and 2. Roche had done all that a responsible pharmaceutical company would and should have done in the circumstances and strictly followed legislative process. Roche noted that pharmaceutical companies supplied an organisation, not an individual and the clinic had a doctor qualified to prescribe Xenical. The fact the owner of the clinic was not qualified was not relevant for this purpose, although Roche genuinely believed at the time that he was a pharmacist. If the clinic had not had a doctor Roche would not have supplied to it.

COMMENTS FROM THE COMPLAINANT

The complainant noted that Roche disagreed that insufficient attention was paid to the supply of its products to the private clinic. The complete process undertaken by Roche when the account opening form was completed and returned was to establish that the doctor whom the medical representative met at the field visit had provided his GMC number. This went through the Roche standard procedure for opening new accounts with the doctor's name and number being checked through the GMC website. The complainant alleged that within the Employment Tribunal evidence was a string of emails dated from 26 April 2000, whereby a Roche employee stated that he believed that the supply of Xenical to the slimming clinics contravened EU Directive 65/65 and the 1968 Medicines Act; he was concerned that Roche was supplying to the clinic and not directly to the doctor. He stated that it was irrelevant that a doctor prescribed/dispensed – the law in question was about supply and that Roche had to legally supply to an authorized body. He emphasized that the onus of the law was clearly on the supplier (Roche) as there was no guarantee that a product would be legally dispensed if it were supplied to an unlicensed body. He clearly told his Roche commercial and legal colleagues that unless the clinics were licensed in some way, Roche was outside the law. Indeed invoices from Roche, which were also supplied to the Employment Tribunal, showed that from 28 March 2002 until 20 January 2005 Xenical shipments all went to a clinic which was not the address of the 'clinic' that the doctor apparently supervised and which appeared on the New Customer Form supplied by Roche in its appeal.

The complainant alleged that also contained in the Employment Tribunal evidence, was an email concerning supply of Xenical to slimming clinics, dated around the time of the announcement of the MHRA Enforcement visit on 4 March 2005. In it the correspondent described his concerns that, as the Responsible Person named on Roche's GDP licence, he was personally accountable if *bona fide* checks of purchasers had not been performed properly. He reminded the recipient of the email he sent him in April 2000 and he repeated that, in his opinion, Roche had not performed sufficient verification checks with respect to the slimming clinics. Although Roche believed the owner was a pharmacist, it had not checked his registration with the RPSGB.

The complainant noted that in response to an item on BBC Radio 4 Today Programme, 4 April 2008 Roche issued two statements to the BBC describing the verification checks that it had done before supplying Xenical to the slimming clinic. In short, Roche changed its story when probed by the BBC journalist. It was therefore difficult to see how Roche's comments regarding its checking of the validity of the centre could be upheld. The complainant strongly suggested that the Appeal Board requested the evidence from Roche that it provided to the Employment Tribunal.

The complainant noted that Roche had stated that it had monitored the sales of Xenical in total and by individual purchaser. At the peak of its sales to the entire private sector the quantity of Xenical sold to all private clinics was 5.5%. Once Roche realized that the quantity purchased through the clinics was higher than expected for the private sector a member of the company's market analyst team visited the centre and other large buying centres to validate their models and patient numbers. In addition to this the analyst also measured sales in the surrounding areas to see whether Roche had experienced a corresponding fall in volume to standard wholesalers. This was done in order to provide additional assurance with regard to supply of Xenical. Roche limited the amount of stock that the diet centre could order, whilst its investigation was underway. The cap on sales quantity was still in place when the MHRA Enforcement team visited.

The Roche commercial person who visited the owner reported to Roche in December 2003 that: 'As yet we have invested almost no money in any of these clinics and we are gaining sales despite this. I am sure that with some often low level investment we can develop many of these models and drive even greater Xenical sales'. He described in detail the fact that the owner wanted to buy out another private clinic which had 16,000 patients on its books of which 5000 were said to be active. From the rough calculations that the owner had carried out he expected that business could almost double. The investment in the clinic would be about £55,000 of which the owner wanted a significant contribution from Roche. The Roche employee reported that the clinic he visited was part of a 'tanning and toning salon', however he did not witness any patients in attendance when he visited. Whilst visiting the owner, he also reviewed confidential patient records

and based on this review he stated that his initial scepticism about the clinic had been drastically reduced and that he was convinced that a large number of patients were going through the clinic. He advised against closing down trading terms with the clinic and stated that the only worst-case scenario would be if they stopped buying Xenical. He stated that: 'I feel that we may be sacrificing sales just because we are scared of the potential of the private sector'. Roche's primary concern was that Xenical shipped to the owner was entering the grey market and it was concerned that the large quantities of Xenical that it shipped to the slimming clinic were being sold on at a profit. He fully supported the investment in the new clinic and advocated the payment be made in two lump sums, '…On the question of funding the expansion in the slimming clinic in ……, it is hard to see an argument against based on the fact that I am almost entirely convinced of the validity of the current business model. The £55k request would be recouped within a few months. 500 packs per month = £15k per month and the full amount would be returned within 4 months. I would possibly recommend a more conservative approach of half this on completion of the purchase and the remainder after a few months of Xenical purchase to remove some of the risk. This depends on the requirement of the funding for the initial purchase'. Based on this evidence, it is difficult to see how Roche could have agreed to the payment of £55,000 to the owner as an 'unrestricted grant' which was what Roche claimed in response to the Today programme and the FT article. The complainant understood that the intent behind allowing pharmaceutical companies to make unrestricted grants was that they were given to a third party for the purpose of research or education and not for the financial benefit of the donor.

Indeed, in it response Roche stated that it had analysed the owner's approach for funds to see if such an investment would be in the company's longer term interest and that it concluded that it would.

The complainant alleged that it was clear that Roche's investment in the new slimming clinic was purely motivated by its desire to increase the sales of Xenical. The complainant questioned whether Roche could provide documentary evidence that it had limited the amount of Xenical that the clinic could order.

The complainant noted that Roche had also sent a member of staff to the existing clinic to act as a new patient, in order to provide additional assurance that Xenical being supplied to the group was being dispensed and the group was not acting as a wholesaler and supplying packs to other chemists/ wholesalers

The person Roche sent to the owner's clinic to act as a patient seeking help with weight loss described in his report how, in May 2003, he attended the clinic which advertised itself as offering health, beauty, skin, nail and massage for men and women. He described the clinic as a former corner shop, with the front room as a reception area and the rear rooms and upstairs having been converted as a beauty clinic. He was seen by the owner. In his report he stated: 'To a lay person he would have passed as a doctor and had the bag, sphygmomanometer etc to almost prove it'. The complainant noted that Roche already knew at this point that he was not a doctor as they believed him to be a pharmacist. The 'patient' had his 'history' taken briefly by the owner and it rapidly became clear that he was going to be prescribed one of three medicines. He asked for Xenical and was given a Welwyn pack of Xenical in exchange for £75.

The complainant alleged that based on this evidence, it was clear that Roche knew that the owner was supplying Xenical without a valid doctor's prescription in May 2003 and yet it continued to supply him with Xenical. Indeed, the invoices for supplies of Xenical to the clinic were dated up to March 2005. In short, following the mystery patient visit, instead of notifying the MHRA and police of his activities, Roche continued to supply him for nearly two years until the MHRA Enforcement visited the Roche Welwyn site in March 2005. Easily-conducted checks with the RPSGB register would have verified if the owner was a pharmacist.

The complainant noted that Roche had stated that over the course of the MHRA investigation the MHRA had seen all related Roche internal documents. Roche had called part of its submission to the Employment Tribunal the 'MHRA Bundle'. However, its table of contents indicated that not all of its contents had been supplied to the MHRA. Documents not disclosed at the time included the transcript of a conversation involving the owner's wife in February 2005. This transcript stated that his wife knew that Roche was giving £55,000 to the owner to set up another clinic. She also stated that he was buying Xenical from Roche at levels of between £79,000 and £89,000 per month. In this transcript, she also stated that a patient who had been given a product by her husband suffered an epileptic fit.

The complainant noted that Roche had stated that as it had confirmed the legitimacy of the doctor it had therefore authorized direct distribution of stock. The complainant alleged that the Xenical sales were made to another clinic. Therefore this did not constitute 'direct distribution of stock' to the location where Roche considered the doctor to be based. The address of the other was the address on a wholesale dealer's licence, which was issued in April 2004 by the MHRA. However, Roche made shipments to this address before the wholesale dealer's licence was obtained.

The complainant noted that Roche had stated that as part of its ongoing discussions with the clinic, the pharmacist positioned himself as owning several

other clinics in the UK and that he proposed to set up another clinic. There was an existing clinic, which was about to close down as the owner was retiring. He asked Roche in 2004 for funds to support the set up costs. Roche had submitted that prior to making any such decision, as in any commercial organization, it had analysed whether the investment would be in the longer term interests of the company and concluded that it would. In addition it would benefit local patients who had used the clinic and others who would do so in the future. Roche therefore agreed to sponsor the clinic with £55,000 in two payments spread over 6 months as evidenced by confirmation from the owner and the invoice. Roche had submitted that this funding was not linked to the prescribing of Xenical. The funding was part paid – Roche paid the first instalment of £20,000 but the final payment of £35,000 was stopped when Roche was contacted by the MHRA and suspicions were raised about the legitimacy of the pharmacist. The complainant was astounded at this submission from Roche. Evidence provided to the Employment Tribunal included an internal Roche report in which the Roche employee stated that '[He] told me he would transfer all his patients over to Xenical in a phased switch if the price was right'. The Roche employee also advocated significant discounts to the price at which Xenical was normally sold and Roche later offered bonus packs to reduce the price. Another document submitted in evidence, described the private clinic funding proposal and stated that the owner requested the company's help in supporting the purchase of particular clinics, adding that he believed 'this undoubtedly makes switching to Xenical easier'.

ROCHE'S COMMENTS ON THE REPORT FROM THE PANEL

Roche restricted its comments to the matter of funding the slimming clinic. Roche explained that the local medical representative's proposals for funding had been rejected a number of times before he found two people in the company willing to agree to it. Those involved had effectively circumvented the normal approval process. The funding was eventually agreed without medical sign off. Roche submitted that since then it had substantially changed its approval procedures and awareness of the Code and its requirements was now much better throughout the company.

JURISDICTION

The week prior to the appeal Roche submitted that, as set out in its appeal, the commercial supply of Xenical to the clinic in question did not constitute promotion, and as such the Code was not applicable and the Panel had no jurisdiction. Roche considered it was for the MHRA rather than the Authority to take action if such supply was considered inappropriate (Roche rejected the contention that this was the case). Roche had cooperated with the MHRA in its prosecution of the owner of the clinic, and Roche's processes relating to the opening of new customer accounts had been reviewed in a Good Manufacturing Practice (GMP) audit independent of the MHRA prosecution. Roche submitted that the Authority had exceeded its powers by assuming jurisdiction in this matter.

The Chairman of the Appeal Board considered the points raised by Roche very carefully. In his view the question of jurisdiction was a matter of law upon which he needed to give a ruling rather than a matter of facts or merits which would be a matter for the Appeal Board. The Chairman decided to invite both parties to make brief submissions on this point at the start of the proceedings after which he would rule upon the question of jurisdiction. Both parties were so advised and a copy of Roche's letter was provided to the complainant in advance of the appeal hearing.

At the hearing Roche's representatives repeated the company's submission as detailed above. The complainant disagreed with Roche's arguments and submitted, *inter alia*, that the funding of the slimming clinics and the supply of Xenical were so inextricably linked that the latter amounted to the promotion of the product and was thus subject to the Code.

The Chairman noted that despite the 2001 and 2003 Codes being applicable to the matters at issue, the substance of Clause 1, which covered the scope of the Code, remained the same. Clause 1.1 stated that the 'Code applies to the promotion of medicines' and further 'to a number of areas which are non-promotional'. Clause 1.2 defined promotion as 'any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines'. The Chairman thus considered that promotion was wider than the obvious understanding of advertisements and marketing, its definition was not restrictive and the examples stated in the Code were not exhaustive. The Shorter Oxford English Dictionary, 2nd volume, defined promotion as 'advancement in position' or 'action of helping forward'. The Chairman considered that for there to be commercial supply there must be a commercial relationship. In this case the extent of the commercial relationship was illustrated by the fact that Roche admitted that it had a number of dealings with the diet clinics. In particular the Chairman noted Roche had sent an employee to a clinic in 2003 on a fact-finding exercise. Roche carried on a business relationship thereafter. The Chairman considered that the act of conducting a business relationship with customers in order to further the sale of prescription only medicines could properly be said to be advancing or helping forward an activity undertaken by a pharmaceutical company which promoted the prescription, supply, sale or administration of its medicines. On facts of this particular case the supply of Xenical came within the scope of the Code and the Authority had jurisdiction in the matter.

APPEAL BOARD RULING

The Appeal Board noted Roche's submission that the MHRA had seen all related Roche internal documents and had cleared the company of any wrong-doing. The Appeal Board noted Roche's submission that it was a victim of criminal activity. The Appeal Board's role was to consider the matter in relation to the Code which was not the role of the MHRA.

The Appeal Board noted that the activities had taken place in 2003 and 2004; the 2001 and 2003 Codes were thus applicable. With regard to Clause 2, there was no difference between the requirements in the 2001 and 2003 Codes. Clause 9.1 in both Codes required high standards to be maintained. Other wording in Clause 9.1 of the 2001 Code had become Clause 9.2 in the 2003 Code. Taking all these factors into account, the Appeal Board decided it would make its rulings in relation to the 2003 Code using the Constitution and Procedure in the 2006 Code.

The Appeal Board noted Roche's concerns about the implications of this case on the interpretation of current UK legislation for wholesaler distribution. The Appeal Board did not agree. This case turned on its own particular facts.

The Appeal Board noted Roche's submission that the supply of Xenical to private slimming clinics was a new area of business for the company. The Appeal Board also noted that internal emails from 2000 onward showed staff concern over the legality of supplying prescription only medicines to such organizations but Roche indicated at the hearing that its legal department had not agreed with the basis of this concern and had concluded that such supply was legal.

The complainant had supplied a copy of a statement from a Roche employee which stated that although he had met the doctor who supervised the clinics once in January 2002, this had been at the doctor's own clinic. This meeting was to ensure that as lead clinician the doctor was familiar with Xenical, the prescribing guidelines and ongoing patient support programmes. All the relevant promotional material was said to be supplied at this meeting. Other than that one meeting with the doctor all other meetings had been with the owner of the clinics, who Roche believed was a pharmacist although it did not have, and never sought, any proof of this. The Appeal Board noted that the Xenical New Account Proposal Form for the Diet Centre, which included the supervising doctor's name and GMC number, did not need to be signed by him and nor was the form dated. The Appeal Board considered that the investigations carried out by Roche in the first instance, when it set up the account, should have been more rigorous but nonetheless it did not consider that Roche's actions were entirely unreasonable given that it appeared satisfied that a qualified health professional was responsible for the operation of the clinics.

The Appeal Board noted that in 2003 Roche became concerned that the large volume of Xenical being provided to the Diet Clinic might indicate that the product was being sold on the grey market. The company thus sent one of its employees to the clinic to act as a new patient seeking help with weight loss. That employee was seen only by the owner who 'eventually' agreed to prescribe him Xenical. The Appeal Board was extremely concerned that a prescription only medicine had been supplied to a patient by someone who Roche knew was not a doctor. The Appeal Board noted that although Roche now submitted that the company assumed that the owner was supplying the Xenical according to a Patient Group Direction Roche provided no evidence to support such an assumption. This raised serious concerns with regard to patients' safety. The visit report ended with the statement that it was 'difficult to see how he/they can be using much Xenical – although it is of course possible that the partner might be a huge fan'.

The Appeal Board noted that although Roche continued to be concerned that the volume of Xenical sold to the Diet Clinic was more than that dispensed, it maintained but capped the amount it would sell to the clinic in 2003. In December of that year a business analyst from Roche visited the Diet Clinic again to ascertain whether Xenical was being dispensed from the clinic or sold onto the grey market. There was no evidence that the Xenical was being sold on locally and thus the analyst advised against closing down trading terms with the clinic, convinced that it had a significant number of patients and that a significant number of them received Xenical. During the course of that visit the Roche employee was shown patient records which he believed were valid and provided evidence to show that it was appropriate to continue to supply Xenical to the clinic. In March 2005 the MHRA advised Roche that it was investigating allegations of criminal activity at the slimming clinic and asked the company to continue supplying Xenical whilst its investigations were ongoing.

The Appeal Board was extremely concerned about the supply of Xenical to the diet clinic. In the Appeal Board's view, by the end of May 2003 the company should have strongly suspected that the manner in which Xenical was prescribed at the clinic was inappropriate and possibly prejudicial to patient safety. The company, however, appeared to act principally with regard to commercial concerns to ensure that Xenical was not entering the grey market. No other action was taken. The Appeal Board acknowledged that from March 2005 Roche had co-operated with the MHRA and in that regard it had to continue to supply the clinics. Nonetheless the Appeal Board considered that between May 2003 and March 2005 Roche had not upheld high standards with regard to its supply of Xenical to the diet clinic. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The Appeal Board further considered that Roche's actions had 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 both points was unsuccessful.

The Appeal Board noted the Panel's report in accordance with Paragraph 8.2 of the Constitution and Procedure was with respect to both the supply of Xenical and the funding of the new slimming clinic. Roche had not appealed the Panel's rulings of breaches of Clauses 2, 9.1, and 18.1 of the 2003 Code in relation to its funding of the clinic to the sum of £55,000 of which £20,000 had been paid.

The Appeal Board was extremely concerned about this case, particularly with reference to Roche's disregard for patient care and its lack of action in 2003. The payment for the purchase of the clinic was clearly linked to the prescribing of Xenical and thus was totally unacceptable. The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure that Roche would be publicly reprimanded. The Appeal Board noted that Roche had already been audited three times in relation to Case AUTH/1819/4/06 and another audit in that case was pending. The Appeal Board decided, in accordance with Paragraph 12.2 of the Constitution and Procedure, to report Roche to the ABPI Board of Management with the recommendation that the company be suspended from membership of the ABPI.

CASE AUTH/2100/2/08

The Financial Times (FT) of 12 February 2008 carried an article critical of the marketing of Xenical (orlistat) by Roche Products Limited. In accordance with established practice the matter was taken up as a complaint under the Code.

COMPLAINT

The article alleged that Roche had sold large quantities of Xenical (a prescription only medicine) to the operator of a chain of private UK diet clinics in spite of suspicion at one stage that the product was being sold illegally. Roche had agreed to provide £55,000 for the purchase of another diet clinic to the individual involved in the clinics who was subsequently convicted of offences against the Medicines Act 1968.

When writing to Roche, the Authority asked it to respond in relation to Clauses 2, 9.1, 17 and 18.

The author of the FT article did not participate in the procedure.

RESPONSE

Roche stated that the background to this complaint was complex and spanned the last five years.

- Roche and other pharmaceutical manufacturers were the victims of criminal activity relating to a group of private diet clinics.
- From March 2005 Roche supported the Medicines and Healthcare products Regulatory Agency (MHRA) at all levels to provide information and intelligence for it to build a criminal case against two individuals. One had posed as a pharmacist and treated patients for obesity, including the provision of prescription medicines.
- It later transpired that the latter was employed by another pharmaceutical company as a medical sales representative and the other was his previous line manager selling their company's anti-obesity treatment.
- The case was heard in court (November 2007) and both defendants pleaded guilty (one to five offences and the other to one offence against the Medicines Act) and awaited sentencing.
- Over the course of its investigation the MHRA had seen all related Roche internal documents and had cleared Roche of any wrong-doing in relation to this complex case. In fact the MHRA had thanked Roche for its co-operation and support to help it prosecute these individuals.
- Similarly, Roche had been engaged in an employment tribunal with the complainant in Case AUTH/2099/2/08 for the last 3 years who claimed her dismissal from the company was a result of 'whistle blowing' when questions about the diet clinic came to light – something which Roche strongly refuted. The employment tribunal found that as Roche did not follow the correct dismissal process the complainant was unfairly dismissed. Roche acknowledged the unfair dismissal, however this was not for whistle blowing. The claimant's whistle blowing claim was therefore not upheld. The employment tribunal was still ongoing as the claimant had appealed the ruling.
- Thus this was a very complex situation of which detailed information had already been heard by a criminal court of law, an employment tribunal, and full documentation had been reviewed by the MHRA.

This response would address every Code matter raised in the article and in relation to Clauses 2, 9.1, 17 and 18.

Roche explained that from 2002 it took the first step into a new market place – that of private slimming clinics. Roche was in contact with over 150 private slimming clinics; however it was approached by the diet clinic in question in April 2002 to provide support. Roche understood that the owner was a pharmacist and that he owned a group of weight management clinics.

A Xenical New Account Proposal Form was completed which provided the name and General Medical Council (GMC) number of the doctor working at the clinic. Roche had met the doctor and pharmacist on a regular basis, though the pharmacist clearly drove the initiative. In addition, Roche was provided with the list of diet clinics that made up the group, the staffing at these clinics as

well as the opening hours. The diet clinic in question requested Roche supplied Xenical directly and in line with standard procedure; the GMC number of the doctor was confirmed and Roche therefore authorised direct distribution of stock, not in breach of Clause 17.

When Roche entered any new market it was standard commercial practice for it to closely monitor progress. Roche noted higher than expected volumes of Xenical being sold to the diet clinic and visited it several times to check that it was providing medicine to patients and not selling Xenical on to the grey market. Roche had no reason to believe that the staff running the clinic were not legitimate and this was not questioned. Roche monitored sales of Xenical in neighbouring regions and noted no change in sales or sales pattern.

Roche sent some of its staff to question the clinic and to review its data and also sent someone to pose as a patient. The rationale for this was to check that patients were consulted at the clinic and Xenical was used directly with patients and not being sold on. Roche had no knowledge or reason to suspect the owner of any criminal activities and its investigations were not into this aspect of the clinic's activities. Following Roche's investigations it was satisfied that the clinics were run properly and the demand for Xenical was appropriate for the local population. Roche provided copies of advertisements placed in local papers which suggested that the clinic worked closely with local surgeries and the community. On that basis Roche continued to supply the clinic, although it monitored and capped the quantity it supplied.

Roche's member of staff who posed as a patient was provided with a pack of Xenical by the pharmacist. Roche did not question this as this was not unusual because there were processes where health professionals other than doctors could provide prescription only medicines to patients - these included patient group directions (PGDs), and supplementary prescribing. With a PGD the qualified health professionals who might supply or administer medicines under such an arrangement included, *inter alia*, pharmacists. As Roche had stated previously, it had no reason to question the credibility of the pharmacist and the member of staff who attended the clinic did not investigate this. Following the MHRA investigation it was discovered that the clinic did not hold a PGD at the time.

The FT article quoted from an internal report of this visit. This document was for internal use only and Roche agreed that it had been written in a flippant way. However given that this member of staff posed as a patient to check if patients were seen and that Xenical was used by the clinic ie it was not sold on to the grey market, this information, together with Roche's previous investigation led it to conclude that the clinic was genuine. Roche did not check the legality of the pharmacist.

The FT referred back to this internal report later in the article and quoted Roche's member of staff as stating 'It is difficult to see how he/they can be using so much Xenical'. The FT did not print the sentence that followed, which was 'although it is of course possible that the partner might be a huge fan'.

Roche noted that it was standard commercial practice for a company to negotiate deals with its customers. The diet clinic negotiated a discount with Roche based on purchasing specific volumes. The discount was offered to all key slimming centres based on purchasing a specific volume. Within the contract there was no added incentive to increase the volume of usage to get a greater discount level.

As part of Roche's ongoing discussions, the pharmacist positioned himself as owning several other clinics in the UK, and that he proposed to set up another clinic which was otherwise about to close due to retirement. He approached Roche on a number of occasions and again in 2004 for funds to support the set up costs. Before it made any decision Roche analysed internally whether such an investment would be in its longer term interests and in this instance it concluded that it would. The provision of sponsorship needed to benefit patient care or benefit the NHS, and Roche thought it would benefit local patients who had used the clinic and others who would do so in future. Roche therefore agreed to sponsor the clinic for £55,000 with two payments spread over six months, as evidenced by letters from the pharmacist confirming the money was for sponsorship, paid in two parts.

An internal document referred to in the FT entitled 'Private Clinic Funding Proposal' was prepared by an ex-Roche employee as part of Roche's internal analysis. The pharmacist referred to the prescribing of Xenical. Roche noted that this was what the pharmacist alone said and was not a condition of funding, once that decision had been taken.

The FT article quoted '… is totally confident of, and gives his guarantee to an early and swift changeover to Xenical'. This quotation appeared in the Private Clinic Funding Proposal prepared by the ex-Roche employee and was not an official document, nor did it form the basis for the agreement to sponsor this initiative. Roche denied there was a link between the payment of sponsorship and the prescription of Xenical and denied this was a breach of Clause 18.

The funding was part paid - Roche paid the first instalment of £20,000 but the final payment of £35,000 was stopped when Roche was contacted by the MHRA and suspicions were raised about the possible criminal activities of the owner.

In March 2005 the Enforcement Division of the MHRA advised Roche that allegations of criminal activity at a diet clinic supplied by Roche and other pharmaceutical companies were being investigated. The MHRA asked Roche to continue supplying the

clinics with Xenical whilst the investigation was ongoing and Roche cooperated fully with this request and the investigation. Roche believed that in working with the MHRA, it had in fact maintained the high standards of the industry and it refuted a breach of Clause 9.1.

Roche was a victim of criminal activity in this case and had worked with the MHRA to ensure that there was sufficient evidence to convict the individuals involved. As victims of a crime, Roche did not consider its actions discredited the industry (Clause 2) and that high standards had been maintained (Clause 9.1). Roche had worked with the MHRA on the fraudulent behaviour and it had been investigated by the MHRA for any improper behaviour and cleared.

As a result of the criminal activity, Roche had subsequently changed its distribution mechanism and no longer supplied any private slimming clinic directly with medicines.

PANEL RULING

The Panel noted Roche's submission that the MHRA had seen all related Roche internal documents and had cleared the company of any wrong-doing. The Panel noted Roche's submission that it was a victim of a criminal activity. The Panel's role was to consider the matter in relation to the Code which was not the role of the MHRA.

The Panel noted that the activities had taken place in 2003 and 2004. The applicable Codes would be the 2001 Code and the 2003 Code. With regard to Clauses 2, 18.1 and the supplementary information to Clause 18.1 referring to terms of trade (paragraph 1) there was no difference between these requirements in the 2001 and 2003 Codes. Clause 9.1 in both the 2001 Code and 2003 Code required that high standards be maintained. Other wording in Clause 9.1 of the 2001 Code had become Clause 9.2 in the 2003 Code. Taking all these factors into account the Panel decided to make its rulings in relation to the 2003 Code using the Constitution and Procedure in the 2006 Code.

The Panel noted that Roche had been asked to respond in relation to a number of clauses of the Code, including Clause 17. On reviewing Roche's response, the Panel did not consider that Clause 17 of the 2003 Code was relevant to the activities in question and thus that clause was not considered.

With regard to the supply of Xenical, the Panel was extremely concerned about the circumstances which had led to a prescription only medicine in effect being supplied to a person who was not a health professional and by that person to patients. The Panel noted Roche's submission that it had validated the GMC number of the doctor named on the new account proposal form. Roche provided details about the contract to supply Xenical to the owner in relation to other clinics also owned by him. The document gave a contract price in relation to 1,500 packs per month which gave a saving to the clinic of approximately £17,280 per month compared with the NHS price. The document was signed and dated 17 August 2004 by the clinic owner. The Panel noted that the Code excluded terms of trade relating to prices, margins and discounts in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 as stated in the supplementary information to Clause 18.1. Discounts were in regular use by the industry on 1 January 1993 and thus were excluded from the Code. Thus no breach of Clause 18.1 of the Code was ruled.

The Panel noted that the contract did not stipulate that the professional status of the signatory be included. Roche had not confirmed the professional status of the clinic owner who Roche submitted had posed as a pharmacist. The Panel considered that in effect Roche had sold a prescription only medicine to a member of the public. The Panel was extremely concerned about the arrangements particularly given that someone from Roche had visited the diet clinic in May 2003 and had been seen by the owner. The report of that visit noted that to the lay person the owner would have passed as a doctor as he 'had the bag and sphygmomanometer etc to almost prove it'. The document used the term 'prescribed' and reported that the owner was clearly not a fan of Xenical. (This seemed at odds with another document on diet centre headed paper dated 18 April 2002 which set out a business proposal to offer Xenical as 'drug of choice' and asking for £6,000 to review the database and switch suitable patients to Xenical. The costs would be offset by revenue generated from Xenical and Roche was asked to provide some if not all of the funding for this to be undertaken in each of the clinics.) The Roche employee arranged to visit the clinic in June 2003 but no details of this visit, if it took place, were provided. The report stated that the Roche employee had paid £75 for a pack of Xenical and some herbal product was provided free of charge. Roche submitted that this visit was to learn more about the use of Xenical rather than the professional qualification of the owner. The Panel considered that companies needed to be particularly careful about the supply of medicines to private clinics. It noted that Roche had made enquiries about the doctor but not about the owner who claimed he was a pharmacist. The clinic visit report in May 2003 from the Roche employee should have led to further action on Roche's part and the company to question supply of Xenical to the clinic in 2004. The Panel considered that Roche had not paid sufficient attention to ensuring that the supply of its product to the private clinic in question was appropriate. Thus the Panel ruled a breach of Clause 9.1. The Panel considered that the arrangements brought discredit upon the pharmaceutical industry and a breach of Clause 2 of the Code was ruled.

The Panel noted that Roche had agreed to sponsor the new clinic initiative. According to documents

from the owner payment was to be in two parts, £20,000 payable in August 2004 and £35,000 in January 2005. According to Roche only £20,000 had been paid. The second payment had been halted following contact by the MHRA. A document prepared by a Roche employee headed 'Private Clinic Funding Proposal' was undated. It stated that if Roche agreed to the proposal it was hoped to complete purchase of the new diet clinic before the end of June 2003. The Private Clinic Funding Proposal also included sales analysis data for 2003 and 2004 showing the return on a £55,000 investment.

The Private Clinic Funding Proposal referred to the diet clinics as 'a real Xenical success story'. The owner was reported as having put enormous efforts into establishing Xenical across his group of clinics as the drug of choice for safe and effective long-term weight loss. At a meeting with two Roche employees the owner asked if Roche would be interested in supporting the purchase of particular clinics. The support would come in the form of Roche financially supporting the purchase. Previously the clinics acquired a stake in another diet clinic. That stake was said to have been bought under the proviso that patients were switched to Xenical in order to provide a more ethical and effective approach to the clinic. This led to an overwhelming increase in Xenical sales 'Thus showing that this winning formula can be easily introduced elsewhere'. The owner was said to be 'totally confident of and gives his guarantee of an early and swift changeover to Xenical' following an 'initial investment £55,000 – Roche'. Within a year the owner was 'confident that 2000 plus packs of Xenical a month will be prescribed at the … diet clinic'.

The Panel noted that Roche had agreed to pay the money in August 2004. This meant that the applicable Code was the 2003 Code.

The supplementary information to Clause 18.1 of the 2003 Code stated that medical and educational goods and services could be provided if they enhanced patient care or benefited the NHS. The provision of such goods and services must not be done in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine.

The Panel considered that the proposed payment of £55,000 for the new diet clinic was linked to the use of Xenical. The proposal had been made on the basis that Xenical would become the medicine of choice at the clinic. The Private Clinic Funding Proposal stated that the current treatment guideline at the new clinic was not to use Xenical. The proposal produced by the Roche employee focussed only on the increased use of Xenical. There was nothing in the proposal to suggest that Roche had considered whether or not this was a medical or educational good or service. There was no evidence to show that Roche considered the proposal in relation to anything other than the potential increased use of Xenical. It was difficult to see how providing £55,000 to an individual to purchase a private diet clinic was a medical and educational good or service that would enhance patient care or benefit the NHS as required by the Code. Thus the Panel ruled a breach of Clause 18.1 of the 2003 Code. The Panel did not consider that Roche had maintained high standards in relation to its agreement to provide an individual with £55,000. A breach of Clause 9.1 was also ruled. The Panel considered that the arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel also considered that the circumstances warranted consideration by the Code of Practice Appeal Board in relation to the possibility of additional sanctions. Thus the Panel decided to report Roche to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY ROCHE

The appeal by Roche was identical to that submitted in relation to Case AUTH/2099/2/08.

APPEAL BOARD RULING

Case AUTH/2100/2/08 was heard separately from Case AUTH/2099/2/08 which had immediately preceded it. Roche's appeal documentation was the same in both cases. At the hearing for Case AUTH/2100/2/08 the representatives from Roche stated that the Appeal Board could take into account Roche's submissions in Case AUTH/2099/2/08. The Appeal Board therefore considered that all submissions made in Case AUTH/2099/2/08 were deemed to have been made in Case AUTH/2100/2/08 as well.

The question of jurisdiction and applicable Codes had been settled in Case AUTH/2099/2/08.

The Appeal Board noted Roche's submission that the MHRA had seen all related Roche internal documents and had cleared the company of any wrong-doing. The Appeal Board noted Roche's submission that it was a victim of criminal activity. The Appeal Board's role was to consider the matter in relation to the Code which was not the role of the MHRA.

The Appeal Board noted Roche's concerns about the implications of this case on the interpretation of current UK legislation for wholesaler distribution. The Appeal Board did not agree. This case turned on its own particular facts.

The Appeal Board noted Roche's submission that the supply of Xenical to private slimming clinics was a new area of business for the company. The Appeal Board also noted that internal emails from

2000 onward showed staff concern over the legality of supplying prescription only medicines to such organizations but Roche indicated at the hearing that its legal department had not agreed with the basis of this concern and had concluded that such supply was legal.

In Case AUTH/2099/2/08 the complainant had supplied a copy of a statement from a Roche employee which stated that although he had met the doctor who supervised the clinics once in January 2002, this had been at the doctor's own clinic. This meeting was to ensure that as lead clinician the doctor was familiar with Xenical, the prescribing guidelines and ongoing patient support programmes. All the relevant promotional material was said to be supplied at this meeting. Other than that one meeting with the doctor all other meetings had been with the owner of the clinics who Roche believed was a pharmacist although it did not have, and never sought, any proof of this. The Appeal Board noted that the Xenical New Account Proposal Form for the diet centre, which included the supervising doctor's name and GMC number, did not need to be signed by him and nor was the form dated. The Appeal Board considered that the investigations carried out by Roche in the first instance, when it set up the account, should have been more rigorous but nonetheless it did not consider that Roche's actions were entirely unreasonable given that it appeared satisfied that a qualified health professional was responsible for the operation of the clinics.

The Appeal Board noted that in 2003 Roche became concerned that the large volume of Xenical being provided to the diet clinic might indicate that the product was being sold on the grey market. The company thus sent one of its employees to the clinic to act as a new patient seeking help with weight loss. That employee was seen only by the owner who 'eventually' agreed to prescribe him Xenical. The Appeal Board was extremely concerned that a prescription only medicine had been supplied to a patient by someone who Roche knew was not a doctor. The Appeal Board noted that although Roche now submitted that the company assumed that the owner was supplying the Xenical according to a Patient Group Direction Roche provided no evidence to support such an assumption. This raised serious concerns with regard to patients' safety. The visit report ended with the statement that it was 'difficult to see how he/they can be using much Xenical – although it is of course possible that the partner might be a huge fan'.

The Appeal Board noted that although Roche continued to be concerned that the volume of Xenical sold to the diet clinic was more than that dispensed, it maintained but capped the amount it would sell to the clinic in 2003. A document submitted in Case AUTH/2099/2/08 showed that in December of that year a business analyst from Roche visited the diet clinic again to ascertain whether Xenical was being dispensed from the clinic or sold onto the grey market. There was no evidence that the Xenical was being sold on locally and thus the analyst advised against closing down trading terms with the clinic, convinced that it had a significant number of patients and that a significant number of them received Xenical. During the course of that visit the Roche employee was shown patient records which he believed were valid and provided evidence to show that it was appropriate to continue to supply Xenical to the clinic. In March 2005 the MHRA advised Roche that it was investigating allegations of criminal activity at the slimming clinic and asked the company to continue supplying Xenical whilst its investigations were ongoing.

The Appeal Board was extremely concerned about the supply of Xenical to the diet clinic. In the Appeal Board's view, by the end of May 2003 the company should have strongly suspected that the manner in which Xenical was prescribed at the clinic was inappropriate and possibly prejudicial to patient safety. The company, however, appeared to act principally with regard to commercial concerns to ensure that Xenical was not entering the grey market. No other action was taken. The Appeal Board acknowledged that from March 2005 Roche had co-operated with the MHRA and in that regard it had to continue to supply the clinics. Nonetheless the Appeal Board considered that between May 2003 and March 2005 Roche had not upheld high standards with regard to its supply of Xenical to the diet clinic. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The Appeal Board further considered that Roche's actions had 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 both points was unsuccessful.

The Appeal Board noted the Panel's report in accordance with Paragraph 8.2 of the Constitution and Procedure was with respect to both the supply of Xenical and the funding of the new slimming clinic. Roche had not appealed the Panel's rulings of breaches of Clauses 2, 9.1, and 18.1 of the 2003 Code in relation to its funding of the clinic to the sum of £55,000 of which £20,000 had been paid.

The Appeal Board was extremely concerned about this case, particularly with reference to Roche's disregard for patient care and its lack of action in 2003. The payment for the purchase of the clinic was clearly linked to the prescribing of Xenical and thus was totally unacceptable. The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure that Roche would be publicly reprimanded. The Appeal Board noted that Roche had already been audited three times in relation to Case AUTH/1819/4/06 and another audit in that case was pending. The Appeal Board decided, in accordance with Paragraph 12.2 of the Constitution and Procedure, to report Roche to the ABPI Board of Management with the recommendation that the company be suspended from membership of the ABPI.

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During its consideration of these cases the Appeal Board had reservations about the conduct of the doctor named on the account form. The Appeal Board was extremely mindful of the privileged nature of the material before it. The Appeal Board considered that in cases involving potential risk to patient safety it had a responsibility to notify the General Medical Council (GMC). It decided that once the cases were completed the case report and the article in the FT should be sent to the GMC.

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CONSIDERATION BY THE ABPI BOARD OF MANAGEMENT

The ABPI Board noted that Roche had been ruled in breach of Clauses 2, 9.1 and 18.1 of the Code. It also noted that Roche had been audited three times and a fourth audit was arranged for September in relation to another unrelated case.

The ABPI Board noted Roche's submission that the MHRA had not suggested any wrong-doing by Roche. However, it believed that funding of the clinic, and Roche not taking any action in relation to the supply of Xenical to the clinic following the visit by the Roche employee posing as a new patient in 2003, were very serious matters. Both had been ruled in breach of the Code. The ABPI Board noted that the Appeal Board had recommended that Roche be suspended from membership of the ABPI and the ABPI Board concurred.

The ABPI Board agreed that Roche would be suspended from membership of the ABPI for a period of six months commencing 14 July 2008 with re-entry conditional upon the audit which the company was to undergo in September proving satisfactory to the Board.

Case AUTH/2099/2/08

Complaint received	**19 February 2008**
Undertaking received	**9 June 2008**
ABPI Board consideration	**17 June 2008**

Case AUTH/2100/2/08

Proceedings commenced	**19 February 2008**
Undertaking received	**9 June 2008**
ABPI Board consideration	**17 June 2008**

CASE AUTH/2101/2/08

ANONYMOUS EMPLOYEE v GLAXOSMITHKLINE

Diabetes care package

An anonymous employee of GlaxoSmithKline complained about the arrangements for the Diabetes Healthcare Partnership (HCP) which existed between GlaxoSmithKline and a primary healthcare service company. The primary healthcare service company delivered a range of services under the contractual opportunities offered by practice based commissioning (PBC).

The complainant stated that (s)he was a Diabetes First Associate (DFA), a non-promotional representative and former nurse, with GlaxoSmithKline. The complainant referred to a voicemail from a senior member of staff in integrated healthcare to UK Pharma.

> **'... some of the feedback from our customers, particularly practice based commissioning groups, is they want a transparent business-to-business relationship with GlaxoSmithKline, so that they are clear when they work with us of the benefit to GlaxoSmithKline, to the NHS, and to patients. So with this in mind we have been working on a new proposition, "The GSK Healthcare partnership." And we have now reached an important milestone where the first partnership contract has been signed with [a primary healthcare service company], a Practice Based Commissioning Group based in [a local area]. This collaboration… involves the delivery of a bespoke diabetes care package, "The Diabetes Intermediate Service". This innovative service created with the assistance of GSK aims to reduce the number of secondary care referrals by the deployment of a consultant lead [sic] team. GSK's expertise has been central to the development of this service, in addition GSK has contributed to the cost of running of the service, while [the primary healthcare service company] has agreed to select Avandamet [rosiglitazone and metformin] as first medicine in it's [sic] class on it's [sic] diabetes protocol for appropriate patients. This is a contractual arrangement between two commercial organisations. Together we have agreed specific roles, responsibilities, and deliverables. All aspects of the collaboration and on-going customer interaction fit with appropriate ethical guidelines. So this … is a major achievement and a significant step forward in establishing a more mature and potentially a more effective business relationship between GSK and the NHS. Where tangible benefits to all parties are clearly defined from the outset and are consistent with our "Sharing the Vision" philosophy ... '.**

The complainant had asked his/her manager about the voicemail and been told everything was completely signed-off, but it did not seem to fit within the spirit of the Code. The voicemail was sent out by customer environment marketing in September 2007, which managed the integrated healthcare managers and did unusual projects with the NHS.

Was it within the Code to have this business-to-business relationship as described? It just seemed like a clever way to pay for a service and generate more prescriptions as a result. The complainant had been told that everything (s)he did was a service to medicine where there was no influence on what a customer prescribed. In this partnership, it seemed that the company had called it a business relationship and only provided the service with the primary healthcare service company's agreement to put Avandamet in its protocol over competitors. The complainant's manager said this was okay because it was only a protocol and the GP could prescribe whatever they wanted. The complainant queried whether (s)he would want to read about this in the newspaper.

The complainant queried whether these healthcare partnerships were in keeping with the relevant and specific sections of the Code, and more importantly in keeping with its spirit.

The Panel noted that joint working between the industry and the NHS was not prohibited by the Code providing all the arrangements complied with it. In general arrangements that increased the potential pool of treated patients were likely to be acceptable. Arrangements that increased the prescribing of one specific product were likely to be unacceptable. The Panel accepted that a service that improved clinical outcomes, standardized continuity of care and reduced the number of secondary care referrals, all aims of the service at issue, would enhance patient care and benefit the NHS.

The Panel noted that the complaint had been prompted by a voicemail message which referred to the company's business relationship with the primary healthcare service company whereby GlaxoSmithKline had agreed to help the primary healthcare service company achieve its objective of reducing the number of diabetic patients referred to secondary care by deploying a specialist team, led by a consultant diabetologist, in the primary care setting. The voicemail stated that '… GlaxoSmithKline has contributed to the cost of running the service, while [the primary healthcare service company] has agreed to select Avandamet as first medicine in its class on its diabetes protocol for appropriate patients. This is a contractual

agreement between two commercial organisations'. The complainant was concerned that GlaxoSmithKline's sponsorship of the service was dependent upon the inclusion of Avandamet on the protocol.

The Panel noted guidance issued by the DoH in January 2008 on joint working between the NHS and the pharmaceutical industry defined joint working as:

> **'Situations where, for the benefit of patients, organisations pool skills, experience and/or resources for the joint development and implementation of patient centred projects and share a commitment to successful delivery. Joint working agreements and management arrangements are conducted in an open and transparent manner. Joint working differs from sponsorship, where pharmaceutical companies simply provide funds for a specific event or work programme…'.**

The Panel noted that GlaxoSmithKline had referred to this definition albeit one that was published some four months after the contract with the primary healthcare service company had been signed. The Panel noted that GlaxoSmithKline had helped the primary healthcare service company to develop its first diabetes pilot project by providing financial support, facilitation and training. In the Panel's view, however, the relationship between the primary healthcare service company and GlaxoSmithKline in the service now at issue did not appear to be one whereby the two organisations had pooled skills, experience and/or resources; it appeared that GlaxoSmithKline had acted simply to co-fund, or sponsor, the primary healthcare service company's diabetes service. In that regard the Panel noted GlaxoSmithKline's submission that its contract with the primary healthcare service company supported the running of the Diabetes Intermediate Service through funding to a maximum of £29,250 and that the company had no other involvement in the selection of the medicine for the management protocol and was not involved in any way in the management or provision of the service.

The Panel noted that GlaxoSmithKline had submitted that its relationship with the primary healthcare service company was at a business-to-business level and not with individual prescribers. GlaxoSmithKline described this as an explicit and transparent separation. In the Panel's view, however, GlaxoSmithKline was in effect working with a third party which it knew would influence the prescribing of individual doctors.

The contract between the primary healthcare service company and GlaxoSmithKline was dated September 2007. Paragraph 3.1 stated 'This project is sponsored by GSK. As a consequence of [the primary healthcare service company's] decision to place GSK's product on [the protocol] in accordance with paragraph 2.6 above, GSK has agreed to provide funding for this service: provisions of such funding is not conditional on the prescription of that product'. Other paragraphs defining GlaxoSmithKline's involvement related to the payment of the agreed funding, the use of any data provided to GlaxoSmithKline and that GlaxoSmithKline would comply with best practice to include codes of practice, relevant laws and guidelines on confidentiality and data protection.

Paragraph 2.6 of the contract stated 'Subject to paragraphs 2.7 and 2.8 below, [the primary healthcare service company] has agreed to select AVANDAMET ("the product") as a first choice medicine in its therapy class for the appropriate patient group on the Protocol ("First Choice Medicine"). Such selection by [the primary healthcare service company] shall include all considerations as per paragraph 2.2 above'. Paragraph 2.2 stated that the choice and use of medicines within a protocol was based upon the medicine's marketing authorization, an up-to-date review of the available evidence and its cost effectiveness. The protocol was for use by all the primary healthcare service company's practices. It was, presumably, paragraph 2.6 which had led to the statement in the voicemail that '[The primary healthcare service company] has agreed to select Avandamet as first medicine in its class on its diabetes protocol …'.

Paragraphs 2.7 and 2.8 of the contract made it clear that GlaxoSmithKline's medicines, including Avandamet, would only be used where appropriate and in accordance with local guidelines. Further, GPs in the group would retain clinical freedom for any individual patients for whom, in the GP's opinion, use of Avandamet was inappropriate. Paragraph 2.16 stated that GlaxoSmithKline would be provided with anonymised data relating to prescribing and outpatient outcomes.

The Panel noted that in response to a request for further information GlaxoSmithKline provided a copy of the diabetes protocol dated March 2007, due for review by March 2008, which it submitted was the first time the company had seen it. Under a heading of 'Glycaemic Control' for type 2 diabetics it was stated that step 2 treatment, for all patients with a body mass index of 25 or more, should be:

'Add Glitazone to metformin
- **1st line: pioglitazone**
- **2nd line: rosiglitazone**

Increase dose up gradually as required to maximum.

Glitazones are slow acting drug so results will not be noticeable immediately; reduction of blood glucose will happen over 4 - 6 weeks.

If there are compliance problems the combination tablets of Glitazone/metformin may be used…'

It thus appeared that the protocol and paragraphs

2.6 and 3.1 of the contract were inconsistent with one another. In the protocol rosiglitazone was stated to be the second line glitazone and in any event the combination tablets ie Avandamet, were only to be used if there were compliance problems. Given the protocol as it existed (effective from March 2007 and due for review by March 2008) the Panel queried why the contract was signed in September 2007 containing paragraph 2.6 specifically referring to Avandamet as a first choice medicine in its therapy class. The protocol referred to products by generic name only.

The Panel considered that, notwithstanding the protocol, paragraph 3.1 of the contract signed by GlaxoSmithKline in effect stated that the company's funding of the diabetes service was dependent upon the inclusion of Avandamet, as a named medicine, on the protocol. This was also the impression given in the voicemail. The Panel noted that the provision of medical and educational goods and services must not be linked to any medicine. In that regard the Panel considered that the diabetes service as described in the voicemail and in the contract was inappropriate. A breach of the Code was ruled. High standards had not been maintained. A breach of the Code was ruled. These rulings were appealed.

With regard to whether or not the arrangements amounted to an inducement to members of the health professions or administrative staff to prescribe, supply, administer, recommend, buy or sell Avandamet, the Panel noted that there was no gift, benefit in kind or pecuniary advantage to the actual prescribers. However the prescribers, as employees of the primary healthcare service company, would be obliged to follow the protocol. As far as GlaxoSmithKline was concerned the effect of the arrangements was that a payment had been made to a private company such that Avandamet was recommended. The Panel was concerned about the arrangements but after much consideration decided that, on balance, the circumstances of providing an inducement to the primary healthcare service company did not amount to a breach of the Code and ruled accordingly.

The Panel was concerned that the diabetes service was seen by some in GlaxoSmithKline as being linked to the use of Avandamet as first medicine in its class. The Panel noted that, given the content of the protocol and unbeknown to GlaxoSmithKline, as operated, the diabetes service was not linked to the use of Avandamet. The Panel thus considered that on balance, taking all the circumstances into account, GlaxoSmithKline had not brought discredit upon, or reduced confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

Upon appeal by GlaxoSmithKline the Appeal Board noted that the question to be answered was 'Did GlaxoSmithKline support the Diabetes HCP in return for Avandamet being named on the group's protocol?' The Appeal Board noted inconsistencies between the voicemail message, the written contract, and the protocol. The Appeal Board considered that it had to make its ruling on the service as described by GlaxoSmithKline in the voicemail and contract, as opposed to the protocol.

The Appeal Board noted that the voicemail message stated that '… GlaxoSmithKline has contributed to the cost of running of the service, while [the primary healthcare service company] has agreed to select Avandamet as first medicine in its class on its diabetes protocol for appropriate patients'. A direct link between the company's support and the potential use of Avandamet was thus implied. Paragraph 3.1 of the contract between the primary healthcare service company and GlaxoSmithKline stated 'This Project is sponsored by GlaxoSmithKline. As a consequence of the Group's decision to place GlaxoSmithKline's product on the Group's Protocol in accordance with paragraph 2.6 above, GlaxoSmithKline has agreed to provide funding for this service: provision of such funding is not conditional on the prescription of that product'. In the Appeal Board's view it was immaterial that the protocol did not refer to Avandamet as a named medicine; that it would do so was the basis upon which the contract was signed.

At the appeal hearing GlaxoSmithKline acknowledged that the wording used in paragraph 3.1 of the contract was not the best it could be.

The Appeal Board noted GlaxoSmithKline's submission that the protocol had existed before its involvement with the Diabetes HCP and that the company had not influenced it in any way; it had not changed as a result of the contract between the primary healthcare service company and GlaxoSmithKline. This was not the impression given by the voicemail and the contract.

The Appeal Board noted the protocol stated that when a glitazone was to be added to metformin, rosiglitazone was second line. Combination tablets of glitazone and metformin were only to be used if there were compliance problems. It also noted GlaxoSmithKline's submission that the positioning described was consistent with National Institute for Health and Clinical Excellence (NICE) guidance.

The Appeal Board further noted GlaxoSmithKline's submission that the naming of Avandamet in the contract was for the purposes of transparency. The Appeal Board considered that in this regard it was not inappropriate *per se* to refer to products but the manner in which they were referred to and the context was important. Encouraging appropriate use of a product in line with national and local guidelines was different to a contractual arrangement that a protocol be changed. The Appeal Board considered that in the voicemail and in the contract there was a very definite, unequivocal link made between the provision of funding and the inclusion of Avandamet, for use as appropriate, on the protocol.

The Appeal Board noted that GlaxoSmithKline's sponsorship of the Diabetes HCP (£29,250) had part-funded a diabetes nurse. The Appeal Board further noted that the Diabetes HCP was the mechanism by which the primary healthcare service company delivered its diabetes service. The relationship between the primary healthcare service company and GlaxoSmithKline was an evolving relationship. GlaxoSmithKline provided the primary healthcare service company with, *inter alia*, education, training and business planning. The two organisations worked together on, *inter alia*, project management, data analysis and communications.

The Appeal Board considered that the Diabetes HCP had merit. However the way it had been described in the voicemail and the manner in which Avandamet had been referred to in the contract was evidence that the provision of funding had been linked to the product. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was thus unsuccessful.

Although noting its ruling above the Appeal Board nonetheless did not consider that taking all the circumstances into account that GlaxoSmithKline had failed to maintain high standards. No breach of the Code was ruled. The appeal on this point was successful.

An anonymous employee of GlaxoSmithKline UK Ltd complained about the arrangements for the Diabetes Healthcare Partnership (HCP) which existed between GlaxoSmithKline and the primary healthcare service company. The primary healthcare service company delivered a range of services to general practice under the contractual opportunities offered by practice based commissioning (PBC).

COMPLAINT

The complainant stated that (s)he was a Diabetes First Associate (DFA), a non-promotional representative and former nurse, with GlaxoSmithKline. The complainant wanted anonymity as the company was currently being restructured and (s)he did not want this to potentially impact the chance of future employment.

The complainant referred to the following voicemail:

> 'Hi, this is … with a message to UK Pharma. As you know I have been looking at ways to improve how effectively we listen to our external customers, particularly in light of our "Temperature Check" scores on this particular area. In some of the feedback from our customers, particularly practice based commissioning groups, is they want a transparent business-to-business relationship with GlaxoSmithKline, so that they are clear when they work with us of the benefit to GlaxoSmithKline, to the NHS, and to patients. So with this in mind we have been working on a new proposition, "The GSK Healthcare partnership." And we have now reached an important milestone where the first partnership contract has been signed with [a primary healthcare service company], a Practice Based Commissioning Group based in [a local area]. This collaboration with GSK and [the primary healthcare service company] involves the delivery of a bespoke diabetes care package, "The Diabetes Intermediate Service". This innovative service created with the assistance of GSK aims to reduce the number of secondary care referrals by the deployment of a consultant lead [sic] team. GSK's expertise has been central to the development of this service, in addition GSK has contributed to the cost of running of the service, while [the primary healthcare service company] has agreed to select Avandamet as first medicine in it's [sic] class on it's [sic] diabetes protocol for appropriate patients. This is a contractual arrangement between two commercial organisations. Together we have agreed specific roles, responsibilities, and deliverables. All aspects of the collaboration and on-going customer interaction fit with appropriate ethical guidelines. So this implementation of this first "GSK Healthcare Partnership" is a major achievement and a significant step forward in establishing a more mature and potentially a more effective business relationship between GSK and the NHS. Where tangible benefits to all parties are clearly defined from the outset and are consistent with our "Sharing the Vision" philosophy. Many of our customers are excited and motivated to explore similar partnerships and to this end at least 40 projects across a range of therapy areas are under consideration. So at this point I'd like to take the opportunity to congratulate our colleagues who have worked tenaciously to get this first partnership up and running. In particular, [four named persons] and [the strategic partnerships manager] from Customer Environment Market Success with its implementation. I'll be in touch again to communicate outputs and further developments in due course. Bye for now.'

The complainant had asked his/her manager about the voicemail and been told everything was completely signed-off, but it did not seem to fit within the spirit of the Code. The voicemail was sent out by a vice president of customer environment marketing in September 2007, who managed the integrated healthcare managers and did unusual projects with the NHS.

Was it within the Code to have this business-to-business relationship as described? It just seemed like a clever way to pay for a service and generate more prescriptions as a result. The complainant had been told that everything (s)he did was a service to medicine where there was no influence on what a customer prescribed. In this partnership, it seemed

that the company had called it a business relationship and only provided the service with the primary healthcare service company's agreement to put Avandamet in its protocol over competitors. The complainant's manager said this was okay because it was only a protocol and the GP could prescribe whatever they wanted. It did not seem to pass the newspaper test – the complainant queried whether (s)he would want to read about this in the paper.

The complainant encouraged the Authority to request information on these healthcare partnerships and investigate whether they were in keeping with the relevant and specific sections of the Code, but more importantly in keeping with spirit of the Code.

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

RESPONSE

GlaxoSmithKline noted that the Ministerial Industry Strategy Group (MISG), a joint industry and Department of Health (DoH) high-level group, brought together government and pharmaceutical industry representatives as part of the follow-up to the implementation of the Pharmaceutical Industry Competitiveness Task Force (PICTF) recommendations. MISG was set up following a conclusion in the March 2001 PICTF Report that a new high-level group was required to take the government/industry relationship forward at a strategic level. MISG was co-chaired by a minister of health and a senior industry executive and included governmental, industry and ABPI representation, including the Director General of the ABPI. The MISG had developed the following agreed vision of partnership working:

'The industry can bring more than just medicines to the NHS and the patients it serves in the form of skills and expertise to support top quality and productive services. For this to happen, however, a more "mature" relationship has to be developed between the industry and the NHS founded on mutual respect and trust and demonstrated through successful working on areas of mutual interest and benefit.'

Further guidance had subsequently been published (18 January 2008) by the DoH supporting joint working between the NHS and the pharmaceutical industry.

'Joint working between the pharmaceutical industry and the NHS must be for the benefit of patients or the NHS and preserve patient care. Any joint working between the NHS and the pharmaceutical industry should be conducted in an open and transparent manner. All such activities, if properly managed, should be of mutual benefit, with the principal beneficiary being the patient. The length of the arrangement, the potential implications for patients and the NHS, together with the perceived benefits for all parties, should be clearly outlined before entering into any joint working.

For the purpose of this guidance, joint working is defined as follows:

Situations where, for the benefit of patients, organisations pool skills, experience and/or resources for the joint development and implementation of patient centred projects and share a commitment to successful delivery. Joint working agreements and management arrangements are conducted in an open and transparent manner. Joint working differs from sponsorship, where pharmaceutical companies simply provide funds for a specific event or work programme.'

GlaxoSmithKline explained that the primary healthcare service company was a limited company which delivered a wide range of services to practices under the contractual opportunities offered by PBC. GlaxoSmithKline referred to a description of the primary healthcare service company as it appeared on that company's website.

PBC groups, provider arms of PBC groups, such as the primary healthcare service company, primary care trusts (PCTs), foundation trusts and private providers operated as businesses. They were often legal entities with formalised corporate structures in place. These groups had financial responsibility for the management of patient care in a locality. Within this, their remit was to purchase and deliver high quality care, including services and medicines. Their roles and responsibilities (as with many health providers both within and outside the NHS) included the use of protocols for patient management and for the rational use of medicines. These were routinely employed to deliver a consistent standard of care to consider the needs of the population. These needs were however different to those of the individual prescribers and health professionals who specifically considered the needs of individual patients within the protocol and formulary framework.

The relationship between GlaxoSmithKline and the primary healthcare service company was at a business-to-business level with those directors who managed the company. In this relationship the roles and responsibilities were clearly defined according to an agreed contract. GlaxoSmithKline's relationship was not with individual prescribers or practices, therefore a clear separation between the business related activities of the organisation and the prescribing activities of individual health professionals was maintained. Given this explicit and transparent separation, GlaxoSmithKline believed that this relationship was compatible with the stated aims of the MISG and the DoH guidance as referred to above. Additionally GlaxoSmithKline rejected any allegation of a breach of the Code given the contractual and ethical safeguards as detailed below.

GlaxoSmithKline explained that the Diabetes Intermediate Service run by the primary healthcare service company was commissioned by a PCT during 2006. In 2007, the primary healthcare service company reviewed and improved its existing consultant-based diabetes service using dedicated staff (the diabetic intermediate team). The aim of the service was to optimally manage all aspects of diabetes in primary care, only referring patients into secondary care when absolutely necessary. The prevalence of type 2 diabetes within the area was 4%, giving a population of approximately 1,320 diabetics. It was estimated that 60-70 patients would be seen each week by the diabetic intermediate team to improve patient control and management within the the primary healthcare service company primary care environment. The projected annual cost of the service was estimated to be £117,000.

As part of the project, the primary healthcare service company reviewed and updated the diabetic database. Patients were identified and read coded appropriately. The primary healthcare service company developed a care pathway, supported by management protocols. All staff involved received training in the use and implementation of this management plan. Routine diabetic care was carried out at practice level by practice nurses which was planned to continue but, in addition, a regular diabetes educational programme was established. Practice nurses were able to access mentoring by the more experienced specialist nurses formally and informally, attending clinics as required. GlaxoSmithKline did not have any involvement in the educational programme or training.

When a referral to the specialist intermediate team was necessary, this was carried out by populating a template on the primary healthcare service company's clinical system, which was then emailed to a dedicated inbox. The Diabetes Intermediate Service lead nurse triaged these referrals and allocated the patient to the most appropriate clinician in the intermediate team. Each referral type had a dedicated read code which would help with auditing. The service was provided over three days per week.

The diabetic team for referral consisted of:

- Consultant diabetologist,
- Diabetic Specialist Nurse (DSN) specialising in poor control, insulin starts and titration,
- DSN specialising in oral management optimisation,
- GP with special interest
- Senior practice nurse, health care assistant and
- Project coordinator.

The consultant would mainly manage patients with complications or whose diabetes was extremely difficult to control. The consultant would also support the whole team as required.

GlaxoSmithKline noted that the wording of the contract underscored the principles by which the company worked with these groups. The requirements of this contract specifically excluded practices or other healthcare providers who did not have a formal protocol process or PBC type capability. The contract required a distinct separation of the contract partners and prescribers, thus ensuring clinical prescribing freedom when necessary. These principles would not allow GlaxoSmithKline to enter into such a relationship where these criteria could not be fulfilled. As such only a small selection of PBC type providers would be suitable for such a relationship. By limiting the nature of the groups available for such a relationship and ensuring these safeguards were in place, GlaxoSmithKline was able to work specifically in this way within the parameters of the MISG and DoH guidance.

The Diabetes Healthcare Partnership (HCP) aimed to bring clear and transparent benefits to patients, the NHS and GlaxoSmithKline by combining industry and NHS resources and expertise in the management of diabetes. The partnership was aligned with and responded to the government's agenda to treat more patients in the primary care environment and to achieve a sustainable improvement to the total healthcare economy.

Through the Diabetes HCP GlaxoSmithKline and the primary healthcare service company had formed a business-to-business relationship bound by a legal contract. The relationship enabled the primary healthcare service company to better manage its Diabetes Intermediate Service and thus the care of its diabetic patients according to its pre-existing protocol. The relationship was held between GlaxoSmithKline and two authorised representatives of the primary healthcare service company, the Managing Director and the Business Manager. GlaxoSmithKline firmly rejected any suggestion that this relationship was inappropriate or in breach of Clause 18.1.

Clause 18.1 referred to gifts, benefits in kind or pecuniary advantage given in relation to inducements to prescribe, supply, administer, recommend, buy or sell any medicine. As was stated above and included in the contract, the primary healthcare service company had selected Avandamet as part of its protocol for diabetes management. This had occurred in advance of the contract with GlaxoSmithKline. Additionally, GlaxoSmithKline and the primary healthcare service company, through the contract, confirmed that there were several safeguards in place to ensure that there could be no possibility of an inducement.

Specifically, the contract stipulated that all prescribers were able to deviate from the protocol to prescribe alternative therapies where clinically appropriate. The contract stipulated that a formulary committee, with distinct separation from the prescribers in the group, was required and affirmed that any medicine selected would be based upon the evidence, cost effectiveness and the

licensed indications. Given that these safeguards were in place and that the decision to place Avandamet on the protocol predated the relationship with GlaxoSmithKline the company firmly rejected any suggestion that this relationship constituted an inducement and a breach of Clause 18.1. Additionally, as this relationship specifically facilitated the primary healthcare service company's own diabetes service which benefited patients, GlaxoSmithKline refuted any breach of Clause 18.4.

GlaxoSmithKline's contract with the primary healthcare service company supported the running of the Diabetes Intermediate Service through funding to a maximum amount of £29,250. GlaxoSmithKline had no other involvement in the selection of the medicine for the management protocol and was not involved in any way in the management or provision of the service.

To ensure appropriately high ethical standards were maintained within this business-to-business relationship, the following detailed principles were stringently followed:

- The relationship was between GlaxoSmithKline and the primary healthcare service company and not with the individual prescribers forming part of the primary healthcare service company.
- The protocol was established by the primary healthcare service company, independently of discussions with GlaxoSmithKline and prior to discussions regarding the Diabetes HCP. GlaxoSmithKline understood that the protocol was in place prior to February 2007.
- The provision of funding for the Diabetes Intermediate Service was not conditional on the prescription of any product (clause 3.1 of the contract).
- The protocol was the responsibility of the primary healthcare service company. Responsibility for the management of individual patients, including prescription of medicines and implementation of appropriate treatment at all times remained with the GPs (clause 2.4 of the contract).
- The implementation of protocols was the sole responsibility of the primary healthcare service company. GlaxoSmithKline was not involved in protocol implementation.
- The creation of such protocols was intended to have an impact on the general patient population rather than determining prescription choice at an individual patient level. In this way the primary healthcare service company took a strategic view of the medicines and services provided to the patient population but left the final decision for the individual patient to the health professionals (clause 2.4 of the contract).
- GPs retained clinical freedom for any individual patients (clause 2.8 of the contract).
- The contract stipulated that where the primary healthcare service company decided to put a product on its protocol, this indicated to GP practices in its group that it considered the use of that product to be preferable to other products from the same therapy class having reviewed the product's licence, evidence and cost effectiveness (clause 2.2 of the contract).
- The primary healthcare service company confirmed that putting Avandamet on its protocol formed part of its business-related activities. The business-related activities were in relation to the general services and medicines provided to the population of patients forming part of the primary healthcare service company (clause 2.3 of the contract).
- The primary healthcare service company confirmed that there was an effective procedure in place to ensure that decisions related to the creation and content of its protocol were only made by personnel who had been duly authorised to make protocol-related decisions. In particular, the procedure required the following:
- At least half of the personnel who made the protocol decisions were non-prescribers.
- Prescribers who were authorised to make protocol-related decisions did not form the majority of prescribers within the primary healthcare service company (clause 2.3 of the contract).
- the primary healthcare service company confirmed that GlaxoSmithKline's medicines, including any product selected as first choice medicine, would only be used where appropriate and in accordance with local guidelines (clause 2.7 of the contract).

For the reasons stated above, GlaxoSmithKline was extremely confident that the Diabetes HCP did not form an inducement, provided a valuable service to medicine that was compatible with the stated aims of the NHS, MISG and the DoH guidance and benefited patient care. Thus it firmly denied any breach of Clauses 18.1, 18.4, 9.1 or 2.

GlaxoSmithKline further explained that having been made aware that the primary healthcare service company was implementing a diabetes service, discussions began to assess whether mutual benefits could be brought to all parties. The Diabetes HCP was formalised through a contract between GlaxoSmithKline and the primary healthcare service company. GlaxoSmithKline did not review or have input into the protocols of the primary healthcare service company and it neither had a copy, nor ever had one, of its diabetes protocols.

To ensure the Diabetes HCP delivered clear benefits to patients, the NHS and GlaxoSmithKline a monitoring document was created to set out responsibilities, timings, analysis required and the proposed measurements. The anticipated benefits to all parties were:

- Patients would benefit from improved and standardised continuity of care and thus improved clinical outcomes and an enhanced ability to benefit from better planned and delivered future healthcare.
- The primary healthcare service company would

benefit through improved healthcare planning, service delivery and patient care, by enhancing and standardising the primary healthcare service company's approach to chronic diseases and thus its ability to engage successfully in PBC.
- PBC would create the potential for appropriate use of medicines, including those of GlaxoSmithKline, in suitable patients and that would give GlaxoSmithKline the opportunity to develop a strong and positive working relationship with the primary healthcare service company with a view to further collaborations in the future.

The specific measurements that GlaxoSmithKline set out initially to monitor the project were:

- Patient clinical outcomes
- Referrals to diabetes clinic in secondary care
- Efficiency of service
- Patient feedback
- Adherence of practices to treatment protocol
- Secondary care emergency admissions
- Patient use of other healthcare resources

The Diabetes HCP was initially discussed with the primary healthcare service company in February 2007 by the strategic partnerships manager within GlaxoSmithKline who was based in head office and was responsible for looking at how the relationship between the pharmaceutical industry and the NHS could achieve common goals and how it should change to reflect the changes in the environment in line with the DoH's guidance and the ABPI's position on joint working. The discussions that took place between the strategic partnerships manager and the primary healthcare service company were not product specific and were focused on identifying a potential project to deliver improved benefits to patients in an open and transparent way.

The strategic partnerships manager was not a product-related role, it was not promotional or remunerated based on sales and reported into the Integrated Healthcare Department within the UK business. The first meeting in February was held between GlaxoSmithKline and the primary healthcare service company where the Diabetes HCP was discussed. GlaxoSmithKline understood that the primary healthcare service company had the protocol in place prior to February 2007 and Avandamet was already selected independently of GlaxoSmithKline as first choice medicine in its therapy class for the appropriate patient group.

Between February and September 2007 GlaxoSmithKline and the primary healthcare service company discussed the Diabetes HCP to develop the contract that would facilitate the implementation of the primary healthcare service company's Intermediate Service. GlaxoSmithKline agreed to support the enhanced diabetes intermediate service by co-funding the service to a maximum value of £29,250 for a six month period.

GlaxoSmithKline and the primary healthcare service company had joined together in partnership through the Diabetes HCP as there was a common agenda of improving the services offered to diabetes patients. This had the aim of improving patient outcomes through facilitating the primary healthcare service company's service provision and thus the appropriate use of medicines in this patient population to achieve diabetes control in a primary care setting. This should also reduce secondary care referrals. As such, all parties (patients, the primary healthcare service company and GlaxoSmithKline) stood to benefit from delivering better diabetes control in a transparent relationship that implemented a diabetes management protocol while protecting prescriber clinical freedom.

The Diabetes HCP was a contractual relationship where the roles, responsibilities and benefits were all clearly defined in an open and transparent way. The contract formalised the relationship between the primary healthcare service company and GlaxoSmithKline. The contract enabled both parties to understand the benefits to each and enabled GlaxoSmithKline to understand how its medicines were used within the primary healthcare service company. However, as stated in the contract, GPs would at all times retain clinical freedom to prescribe the most appropriate medicine for their patients. As previously stated, the protocol was defined by the primary healthcare service company independently of GlaxoSmithKline and prior to any conversations regarding the Diabetes HCP. The primary healthcare service company was responsible for the development of its own protocol, which GlaxoSmithKline understood took place in 2006. GlaxoSmithKline was not involved in the development of this protocol. GlaxoSmithKline understood that the protocol was developed by the primary healthcare service company in conjunction with the secondary care diabetes consultant from a hospital, a diabetes specialist nurse and a medicines management pharmacist in 2006.

GlaxoSmithKline was disappointed to receive this complaint as it believed it had worked to the highest ethical standards. It also had a procedure to enable employees to escalate their concerns internally and again, it was disappointed that this had not happened. The company had recently been significantly restructured which unfortunately resulted in the displacement of the DFA team; the complaint might be from an employee who had been affected by the restructure.

GlaxoSmithKline believed the Diabetes HCP was an ethical way of working. The partnership reflected the principles set out in the recent communication from the ABPI and the DoH 'Moving Beyond Sponsorship'. In addition, GlaxoSmithKline noted that a toolkit had been launched by the ABPI and the DoH on 5 March 2008 supporting joint working. GlaxoSmithKline believed that the Diabetes HCP was in line with the remit of this document to explore ways in which:

- The pharmaceutical industry could work with and

within the NHS, such that government objectives to improve the quality and value of NHS services, and the overall productivity of the system, could be achieved.
- Industry activities supported the operation of new NHS structures and processes, and industry skills were deployed appropriately.
- Innovative, clinical and cost effective solutions (both products and services) to address patients' health needs were embraced by the NHS and suitably rewarded and hence the UK's position as the slowest adopter of modern medicines was addressed.
- A more 'mature' relationship could be developed between the industry and the NHS (at both national and local levels) through joint working on areas of mutual interest and benefit.

For these reasons GlaxoSmithKline believed that the arrangements in this relationship were completely compatible with the ABPI's own principles, and it had strived to ensure that these and the principles of patient benefit were upheld.

Finally GlaxoSmithKline reiterated that it believed that it had not breached the Code with respect to Clauses 2, 9.1, 18.1 or 18.4 as alleged.

FURTHER RESPONSE

In response to a request from the Panel for further information GlaxoSmithKline emphasised the fact that the fundamental relationship established between GlaxoSmithKline and the primary healthcare service company was different in nature to that which it would have with prescribers. As set out above the Diabetes HCP aimed to bring clear and transparent benefits to patients, the NHS and GlaxoSmithKline by combining industry and NHS resources and expertise in the management of diabetes. The partnership was aligned with and responded to the government's agenda to treat more patients in the primary care environment and to achieve a sustainable improvement to the total healthcare economy.

Through the Diabetes HCP GlaxoSmithKline and the primary healthcare service company had formed a business-to-business relationship bound by a legal contract. The relationship enabled the primary healthcare service company to better manage its Diabetes Intermediate Service and thus the care of its diabetic patients according to its pre-existing protocol. The relationship was held between GlaxoSmithKline and two authorised representatives of the primary healthcare service company, the Managing Director and the Business Manager. GlaxoSmithKline firmly rejected any suggestion that this relationship was inappropriate or in breach of Clause 18.1.

It was important to emphasise that the wording of the contract underscored the principles of GlaxoSmithKline's ways of working with these groups. The contract specifically excluded practices or other healthcare providers which did not have a formal protocol process or PBC type capability. The contract required a distinct separation of the contract partners and prescribers, thus ensuring clinical prescribing freedom when necessary. These principles would not allow GlaxoSmithKline to enter into such a relationship where these criteria could not be fulfilled. As such only a small selection of PBC type providers would be suitable for such a relationship. By limiting the nature of the groups available for such a relationship and ensuring these safeguards were in place, GlaxoSmithKline was able to work specifically in this way within the parameters of the MISG and DoH guidance.

The primary healthcare service company and GlaxoSmithKline had successfully worked together for a number of years. In 2005, an integrated healthcare manager from GlaxoSmithKline became aware through the course of routine business that the primary healthcare service company was evolving and growing into a key customer group which was already engaged in PBC. A key focus of the group was to develop and improve the services provided to patients in its local area while expanding the remit of the practices in its group. GlaxoSmithKline understood that the primary healthcare service company had established protocols across numerous disease areas, including diabetes, as part of its standard ways of working. the primary healthcare service company in its discussions with GlaxoSmithKline recognised that there were likely to be benefits of working in partnership with the pharmaceutical industry as supported by the DoH, MISG and the ABPI.

In September 2005, the primary healthcare service company was keen to provide an improved Intermediate Diabetes Service with the vision that once this concept was able to prove its value to patient care pathways, it would be commissioned by a PCT. A GlaxoSmithKline integrated healthcare manager worked with the primary healthcare service company to help support and develop the first diabetes pilot project. The key members of the primary healthcare service company that were involved in the development and set up of this project were the Managing Director and the Business Manager. To support the primary healthcare service company's objectives, GlaxoSmithKline provided financial support to the pilot project commencing 1 November 2006 together with facilitation, education and training via a DFA to enable the primary healthcare service company to provide the Intermediate Diabetes Service. This support was entirely non promotional and did not relate to any products, but was solely related to diabetes.

The diabetes pilot project in 2006 was set up between GlaxoSmithKline and the primary healthcare service company to support the primary healthcare service company achieving the following goals:

- Meet its quality outcome framework (QOF)

targets and to provide improved diabetic care to patients.
- Provide a comprehensive diabetes service without referral to secondary care unless absolutely necessary
- Avoid use of a secondary care service
- Allow the practice and the PCT to make savings by reducing secondary care referrals and move routine management to primary care
- Allow proposed diabetes services to be recognised by the PCT as a locally enhanced service thus allowing other practices to refer in and create a revenue stream for the primary healthcare service company
- Allow practices to maximise GMS points within the clinical domain of diabetes.

As referred to above, GlaxoSmithKline supported the primary healthcare service company during the pilot phase of the Diabetes Intermediate Service. The support in this pilot phase involved financial support (£12,000) towards the provision of the primary healthcare service company employing a DSN, independently of GlaxoSmithKline, for two days a week over a 6 month period from 1 November 2006. GlaxoSmithKline had no input to the activities or objectives of the DSN. The DSN was to deliver a comprehensive diabetes service across the practices within the the primary healthcare service company group. Clinics were run by the DSN to review the appropriate patients and an HbA1c check was performed during the consultation. Lifestyle and dietary advice was also given as required. A DFA provided additional education and training to the group where necessary.

The support provided to the primary healthcare service company during the pilot phase in 2006 was non promotional. The project was initiated as a pilot project, as it was one of the first projects GlaxoSmithKline had undertaken with a customer to help achieve the goals of PBC.

GlaxoSmithKline was not involved in the creation or implementation of a diabetes protocol, and did not see or review the primary healthcare service company's protocol during this time.

In January 2007, while the pilot project was ongoing, GlaxoSmithKline and the primary healthcare service company discussed the potential for future partnership working. Present at the meeting was the Managing Director and Business Manager of the primary healthcare service company, and the Integrated Healthcare Manager, Regional Healthcare Manager (RHM), and the Strategic Partnerships Manager of GlaxoSmithKline. The primary healthcare service company was keen to continue providing the Diabetes Intermediate Service that had, as expected, been commissioned by the PCT, and to improve the service where possible. A meeting was scheduled for February 2007 to discuss how GlaxoSmithKline and the primary healthcare service company could work together in partnership on a different basis regarding the Diabetes Intermediate Service. The meeting in February 2007 was the first meeting where the primary healthcare service company and GlaxoSmithKline discussed and developed the Diabetes HCP. At this meeting the primary healthcare service company informed GlaxoSmithKline that it had a diabetes patient management protocol already in place, and this was in place as part of its normal patient management plans. The primary healthcare service company's protocol had existed before any conversations with GlaxoSmithKline regarding diabetes projects ie prior to September 2005. GlaxoSmithKline did not review or have input into the primary healthcare service company's protocols; it had never seen a copy of the protocols, until specifically requested to obtain a copy by the Authority. GlaxoSmithKline understood from the primary healthcare service company that Avandamet was named on its protocol as first choice medicine within class where appropriate. On receipt of a copy of the primary healthcare service company's protocol on 18 March 2008, GlaxoSmithKline found out for the first time that Avandamet was not specifically named on the primary healthcare service company's protocol. The protocol set out the use of a combination glitazone/metformin at the appropriate place, of which Avandamet would be one option.

As stated above, PBC groups, provider arms of PBC groups, such as the primary healthcare service company, PCTs, foundation trusts and private providers operated as businesses. They were often legal entities with formalised corporate structures in place. These groups had financial responsibility for the management of patient care in a locality. Within this, their remit was to purchase and deliver high quality care, including services and medicines to a patient population. Their roles and responsibilities (as with many health providers both within and outside the NHS) included the use of protocols for patient management and for the rational use of medicines. These were routinely employed to deliver a consistent standard of healthcare to consider the needs of the population. These needs were however different to those of the individual prescribers and health professionals who were specifically considering the needs of individual patients within the protocol and formulary framework.

The relationship between GlaxoSmithKline and the primary healthcare service company through the Diabetes HCP was at a business-to-business level with the directors who managed the company. In this relationship the roles and responsibilities were clearly defined according to an agreed contract. GlaxoSmithKline's relationship was not with individual prescribers or practices, therefore a clear separation between the business-related activities of the organisation and the prescribing activities of individual health professionals was maintained. Given this explicit and transparent separation, GlaxoSmithKline believed that this relationship was compatible with the stated aims of the MISG and the DoH guidance regarding joint working.

GlaxoSmithKline did not know about the formal protocol review that took place in March 2007 until it clarified the chronology of events with the primary healthcare service company to enable the company to respond to this complaint. The primary healthcare service company confirmed that there was no amendment to the positioning of Avandamet on its protocol during the review that took place in March 2007. GlaxoSmithKline did not have any involvement in the creation or implementation of a diabetes protocol during this time.

GlaxoSmithKline provided a document which set out the chronology of its relationship with the primary healthcare service company, what was agreed when and how the protocol changed over time. A copy of the diabetes protocol was also provided.

As GlaxoSmithKline had not previously seen the protocol, nor had input into it, it had never made any contemporaneous comments upon it. Having now, as part of the Authority's investigation into this case, seen a copy of the protocol it noted that the position of glitazones and their fixed dose combination with metformin, was consistent with NICE guidance and generally accepted therapeutic principles, based on evidence based medicine.

GlaxoSmithKline understood from the primary healthcare service company that its protocol had been in place for a number of years. As described above, the protocol was established before GlaxoSmithKline's involvement in the pilot Diabetes Intermediate Service in 2006 and the Diabetes HCP in 2007. The primary healthcare service company reviewed its protocol in March 2007 without any involvement from GlaxoSmithKline and to GlaxoSmithKline's knowledge there was no amendment to the positioning of Avandamet on the primary healthcare service company's protocol during 2006 and 2007.

The protocol review that took place by the primary healthcare service company in March 2007 was a standard review, independent of any relationship with GlaxoSmithKline.

GlaxoSmithKline understood, until receipt of the protocol on 18 March 2008, that Avandamet was specifically named on the protocol. However, the primary healthcare service company had subsequently clarified that the terminology included on its protocol at this specific stage of treatment was in fact the use of a combination drug; Avandamet would fall into this classification. Avandamet was specifically named in the contract as GlaxoSmithKline understood that the primary healthcare service company's established protocol specifically named Avandamet in the appropriate place. This had proven not to be the case, however Avandamet would fit into the combination of metformin and a glitazone as named on the protocol.

GlaxoSmithKline submitted that its sponsorship was not dependent upon the primary healthcare service company's decision to place Avandamet on the protocol. The primary healthcare service company's protocol had already been finalised prior to any conversations regarding the diabetes HCP. The protocol was the primary healthcare service company's property and responsibility and was able to be reviewed at any time by the primary healthcare service company as deemed necessary. A copy of the protocol that was signed off in March 2007 was provided. The primary healthcare service company confirmed that this was the latest protocol approved.

The responsibility for the implementation and communication of the protocol was the primary healthcare service company's. This was referred to in the Diabetes HCP contract between the primary healthcare service company and GlaxoSmithKline, clause 2.4 as follows:

- Responsibility for the management of individual patients, including prescription of medicines and implementation of appropriate treatment shall at all times remain with the GPs at the practices comprised in the Group, the primary healthcare service company.

GlaxoSmithKline had had no involvement in the creation, training, communication or implementation of the protocol within the the primary healthcare service company group.

A key principle behind the Diabetes HCP was that the protocol was owned and defined by the primary healthcare service company. The communication and implementation of a protocol was part of the normal business activities of the primary healthcare service company in the same way as a hospital would manage a formulary.

GlaxoSmithKline explained that the request to measure the adherence of practices to the treatment protocol was made by the primary healthcare service company to understand how protocols and treatment pathways were being followed within the group. GlaxoSmithKline understood that this was part of its standard audit procedures. The primary healthcare service company was not required to assess the number of Avandamet prescriptions or for this information to be shared with GlaxoSmithKline. No payment or activity was contingent on the extent of prescription of any medicine

GlaxoSmithKline explained that the Diabetes Intermediate Service and the Diabetes HPC were not the same. The Diabetes Intermediate Service was the overall service run by the primary healthcare service company. The Diabetes HPC described the contractual relationship between GlaxoSmithKline and The primary healthcare service company. As part of the Diabetes HCP, GlaxoSmithKline agreed to financially support the primary healthcare service company to the amount of £29,250 to support its Diabetes Intermediate Service.

PANEL RULING

The Panel noted GlaxoSmithKline's comments about joint working between the industry and the NHS. Such activities were not prohibited by the Code providing all the arrangements complied with it, in particular Clauses 18.1 and 18.4.

The Panel noted GlaxoSmithKline's submission regarding the arrangements to ensure compliance with the Code. The Panel considered that in general arrangements that increased the potential pool of treated patients were likely to be acceptable. Arrangements that increased the prescribing of one specific product were likely to be unacceptable. The Panel accepted that a service that improved clinical outcomes, standardized continuity of care and reduced the number of secondary care referrals, all aims of the service at issue, would enhance patient care and benefit the NHS.

The Panel noted that the complaint had been prompted by a voicemail message sent from within GlaxoSmithKline. The voicemail referred to the company's business relationship with the primary healthcare service company whereby GlaxoSmithKline had agreed to help The primary healthcare service company achieve its objective of reducing the number of diabetic patients referred to secondary care by deploying a specialist team, led by a consultant diabetologist, in the primary care setting. It was stated in the voicemail that '… GlaxoSmithKline has contributed to the cost of running the service, while [the primary healthcare service company] has agreed to select Avandamet as first medicine in its class on its diabetes protocol for appropriate patients. This is a contractual agreement between two commercial organisations'. The complainant was concerned that GlaxoSmithKline's sponsorship of the service was dependent upon the inclusion of Avandamet on the protocol.

The contract that existed between GlaxoSmithKline and The primary healthcare service company was dated 3 September 2007 and headed 'Enhanced PBC Service – Diabetes Pilot Project'. It was stated in an appendix to the contract that in 2006 GlaxoSmithKline had helped create a new diabetes service by providing some of the funding and identifying a suitable consultant diabetologist and diabetic specialist nurse. The primary healthcare service company now wanted to maintain and improve this service the aim of which would be to manage optimally all aspects of diabetes in primary care, only referring patients into secondary care when absolutely necessary. Point 9 of the appendix stated 'The proposal is for GSK to help [the primary healthcare service company] with the creation of this enhanced Diabetes Intermediate Service by co-funding it'. It was stated that staff forming part of the specialist team would be employees or contractors of the primary healthcare service company; none of the staff would be employees of GlaxoSmithKline.

According to its website the primary healthcare service company was a private limited company and a provider of primary healthcare services.

The Panel noted guidance issued by the DoH in January 2008 on joint working between the NHS and the pharmaceutical industry defined joint working as:

'Situations where, for the benefit of patients, organisations pool skills, experience and/or resources for the joint development and implementation of patient centred projects and share a commitment to successful delivery. Joint working agreements and management arrangements are conducted in an open and transparent manner. Joint working differs from sponsorship, where pharmaceutical companies simply provide funds for a specific event or work programme…'.

The Panel noted that GlaxoSmithKline had referred to this definition albeit one that was published some four months after the contract with the primary healthcare service company had been signed. The Panel noted that GlaxoSmithKline had helped the primary healthcare service company to develop its first diabetes pilot project by providing financial support, facilitation and training via a Diabetes First Associate. In the Panel's view, however, the relationship between the primary healthcare service company and GlaxoSmithKline in the service now at issue did not appear to be one whereby the two organisations had pooled skills, experience and/or resources; it appeared that GlaxoSmithKline had acted simply to co-fund, or sponsor, the primary healthcare service company's diabetes service. In that regard the Panel noted GlaxoSmithKline's submission that its contract with the primary healthcare service company supported the running of the Diabetes Intermediate Service through funding to a maximum of £29,250 and that the company had no other involvement in the selection of the medicine for the management protocol and was not involved in any way in the management or provision of the service.

The Panel noted that GlaxoSmithKline had submitted that its relationship with the primary healthcare service company was at a business-to-business level and not with individual prescribers. GlaxoSmithKline described this as an explicit and transparent separation. In the Panel's view, however, GlaxoSmithKline was in effect working with a third party which it knew would influence the prescribing activities of individual doctors.

The Panel noted that the contract between the primary healthcare service company and GlaxoSmithKline set out the roles and responsibilities of each party. Paragraph 3.1 of the contract stated 'This project is sponsored by GSK. As a consequence of [the primary healthcare service company's] decision to place GSK's product on [the protocol] in accordance with paragraph 2.6 above,

GSK has agreed to provide funding for this service: provisions of such funding is not conditional on the prescription of that product'. Other paragraphs defining GlaxoSmithKline's involvement related to the payment of the agreed funding, the use of any data provided to the company by the primary healthcare service company and the fact that GlaxoSmithKline would comply with best practice to include codes of practice, relevant laws and guidelines on confidentiality and data protection.

The contract between the primary healthcare service company and GlaxoSmithKline stated, at paragraph 2.6 'Subject to paragraphs 2.7 and 2.8 below, [the primary healthcare service company] has agreed to select AVANDAMET ("the product") as a first choice medicine in its therapy class for the appropriate patient group on the Protocol ("First Choice Medicine"). Such selection by [the primary healthcare service company] shall include all considerations as per paragraph 2.2 above'. Paragraph 2.2 stated that the choice and use of medicines within a protocol was based upon the medicine's marketing authorization, an up-to-date review of the available evidence and its cost effectiveness. The protocol was for use by all the primary healthcare service company practices. It was, presumably, paragraph 2.6 which had led to the statement in the voicemail that '[the primary healthcare service company] has agreed to select Avandamet as first medicine in its class on its diabetes protocol …'.

Paragraphs 2.7 and 2.8 of the contract made it clear that GlaxoSmithKline's medicines, including Avandamet, would only be used where appropriate and in accordance with local guidelines. Further, GPs in the group would retain clinical freedom for any individual patients for whom, in the GP's opinion, use of Avandamet was inappropriate. Paragraph 2.16 stated that GlaxoSmithKline would be provided with anonymised data relating to prescribing and outpatient outcomes.

The Panel noted that in response to a request for further information GlaxoSmithKline provided a copy of the diabetes protocol dated March 2007 and due for review by March 2008, which it submitted was the first time the company had seen it. Under a heading of 'Glycaemic Control' for type 2 diabetics it was stated that step 2 treatment, for all patients with a body mass index of 25 or more, should be:

'Add Glitazone to metformin
- 1st line: pioglitazone
- 2nd line: rosiglitazone

Increase dose up gradually as required to maximum.

Glitazones are slow acting drug so results will not be noticeable immediately; reduction of blood glucose will happen over 4 - 6 weeks.

If there are compliance problems the combination tablets of Glitazone/metformin may be used…'

It thus appeared that the protocol and paragraphs 2.6 and 3.1 of the contract were inconsistent with one another. In the protocol rosiglitazone, the glitazone in Avandamet, was stated to be the second line glitazone and in any event the combination tablets ie Avandamet, were only to be used if there were compliance problems. Given the protocol as it existed (effective from March 2007 and due for review by March 2008) the Panel queried why the contract was signed in September 2007 containing paragraph 2.6 specifically referring to Avandamet as a first choice medicine in its therapy class. The protocol referred to products by generic name only. The contract had been signed by senior managers in both GlaxoSmithKline and the primary healthcare service company. One of GlaxoSmithKline's signatories appeared to be responsible for the voicemail to the complainant.

The Panel considered that, notwithstanding the protocol, paragraph 3.1 of the contract signed by GlaxoSmithKline in effect stated that the company's funding of the diabetes service was dependent upon the inclusion of Avandamet, as a named medicine, on the protocol. This was also the impression given in the voicemail. The Panel noted that the provision of medical and educational goods and services must not be linked to any medicine. In that regard the Panel considered that the diabetes service as described in the voicemail and in the contract was inappropriate. A breach of Clause 18.4 of the Code was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. These rulings were appealed.

With regard to whether or not the arrangements amounted to an inducement to members of the health professions or administrative staff to prescribe, supply, administer, recommend, buy or sell Avandamet, the Panel noted that there was no gift, benefit in kind or pecuniary advantage to the actual prescribers. However the prescribers, as employees of the primary healthcare service company, would be obliged to follow the protocol. As far as GlaxoSmithKline was concerned the effect of the arrangements was that a payment had been made to a private company such that Avandamet was recommended. The Panel was concerned about the arrangements but after much consideration decided that, on balance, the circumstances of providing an inducement to the primary healthcare service company did not amount to a breach of Clause 18.1 of the Code and ruled accordingly.

The Panel was concerned that the diabetes service was seen by some in GlaxoSmithKline as being linked to the use of Avandamet as first medicine in its class. The Panel noted that, given the content of the protocol and unbeknown to GlaxoSmithKline, as operated, the diabetes service was not linked to the use of Avandamet. The Panel thus considered that on balance, taking all the circumstances into account, GlaxoSmithKline had not brought discredit upon, or reduced confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline submitted that the evolving structural changes within the NHS had given rise to a number of new customer groups for the pharmaceutical industry including PCTs, PBC groups, private providers and Foundation Trusts. These groups purchased healthcare rather than simply delivered it and they might also be businesses. Hence, as recognised by the ABPI, the DoH and these groups themselves they required a different type of relationship to traditional health practitioners with the pharmaceutical industry to effectively deliver healthcare in an efficient and ethical manner. The primary healthcare service company was an example of a new, specific customer group, ie a limited company which operated to deliver a wide range of services to practices under the contractual opportunities offered by PBC.

GlaxoSmithKline submitted that the fundamental premise of its appeal was that the diabetes care package was a corporate agreement between itself and the primary healthcare service company. The partnership was transparent, of high ethical standard and importantly was a collaboration that had patient benefit as the prime objective for both parties. The partnership between GlaxoSmithKline and the primary healthcare service company set out how the pharmaceutical industry and the NHS could work together to deliver improved patient outcomes within this new and changing environment.

GlaxoSmithKline submitted that the principles underpinning the diabetes care package were fully ethical and appropriate and were not in breach of Clauses 9.1 and 18.4 of the Code.

Background for the Diabetes HCP

GlaxoSmithKline submitted that the Diabetes HCP was established with response to four key factors:

- The emergence of new, specific customer groups within the NHS
- The requirement for a different type of working relationship between these customer groups and the pharmaceutical industry
- Guidance from the DoH and other key groups regarding joint working
- To demonstrate the value that joint working could bring to patients through improving patient outcomes and delivering better patient focused services.

Joint working between the NHS and the pharmaceutical industry

GlaxoSmithKline submitted that the Ministerial Industry Strategy Group (MISG) was a joint industry and DoH high-level group bringing together government and pharmaceutical industry representatives as part of the follow-up to the implementation of the Pharmaceutical Industry Competitiveness Task Force (PICTF) recommendations. MISG was set up following a conclusion in the March 2001 PICTF report that a new high-level group was required to take the government industry relationship forward at a strategic level. MISG was co-chaired by a minister of health and a senior industry executive and included governmental, industry and ABPI representation, including the Director General of the ABPI. Hence, the principles and objectives of the MISG were supported by the ABPI. The MISG had developed an agreed vision of partnership which stated:

'The industry can bring more than just medicines to the NHS and the patients it serves in the form of skills and expertise to support top quality and productive services. For this to happen, however, a more "mature" relationship has to be developed between the industry and the NHS founded on mutual respect and trust and demonstrated through successful working on areas of mutual interest and benefit.'

Further guidance from the DoH supporting joint working between the NHS and the pharmaceutical industry stated:

'Joint working between the pharmaceutical industry and the NHS must be for the benefit of patients or the NHS and preserve patient care. Any joint working between the NHS and the pharmaceutical industry should be conducted in an open and transparent manner. All such activities, if properly managed, should be of mutual benefit, with the principal beneficiary being the patient. The length of the arrangement, the potential implications for patients and the NHS, together with the perceived benefits for all parties, should be clearly outlined before entering into any joint working.

For the purpose of this guidance, joint working is defined as follows:

Situations where, for the benefit of patients, organisations pool skills, experience and/or resources for the joint development and implementation of patient centred projects and share a commitment to successful delivery. Joint working agreements and management arrangements are conducted in an open and transparent manner. Joint working differs from sponsorship, where pharmaceutical companies simply provide funds for a specific event or work programme.'

GlaxoSmithKline submitted that there had been considerable guidance issued recently encouraging joint working and recognising the considerable benefits, especially to patients, that joint working could bring. Examples of this guidance were:

- DoH Best Practice Guidance on Joint Working between the NHS and Pharmaceutical Industry and Other Relevant Commercial Organisations
- ABPI, Moving Beyond Sponsorship
- ABPI, Moving Beyond Sponsorship, Joint

Working Between the NHS and Pharmaceutical Industry Toolkit

Given that this was a relatively new area of working, the guidance from MISG had been important in how GlaxoSmithKline had set up this relationship, given that the Code did not explicitly address these types of arrangements, but dealt in general terms with medical and educational goods and services. GlaxoSmithKline and other member companies were willing to ensure that the revised Code made provision for appropriate working between these bodies and the industry to ensure that patient benefit remained at the centre of the relationship. A work stream had been established by the ABPI recognised that the current Code did not explicitly reflect these new principles that needed to be established in joint working between the NHS and the pharmaceutical industry. Nevertheless GlaxoSmithKline had operated within the current guidance of the Code, MISG and DoH.

The emergence of new customer groups within the NHS

GlaxoSmithKline submitted that PBC groups, provider arms of PBC groups, such as the primary healthcare service company, PCTs, Foundation Trusts and private providers operated as businesses. They were often legal entities with formalised corporate structures in place. These groups had financial responsibility for the management of patient care in a locality. Within this, their remit was to purchase and deliver high quality care, including services and medicines to a patient population. Their roles and responsibilities (as with many health providers both within and outside the NHS) included the use of protocols for patient management including the rational use of medicines. These were routinely employed to deliver a consistent standard of healthcare according to the needs of the population. These needs were however different to those of the individual prescribers and health professionals who specifically considered the needs of individual patients within the protocol and formulary framework.

Protocols and pathways played an important role in patient management. This had become increasingly so with the introduction of PBC and World Class Commissioning where health professionals formed groups and were therefore responsible for the management of patients across larger patient populations. Their approach to disease management had become more strategic and the implementation of protocols assisted in this. In addition, with the government's goal of providing more accessible healthcare within primary care, pathways and services were being reviewed.

The role of a formulary committee within a PBC group or provider arm of a PBC group was similar to that within a hospital environment. The formulary committee, with distinct separation from the prescribers in the group, was required to independently select an appropriate medicine based upon the evidence, cost effectiveness and the licensed indications. The role of a hospital formulary was to make decisions on behalf of the hospital and looked strategically at the medicines that would provide the best outcomes for patients. The pharmaceutical industry would provide a formulary committee with all the information about their medicines required to enable it to make an informed decision. This was distinct from influencing individual prescribers. In a similar way, the role of the formulary committee had transitioned into primary care through the emergence of PBC groups, provider arms and PCTs. A different type of relationship was therefore required between the pharmaceutical industry and these customer groups to reflect their changing structure and needs. The primary healthcare service company was an example of a new and specific customer group which had a common agenda with GlaxoSmithKline of improving the services and medicines provided to patients with type II diabetes.

Background to the primary healthcare service company

GlaxoSmithKline submitted that the primary healthcare service company was a limited company which delivered a wide range of services to practices under the contractual opportunities offered by PBC. GlaxoSmithKline referred to a description of the primary healthcare service company as it appeared on that company's website.

GlaxoSmithKline submitted that as the primary healthcare service company operated across a large patient population, the Diabetes HCP was established as a mechanism of delivering improved services and medicines to its diabetic patients.

The benefits of joint working between the NHS and the pharmaceutical industry

GlaxoSmithKline submitted that the principles established as part of the HCP were consistent with the points highlighted below from the Joint Working Toolkit, supported by the ABPI:

- Shared vision: Each party must have a mutually shared vision of the aims and outcomes of any arrangement that underpinned all aspects of working together.
- Equity: Recognition, backed by behaviour, that each party had the right to be at the table and their contributions valued.
- Transparency: Openness and honesty (a precondition to trust); access to and sharing of information.
- Mutual benefit: Each party should be entitled to benefit from the arrangement – ideally working to specific benefits for each party as well as the common benefits to all.
- Respect: Respect for the other parties and for their ability to add value.

The anticipated benefits to all parties were as follows:

- Patients would benefit from improved and standardised continuity of the care provided, and thus improved clinical outcomes and an enhanced ability to benefit from better planned and delivered future healthcare.
- The primary healthcare service company would benefit through improved healthcare planning, service delivery and patient care, by enhancing and standardising the primary healthcare service company's approach to chronic diseases and thus its ability to engage successfully in PBC. The primary healthcare service company would also benefit from the expertise provided by GlaxoSmithKline through resource, education and training within the diabetes disease area to assist in the implementation of its Diabetes Intermediate Service.
- PBC would create the potential for appropriate use of medicines, including GlaxoSmithKline's, in suitable patients and that this would give GlaxoSmithKline the opportunity to develop a strong and positive working relationship with the the primary healthcare service company with a view to further collaborations in the future.

As a commercial organisation, GlaxoSmithKline needed to ensure that its medicines had maximum impact on patients' lives. This meant identifying the right patient to get the right treatment to get the right outcome and was not a simple equation of influencing prescriptions as alleged in the Panel ruling. GlaxoSmithKline aimed to partner with such organisations for long term collaborations that delivered the joint benefits to all parties as outlined above. This meant establishing a long term beneficial relationship and not a short term prescription goal. This could be seen in the structure of the contract where there was no link to the number of prescriptions of GlaxoSmithKline products required for the contract to proceed.

GlaxoSmithKline submitted that it was highly ethical to work with groups such as the primary healthcare service company which had already, independently agreed its protocol. This removed the risk of inducement to prescribe at individual prescribing level and influencing the protocol positioning of medicines. This was supported by the rationale set out in clause 2.2 of the contract. the primary healthcare service company, already with a GlaxoSmithKline medicine in a position on the protocol, was seen as a suitable partner to establish the principles of joint working and benefits whilst ensuring appropriate safeguards were in place. Without those safeguards GlaxoSmithKline would not have entered into the contract.

The Diabetes HCP

The relationship between GlaxoSmithKline and the primary healthcare service company was at a business-to-business level with those directors who managed the company. In this relationship the roles and responsibilities were clearly defined according to an agreed contract. The relationship was held between GlaxoSmithKline and the Managing Director and the Business Manager of the primary healthcare service company; it was not with individual prescribers or practices, therefore a clear separation between the business related activities of the organisation and the prescriber's activities professionals was maintained.

GlaxoSmithKline noted that the wording of the contract underscored the principles of its ways of working with these groups. The requirements of the contract specifically excluded practices or other healthcare providers who did not have a formal protocol process, specifically constituted formulary committee/group or PBC type capability. The contract required a distinct separation of the contract partners and prescribers, thus ensuring clinical prescribing freedom at all times. These principles would not allow GlaxoSmithKline to enter into such a relationship where these criteria could not be fulfilled. As such only a small selection of PBC type providers would be suitable for such a relationship. By limiting the nature of the groups available for such a relationship and ensuring these safeguards were in place, GlaxoSmithKline was able to work specifically in this way within the parameters of the MISG and DoH guidance.
With reference to clause 3.1 of the contract, as a consequence of the decision to place GlaxoSmithKline's product on the protocol in accordance with clause 2.6 above, GlaxoSmithKline had agreed to fund this service; such funding was not conditional on the prescription of that product. This was explained in further detail below:

- The protocol was established by the primary healthcare service company, independently of any discussions with GlaxoSmithKline and prior to the discussions regarding the Diabetes HCP.
- Avandamet should be used as first choice medicine within its class where appropriate.
- Inclusion of a product onto a protocol should be based upon the medicine's licence, an up-to-date review of the evidence available and its cost effectiveness in the patient group in question. These principles must be adhered to in the selection of any particular medicine for inclusion in a protocol (clause 2.2 of the contract). GlaxoSmithKline noted that the positioning described was consistent with guidance from the National Institute of health and Clinical Excellence (NICE).
- Treatment decisions should be determined in accordance with licence, indication, guidelines and also by the individual prescriber.

In addition, to ensure appropriate high ethical standards were maintained within this business to business relationship, the following detailed principles were stringently followed:

- The relationship was between GlaxoSmithKline and the primary healthcare service company and

not with individual prescribers forming part of the primary healthcare service company.
- The funding of the Diabetes Intermediate Service was not conditional on the prescription of any product (clause 3.1 of the contract).
- Responsibility for the management of individual patients, including prescription of medicines and implementation of appropriate treatment at all times remained with the GPs at the practices within the primary healthcare service company (clause 2.4 of the contract).
- The creation of such protocols was intended to have an impact on the general patient population rather than determining prescription choice at an individual patient level. In this way the primary healthcare service company could take a strategic view of the medicines and services provided to the patient population which left the final decision for the individual patient to the prescriber (clause 2.4 of the contract).
- GPs within the primary healthcare service company retained clinical freedom for any individual patients (clause 2.8 of the contract).
- The primary healthcare service company confirmed that the selection of Avandamet to appear on its protocol formed part of its business related activities. The business related activities were in relation to the general services and medicines provided to the population of patients forming part of the the primary healthcare service company (clause 2.3 of the contract).
- The primary healthcare service company confirmed that there was an effective procedure in place to ensure that decisions related to the creation and content of its protocol were only made by those who had been authorised to make protocol related decisions. In particular, the procedure required that:
  - At least half of those who made the protocol decisions were non-prescribers
  - Prescribers who were authorised to make protocol related decisions did not form the majority of prescribers within the primary healthcare service company (clause 2.3 of the contract).

For the reasons stated above, GlaxoSmithKline was confident that the Diabetes HCP did not form an inducement to prescribe but provided a valuable service to medicine of mutual benefit to all parties that was compatible with the stated aims of the NHS, MISG and the DoH guidance and benefited patient care. Thus GlaxoSmithKline submitted that this agreement was neither in breach of Clauses 18.4 nor 9.1.

Response to the specific Panel comments

GlaxoSmithKline noted that in the Panel's view the relationship between the primary healthcare service company and GlaxoSmithKline in the services now as issue did not appear to be one whereby the two organisations had pooled skills, experiences and/or resources; it appeared that GlaxoSmithKline had acted simply to co-fund, or sponsor, the primary healthcare service company's diabetes service.

GlaxoSmithKline submitted that the relationship between it and the primary healthcare service company had been ongoing for several years. In September 2005, the primary healthcare service company was keen to provide an improved intermediate diabetes service with the vision that once this concept was able to prove its value to patient care pathways, the service would be commissioned by the PCT. GlaxoSmithKline through its local Integrated Healthcare Manager worked with the primary healthcare service company to help support and develop the primary healthcare service company's first diabetes pilot project.

During the pilot phase of the Diabetes Intermediate Service in 2006 GlaxoSmithKline supported the primary healthcare service company through education, training, resource and expertise. A key focus in this pilot phase was to up skill the health professionals within the primary healthcare service company to enable a high quality service to be delivered. GlaxoSmithKline provided financial support to the primary healthcare service company's pilot project together with facilitation, education and training via a GlaxoSmithKline employed Diabetes First Associate. This support was entirely non-promotional and did not relate to any products, but was solely related to the diabetes disease area. The support provided in the diabetes pilot project in 2006 was set up to achieve the following goals:

- Meet their quality and outcomes framework (QOF) targets and to provide improved diabetic care to their patients
- Provide a comprehensive diabetes service to all diabetics without referral to secondary care unless absolutely necessary
- Allow the practice and the PCT to make savings and move 'routine' management to primary care
- Allow proposed diabetes services to be recognised by the PCT as a locally enhanced service thus allowing other practices to refer in and creating a revenue stream for the primary healthcare service company

In 2007, GlaxoSmithKline entered into the Diabetes HCP with the primary healthcare service company. The relationship was of a balanced nature where both parties shared experience, skills and resource to enable the Diabetes Intermediate Service, run by the primary healthcare service company, to be implemented and hence deliver improved benefits to patients. The support provided to the primary healthcare service company had changed over the last few years as its expertise and needs had evolved. GlaxoSmithKline had considerable expertise in this disease area through significant investment in the research and development of medicines. The ability to share this expertise through collaborations with customers such as the primary healthcare service company was key in delivering improved benefits to patients.

The Diabetes HCP differed from sponsorship, where

funding was provided for a specific event or programme. While the primary healthcare service company provided the underpinning service, GlaxoSmithKline provided a mix of resource and expertise as follows to enable the Diabetes HCP to be successfully implemented.

- Education and training
  - Education and training sessions for clinical staff via the GlaxoSmithKline employed Diabetes First Associate and through support of the the primary healthcare service company monthly meeting
  - Needs assessment of training requirements for Diabetes Specialist Nurses followed by delivery of applicable training modules
  - Data and education about the appropriate use of GlaxoSmithKline's medicines
  - Provision of appropriate clinical data
  - Facilitation of knowledge and best practice sharing
  - Business support through expertise on PBC and the changing requirements within healthcare
  - Support provided by the National Pharmacy Advisor within GlaxoSmithKline to help the primary healthcare service company with its pharmacy objectives.

- Data analysis and review
  - Detailed Hospital Episode Statistics (HES) data analysis was performed in 2007 on the 2005/2006 data to identify and prioritise opportunities for potential savings and for redesign of patient care in line with the DoH agenda. HES data provided groups with a clear and concise overview of their use of hospital services
  - GlaxoSmithKline personalised and tailored the support to help optimise the business opportunities for modelling future services

- Health outcomes information and expertise
  - IT support for a group audit on the identification of high risk patients
  - During the HCP, support was provided to the the primary healthcare service company team to extract and measure clinical outcomes
  - Measurement of efficacy of service through patient and practice surveys
  - Changes to secondary care emergency admissions through bespoke HES data analysis is to be performed on completion of the project

- Financial support for the Diabetes Specialist Nurse

- Communication and skills training
  - GlaxoSmithKline provided a workshop to support communication within the primary healthcare service company and also to help communication with other stakeholders such as the PCT.

GlaxoSmithKline reiterated that it was not involved in the training and implementation of the primary healthcare service company protocol or the specific diabetes training forming part of the Diabetes Intermediate Service. However, over the last few years GlaxoSmithKline continued to provide the primary healthcare service company with the above resource and expertise to enhance its Intermediate Service, outside of the Diabetes HCP contract, via the appropriate non-promotional or promotional staff in accordance with the principles of the Code.

GlaxoSmithKline submitted that it had demonstrated that its role in the pilot phase and through the Diabetes HCP was significantly more than funding and it was integral to the success of delivering the improved service to patients. As such GlaxoSmithKline respectfully disagreed with the Panel's interpretation and ruling on this point.

GlaxoSmithKline further noted that the Panel's view was that GlaxoSmithKline was in effect working with a third party which it knew would influence the prescribing activities of individual doctors. GlaxoSmithKline submitted that a key principle within the Diabetes HCP was that all health professionals retained clinical freedom to prescribe the medicine that was in the best interest of individual patients (clause 2.8 of the contract). In addition, the protocol had already been established and implemented by the primary healthcare service company independently of GlaxoSmithKline prior to the Diabetes HCP commencing. Therefore, responsibility for implementation of the protocol and influence over prescribing lay with the primary healthcare service company only.

The relationship between GlaxoSmithKline and the primary healthcare service company was at a business-to-business level and therefore it was not able to influence the individual doctors. The contract between GlaxoSmithKline and the primary healthcare service company stipulated numerous safeguards as described in detail above to ensure this was enforced. This included responsibility for the relationship with GlaxoSmithKline sitting with a combination of business personnel and health professionals and also the requirement for health professionals to retain clinical freedom and the ability to prescribe the medicine that was in the best interest of patients. Again, for these reasons GlaxoSmithKline respectfully disagreed with the Panel's ruling on this point.

GlaxoSmithKline noted that the Panel had noted that the provision of medical and educational goods and services must not be linked to any medicine. In that regard, the Panel considered that the diabetes services as described in the voicemail and the contract was inappropriate in breach of Clause 18.4 of the Code. The Panel had also considered that high standards had not been maintained in breach of Clause 9.1. GlaxoSmithKline submitted that the description of the Diabetes HCP and associated contract was in line with the MISG, DoH and ABPI guidance regarding joint working by setting out clear roles, responsibilities and the benefits to all

parties in a formal and transparent way.

Although a GlaxoSmithKline medicine was stipulated within the contract, freedom to prescribe the most appropriate medicine for the patient was maintained as a guiding principle and also clearly articulated in the contract. The protocol was established before the Diabetes HCP started and the protocol referred to generic name only. Nowhere in the contract was GlaxoSmithKline's participation linked to prescription volumes. Given the strategic nature of the relationship and the safeguards in place, GlaxoSmithKline disagreed with the Panel's interpretation and subsequent rulings and submitted that the mention of Avandamet was completely appropriate and transparent as required by the MISG principles. As such GlaxoSmithKline denied a breach of Clause 18.4. GlaxoSmithKline had striven to adopt and maintain the highest standards and had engaged senior managers who were aware of the environmental considerations and the Code in setting up these relationships and refuted the breach of Clause 9.1.

In summary, GlaxoSmithKline submitted that it had operated in a transparent, open way to the highest of ethical standards, in accordance with the guidance issued from the MISG, DoH and ABPI. GlaxoSmithKline's overarching principle was to deliver improved benefits to patients through joint working. GlaxoSmithKline and the primary healthcare service company had worked together, sharing expertise and resource to enable the Diabetes Intermediate Service to be delivered in the best possible way. For the reasons stated above, GlaxoSmithKline considered that the Diabetes HCP was not in breach of Clause 18.4 and 9.1 and had maintained the high standards of the industry.

GlaxoSmithKline noted the precedent that might be set if the Panel's rulings were upheld. With the importance of these new relationships being underpinned by the agreed MISG position, GlaxoSmithKline was concerned that the precedent maybe at a variance with the strategic direction regarding joint working between the NHS and the pharmaceutical industry. It was for this reason, as well as the fact that all of GlaxoSmithKline's dealings had been ethical and appropriate that it appealed the Panel's rulings.

APPEAL BOARD RULING

The Appeal Board noted GlaxoSmithKline's comments about joint working between the industry and the NHS. Such activities were not prohibited by the Code providing all the arrangements complied with it. The Appeal Board accepted that a service that improved clinical outcomes in diabetes, standardized continuity of care and reduced the number of secondary care referrals, all aims of the service at issue, would enhance patient care and benefit the NHS.

The Appeal Board noted GlaxoSmithKline's concerns about the adverse implications of this case on the future of the joint working initiative should the Panel's rulings be upheld. The Appeal Board disagreed; each case turned on its own merits.

The Appeal Board noted that the question to be answered was 'Did GlaxoSmithKline support the Diabetes HCP in return for Avandamet being named on the group's treatment protocol?' The Appeal Board noted inconsistencies between the voicemail message, which had prompted the complaint, the written contract between GlaxoSmithKline and the primary healthcare service company, and the protocol employed by the primary healthcare service company for the treatment of type 2 diabetes. In that regard the Appeal Board considered that it had to make its ruling on the service as described by GlaxoSmithKline in its voicemail and in the contract which it signed, as opposed to the protocol.

The Appeal Board noted that the voicemail message stated that '… GlaxoSmithKline has contributed to the cost of running of the service, while [the primary healthcare service company] has agreed to select Avandamet as first medicine in its class on its diabetes protocol for appropriate patients'. A direct link between the company's support and the potential use of Avandamet was thus implied. Paragraph 3.1 of the contract between the primary healthcare service company and GlaxoSmithKline stated 'This Project is sponsored by GlaxoSmithKline. As a consequence of the Group's decision to place GlaxoSmithKline's product on the Group's Protocol in accordance with paragraph 2.6 above, GlaxoSmithKline has agreed to provide funding for this service: provision of such funding is not conditional on the prescription of that product'. In the Appeal Board's view it was immaterial that the protocol did not refer to Avandamet as a named medicine; that it would do so was the basis upon which the contract was signed.

At the appeal GlaxoSmithKline acknowledged that the wording used in paragraph 3.1 of the contract was not the best it could be.

The Appeal Board noted GlaxoSmithKline's submission that the treatment protocol had existed before its involvement with the Diabetes HCP and that the company had not influenced it in any way; it had not changed as a result of the contract between the primary healthcare service company and GlaxoSmithKline. This was not the impression given by the voicemail and the contract.

The Appeal Board noted the content of the protocol which stated that when a glitazone was to be added to metformin, rosiglitazone was second line. Combination tablets of glitazone and metformin were only to be used if there were compliance problems. It also noted GlaxoSmithKline's submission that the positioning described was consistent with NICE guidance.

The Appeal Board further noted GlaxoSmithKline's submission that the naming of Avandamet in the contract was for the purposes of transparency. The Appeal Board considered that in this regard it was not inappropriate *per se* to refer to products but the manner in which they were referred to and the context was important. Encouraging appropriate use of a product in line with national and local guidelines was different to a contractual arrangement that a protocol be changed. The Appeal Board considered that in the voicemail and in the contract there was a very definite, unequivocal link made between the provision of funding and the inclusion of Avandamet, for use as appropriate, on the protocol.

The Appeal Board noted that in response to questioning at the appeal GlaxoSmithKline stated that the company's sponsorship of the Diabetes HCP (£29,250) had part-funded the provision of a diabetes nurse. The Appeal Board further noted that the Diabetes HCP was the mechanism by which the primary healthcare service company delivered its diabetes service. The relationship between the primary healthcare service company and GlaxoSmithKline was an evolving relationship. GlaxoSmithKline provided the primary healthcare service company with, *inter alia*, education, training and business planning. The two organisations worked together on, *inter alia*, project management, data analysis and communications.

The Appeal Board considered that the Diabetes HCP had merit. However the way it had been described in the voicemail and the manner in which Avandamet had been referred to in the contract was evidence that the provision of funding had been linked to the product. The Appeal Board upheld the Panel's ruling of a breach of Clause 18.4. The appeal on this point was thus unsuccessful.

Although noting its ruling above the Appeal Board nonetheless did not consider that taking all the circumstances into account that GlaxoSmithKline had failed to maintain high standards. No breach of Clause 9.1 was ruled. The appeal on this point was thus successful.

Complaint received	**20 February 2008**
Case completed	**1 July 2008**

CASE AUTH/2102/3/08

ANONYMOUS REPRESENTATIVE v MEDA

Promotion of Aldara and activities of representatives

An anonymous representative alleged that he was being encouraged to promote Aldara (iniquimod cream) off license to maxillofacial and plastic surgeons. The complainant was also concerned about the call rates Meda had recently introduced and a letter that representatives gave to doctors.

In relation to call rates, the Panel noted that the supplementary information to the Code stated that the number of calls made on a doctor or other prescriber by a representative each year should normally not exceed three on average excluding attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction. Thus although a representative might speculatively call upon or proactively make an appointment to see a doctor or other prescriber three times in a year, the number of contacts with that health professional in the year might be more than that. In the Panel's view briefing material should clearly distinguish between expected call rates and expected contact rates.

The Panel noted the January regional meetings included slides about customer targets. One slide stated that call frequency was to be within ABPI guidelines. The expectations for 2008 were set out on the same slide. These being of 100 target GPs the minimum requirement was 1:1 contacts. In quarter 1, 25% were to be seen twice, the equivalent figures for quarters 2, 3 and 4 were 50%, 75% and 90% respectively. In addition in quarter 2, 30% were to be seen 3 times with 60% and 90% in quarters 3 and 4 respectively. Targets were only given for primary care.

One of the slides used on the initial training course (ITC) referred to calls but no details were given regarding call frequency. One of the questions in the test on the Code also referred to calls.

The Panel noted an email from the commercial manager provided by the complainant. This reproduced the second part of the slide ie that relating to the quarterly requirements for coverage and frequency. The email included '… however we need to be seeing more of them and more frequently. We have minimum expectations around customer contacts in particular GP activity which as a minimum we must be achieving'.

The Panel was concerned that it appeared that the representatives had not been provided with the details of the requirements of the Code and clear definitions of 'contact rate' and 'call rate' and why the differences were important. The Panel noted Meda's response but considered that the slide regarding customer targets used at the January salesforce meetings could have been more explicit. It did not state that the rates were cumulative. Although it stated the call frequency had to be within ABPI guidelines it did not appear that these had been explained to the salesforce. It was also concerned that the contact rates were described as minimum when the Code did not permit more than three unsolicited calls in a year. On balance the Panel considered that the slide presentation and other instructions advocated a course of action which was likely to lead to a breach of the Code. A breach of the Code was ruled.

The Panel considered that there was no evidence that over calling had occurred and thus no breach was ruled in that regard.

In relation to the letter sent to doctors by representatives, the Panel noted Meda's submission that this letter had been certified and prescribing information had been provided on the reverse. The complainant had not been entirely clear as to what his complaint was about the letter. It was not necessarily unacceptable to use a letter to try to gain an appointment with a health professional and no breach was ruled.

In relation to the alleged off licence promotion, the Panel was concerned that original minutes (undated) of a 10 March regional salesforce teleconference stated that a representative had had success with plastic surgery in that he was '…successfully promoting to plastics, and they tend to be using Aldara for shrinking of lesions, prior to surgical excision. There was concern expressed by [a named representative] that this could be an off label promotion, but as we would only be talking about [certain] lesions, this should not be too much of a problem ...' The amended copy of the minutes (also undated) for the same teleconference included additional information 'I just want to confirm what I said on the TC and that is we should never promote Aldara off-licence, and if other specialties have expressed an interest then we can follow up to find out what their interest in Aldara is? We should not be contacting this specialty directly, only following up requests'.

The Panel noted the submission that two specialist account managers had made specific contact with maxillofacial customers as a direct result of a referral from a dermatologist who worked closely with the maxillofacial surgeons for managing small, superficial basal cell carcinomas (sBCCs).

The Panel was concerned that Meda was promoting Aldara to plastic surgeons to shrink lesions prior to surgery. This was inconsistent with the summary of product characteristics which stated, *inter alia*, that Aldara was indicated for the topical treatment of sBCCs. The Panel ruled a breach of the Code.

An anonymous company representative complained about the promotion of Aldara (iniquimod cream) by Meda Pharmaceuticals Limited and about the activities of its representatives.

Aldara had three indications: external genital and perianal warts (condylomata acuminate) in adults; small superficial basal cell carcinomas (sBCCs) in adults; and clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AKs) on the face or scalp in immunocompetent adult patients when size or number of lesions limited the efficacy and/or acceptability of cryotherapy and other topical treatment options were contraindicated or less appropriate.

COMPLAINT

The complainant stated that he was concerned about the total lack of knowledge within the company around ABPI and it was only due to representatives showing concern that some actions had been changed. However the company still behaved in an unethical manner and examples were cited.

1 Call rates were only introduced in January 2008, however representatives were concerned there was a breach here. (Copy email provided).

2 Representatives were encouraged to write to doctors using 'the GPwSI letter' which was self written' by an ex-representative, not the company; this had a reply slip on the bottom to gain an appointment from the clinician. (Copy provided).

3 Representatives were also encouraged to promote Aldara off licence into maxillofacial units and plastic surgeons to obtain business. Others had raised this as a breach, but whilst on a recent teleconference, one representative claimed he got a lot of response from this focus, one other person raised concerns, and the manager replied: 'well it is off licence, but just do it, but be careful'. This was totally wrong and it was the complainant's job and ABPI qualification too! (It had also been seen on business plans where people had written they would promote off licence).

There was a lot of concern around the conduct of Meda in general, and the complainant had also witnessed clinicians' complaints.

When writing to Meda, the Authority asked it to respond in relation to Clauses 2, 3, 9.1, 14.1, 15.4 and 15.9 of the Code.

1 Call rates

RESPONSE

Meda explained that it had a salesforce of 41 specialist account managers, four commercial managers and one head of sales. Each specialist account manager worked a defined geography and took responsibility for the customers within the NHS for their promoted products. The company's salesforce was divided into two teams, one of which promoted Aldara. The Aldara salesforce was divided into two regions (northern and southern) of ten specialist account managers, each region was managed by one commercial manager.

As the complaint referred to Aldara, then the response below was based specifically on communications to the Aldara salesforce.

Meda stated that regional salesforce meetings were held on Tuesday, 8 January and Wednesday. The agenda for these meetings was provided.

There was a session relating to Salesforce Expectations that was part of the session 'Setting the Pace'. This was a joint session between the senior product manager for Aldara, medical advisor and the respective commercial manager for that region.

This session positioned the Aldara campaign for both primary and secondary care in 2008 and gave an overview of what the salesforce could expect in terms of promotional materials, meetings support and mailings. Then each commercial manager set out the expectations of the Aldara salesforce for quarter 1, 2008. This was the same presentation for both meetings.

The presentation covered all aspects of the Aldara salesforce. Call rates were discussed and outlined in a slide which focussed on what needed to be delivered for quarter 1, 2008 to enable a good start to the year. The communication plan for 2008 was that at the end of each quarter the salesforce would be given an updated set of expectations for the forthcoming quarter and these were called operational plans. This allowed the sales management team the flexibility to adapt the implementation of the Aldara campaign and provide the necessary focus for each given quarter and follow the same timelines as the business planning process which was quarterly. Details about each representative's customer activity was provided.

Coverage and frequency were discussed and outlined in another slide. The coverage and frequency expectations were only given with reference to the primary care campaign and not hospital contacts. This slide covered the whole of

2008 because the main focus of the salesforce activity was in primary care and the commercial managers wanted to provide the context to the salesforce to demonstrate how this would evolve over 2008 across all quarters. Hence reference to the coverage and frequency expectation being in line with the Code was clearly stated on the slide and verbalised. The content of this slide was also repeated in subsequent emails from the commercial manager to the southern region. No commercial manager had requested additional contacts outside of the Code in either primary care or secondary care.

In response to a request for further information Meda stated that the salesforce had been briefed on the Code in February 2007 using the same materials that were used on the initial training course (ITC). All new starters to Meda undertook an ITC which included a specific session that covered the Code. This session was an interactive session with supporting PowerPoint slides (copies provided) and specifically covered the Code from a salesforce perspective. Within this presentation one slide covered the aspects of call frequency which was verbalised and expanded upon by the presenter. The slide stated:

'Calls (Clause 15)
- No inducement for an interview
- Clarity regarding your identification
- No fee for an interview
- Convenience of calls
- Call Frequency
- Delivery of 'endurance items'

- **Members of the MEDA salesforce must at all times maintain a high standard of ethical behaviour.'**

In addition each delegate received a hard copy of the Code as well as a copy of the Code in the Field book. Specific instructions were given to each ITC delegate that they needed to have read and understood the Code. As from January 2008, each ITC delegate's knowledge and understanding of the Code was tested the day after the Code training session. A written test devised by an external medical consultant was used with a pass mark of 80%. The test included a specific question relating to contact rates and call frequency. The tests were marked and returned to the delegates and any incorrect answers were clarified to ensure understanding. Any advice required by specialist account managers relating to contact rates, call rates and the Code were discussed with individuals on the telephone, field visits or one to one meetings with their commercial manager.

With regard to customer targets the slide used at the January salesforce meetings stated:

'Customer Targets

- Pathfinder to be set up to track coverage and frequency
- Call frequency to be within ABPI guidelines.

Of 100 Target GP's (minimum requirements – 1:1 Contacts)
Q1 – 40% coverage – 25% seen twice
Q2 – 80% coverage – 50% seen twice – 30% seen 3 times
Q3 – 90% coverage – 75% seen twice – 60% seen 3 times
Q4 – 95% coverage – 90% seen twice – 90% seen 3 times

275 contacts needed – 23 per month – 1 per day'

Meda stated that the figures for customer targets, coverage and frequency demonstrated the expectations of the salesforce through each quarter of 2008. The figures for each quarter related to the cumulative perspective for 2008 and this was clarified in the briefing. The GPs to be seen three times were all a subset of those to be seen twice and this was explicit in the briefing. Each commercial manager undertaking the presentation verbally clarified and illustrated the figures eg 'If you have 100 target customers by the end of 2008 you will need to have seen 95 of them once, of which a subset of 90 needs to have been seen twice, of which a subset of 90 needs to have been seen three times.'

PANEL RULING

The Panel noted that the supplementary information to Clause 15.4 stated that the number of calls made on a doctor or other prescriber by a representative each year should normally not exceed three on average excluding attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction. Thus although a representative might speculatively call upon or proactively make an appointment to see a doctor or other prescriber three times in a year, the number of contacts with that health professional in the year might be more than that. In the Panel's view briefing material should clearly distinguish between expected call rates and expected contact rates.

The Panel noted that at the January regional meetings the presentations included slides about customer targets. One slide stated that call frequency was to be within ABPI guidelines. The expectations for 2008 were set out on the same slide. These being of 100 target GPs the minimum requirement was 1:1 contacts. In quarter 1, 25% were to be seen twice, the equivalent figures for quarters 2, 3 and 4 were 50%, 75% and 90% respectively. In addition in quarter 2, 30% were to be seen 3 times with 60% and 90% in quarters 3 and 4 respectively. Targets were only given for primary care.

One of the slides used on the ITC referred to calls but no details were given regarding call frequency. One of the questions in the test on the Code also referred to calls.

The Panel noted an email from the commercial manager provided by the complainant. This reproduced the second part of the slide ie that relating to the quarterly requirements for coverage and frequency. The email included '… however we need to be seeing more of them and more frequently. We have minimum expectations around customer contacts in particular GP activity which as a minimum we must be achieving'.

The Panel was concerned that it appeared that the representatives had not been provided with the details of the requirements of the Code and clear definitions of 'contact rate' and 'call rate' and why the differences were important. The Panel noted Meda's response but considered that the slide regarding customer targets used at the January salesforce meetings could have been more explicit. It did not state that the rates were cumulative. Although it stated the call frequency had to be within ABPI guidelines it did not appear that these had been explained to the salesforce. It was also concerned that the contact rates were described as minimum when the Code did not permit more than 3 unsolicited calls in a year. On balance the Panel considered that the slide presentation and other instructions advocated a course of action which was likely to lead to a breach of the Code. A breach of Clause 15.9 was ruled.

The Panel considered that there was no evidence that over calling had occurred and thus no breach of Clause 15.4 was ruled.

The Panel did not consider the circumstances warranted a ruling of a breach of Clause 9.1 nor Clause 2 which was used as a sign of particular censure and reserved for such use.

2 Letter about Aldara sent to doctors

RESPONSE

Meda stated that the primary care campaign for Aldara focussed on accessing a key group of approximately 800 GPs who had a registered interest in dermatology and were called GPs with special interests (GPwSI). In terms of the dermatology indications these were a key group of customers to contact.

The letter in question introduced the specialist account manager to this specific customer group. This letter was previously created by another company through the product development team and was reintroduced by a commercial manager within Meda to help specialist account managers access this group. The letter was re-approved for use by the Meda salesforce using the Meda promotional material approval process and signed off by all relevant ABPI signatories in July 2007. This letter was then given to the representatives for them to use with their customers.

PANEL RULING

The Panel noted Meda's submission that this letter had been certified and prescribing information had been provided on the reverse. Prescribing information did not appear on the version supplied by the complainant. It was not clear how the letter had been made available to the sales force. It should have been such that it was not possible for it to be used without the requisite prescribing information. The complainant had not been entirely clear as to what his complaint was about the letter. It was not necessarily unacceptable to use a letter to try to gain an appointment with a health professional. In the circumstances the Panel decided there was no breach of Clause 14.1 of the Code and ruled accordingly.

3 Alleged promotion outside the marketing authorization

RESPONSE

Meda explained that Aldara was launched in the UK in 1997 for the treatment of external genital and perianal warts in adults. Following that it was licensed in 2005 for small superficial basal cell carcinomas (sBCCs) in adults and finally in 2007 it was licensed for clinically typical, nonhyperkeratotic, nonhypertrophic actinic kertoses (AKs) on the face or scalp in immunocompetent adult patients when size or number of lesions limited the efficacy and/or acceptability of crytherapy and other topical treatment options were contraindicated or less appropriate.

Due to the mode of action of Aldara this had stimulated other customers' potential use. Representatives were briefed on the ITC about dealing with specific queries on the use of Aldara for indications outside of the licence and what they needed to do in terms of passing the lead/contact onto the medical advisor via email or telephone. At all briefings any specific enquiries outside of the licence raised by a member of the salesforce were clarified by a member of the Meda management team and passed on to the medical advisor.

Meda had two specialist account managers who had made specific contact with maxillofacial customers as a direct result of a referral from a dermatologist who worked closely with the maxillofacial surgeons for managing sBCCs in adults.

With specific reference to a teleconference mentioned, there had been two teleconferences, one in January and the other in March for one of the Aldara teams. The minutes of the teleconferences and the amendments by the commercial manager were provided. The minutes of the teleconference on 14 March clearly showed that off-licence use was raised by the specialist account managers themselves, and on that teleconference the commercial manager restated

that they should never promote Aldara outside of the licence.

In addition the amendments of the minutes of the teleconference by the commercial manager stated 'I just want to confirm what I said on the [teleconference] and that is we should never promote Aldara off-licence, and if other specialties have expressed an interest then we can follow up to find out what their interest in Aldara is? We should not be contacting this specialty directly, only following up requests'.

Meda submitted that there was one specialist account manager who had a task relating to maxillofacial but this was in reference to a specific customer follow-up from a dermatologist in line with Aldara licensed use.

PANEL RULING

The Panel was concerned that the original minutes (undated) of the 10 March teleconference stated that a representative had had success with plastic surgery in that he was '…successfully promoting to plastics, and they tend to be using Aldara for shrinking of lesions, prior to surgical excision. There was concern expressed by [a named representative] that this could be an off label promotion, but as we would only be talking about AK/SCC lesions, this should not be too much of a problem ...'. The amended copy of the minutes (also undated) for the same teleconference included additional information '**I just want to confirm what I said on the TC and that is we should never promote Aldara off-licence**, and if other specialties have expressed an interest then we can follow up to find out what their interest in Aldara is? We should not be contacting this specialty directly, only following up requests'.

The Panel noted the submission that two specialist account managers had made specific contact with maxillofacial customers as a direct result of a referral from a dermatologist who worked closely with the maxillofacial surgeons for managing sBCCs.

The Panel was concerned that Meda was promoting Aldara to plastic surgeons to shrink lesions prior to surgery. This was inconsistent with the summary of product characteristics (SPC) which stated, *inter alia*, that Aldara was indicated for the topical treatment of sBCCs. The Panel ruled a breach of Clause 3.2 of the Code.

The Panel did not consider the circumstances warranted a ruling of a breach of Clause 9.1 nor Clause 2 which was used as a sign of censure and reserved for such use.

Complaint received **7 March 2008**

Case completed **22 April 2008**

ANONYMOUS MEMBER OF A PRIMARY CARE TRUST MEDICINES MANAGEMENT TEAM v TRINITY-CHIESI

Therapeutic review service

An anonymous member of a primary care trust (PCT) medicines management team complained that a programme being run by Trinity-Chiesi in one of the complainant's practices, which advocated a switch from beclometasone CFC and beclometasone CFC-free to its branded beclometasone CFC-free product, Clenil, was in breach of the Code. The complainant noted that the Code prohibited pharmaceutical companies from sponsoring switch services.

The Panel noted that switch services paid for or facilitated directly or indirectly by a pharmaceutical company whereby a patient's medicine was simply changed to another without clinical assessment were prohibited. Companies could promote a simple switch from one product to another but not assist in its implementation.

The Panel noted that the complainant had made a very broad allegation but no details had been provided. The complainant was anonymous and non-contactable.

The Panel noted that a document headed 'Prescribing Review Service – Protocol' stated that the service, provided by Trinity-Chiesi's Clinical Support Services (CSS) team, was not linked to the use of any particular products. Briefing material for the representatives clearly explained that the Code prohibited a pharmaceutical company from assisting a health professional with a switch programme. Representatives were thus told that they could not provide any support for a health professional to switch a patient's medicine simply to Trinity-Chiesi's products, although the health professionals were free to do this without support if they wished. The service could only be offered to a practice which required support to undertake a therapeutic review which was a review of patient management which aimed to ensure that patients received optimal treatment following a clinical assessment. There were no criteria listed in the documents as the basis for deciding when patients were not receiving optimal treatment. This was reinforced by the preprinted Respiratory Review Authorization Form for completion by the GP. The form listed a number of medications, for example 'all beclometasone pmdis', with details of the doses and then a section beneath the heading 'Treatment of choice' which was left blank for the GP to complete as was a box beneath the heading 'Special conditions/patient specific directions'.

The Panel also noted from other documents supplied that the representatives had no input into the service other than to introduce the service to GPs and liaise between the parties in the early stages to ensure that appointments for CSS pharmacists to go to the practices were made. There was to be little contact between the CSS pharmacist and the representatives although the representatives were expected to meet the CSS pharmacists on their first visit to any surgery to introduce them to the practice staff. No reference to the service being provided or to any Trinity-Chiesi products was to be made at that introductory meeting. Once the CSS pharmacist had been introduced the representative had to leave the surgery.

The Panel noted that the CSS pharmacist and the GP decided which patients to review. Patients were not clinically assessed in person but their individual medical records were reviewed. Any medication changes were noted together with the rationale for such. At the end of the day the authorizing GP had to go through the patient lists generated by the CSS pharmacist and approve all the changes made. The Panel was concerned that medication changes were made by the CSS pharmacist and these were then authorized at the end of the day by the GP even though the meeting at the start of the day would give the CSS pharmacist clear direction of the GPs wishes. The Medication Summary Form stated that the form was a breakdown of the patient numbers on each of the strengths of branded/generic medication that the GP asked the CSS pharmacist to review. It appeared that the review was product led rather than patient led. However patients taking asthma medication would have to be moved to a CFC free medication due to the non availability of CFC containing medication.

The Panel was concerned that some examples of patient letters which had been provided appeared to indicate that it was anticipated that as a result of the CSS patients would be changed onto Trinity-Chiesi's product Clenil Modulite. Nonetheless the Panel considered, on the basis of the information before it, that there was no evidence to show that the CSS acted as a switch service whereby patients were simply switched from one product to another without clinical review. No breach of the Code was ruled.

An anonymous member of a primary care trust (PCT) medicines management team complained about the promotion of Clenil (CFC-free beclometasone) by Trinity-Chiesi Pharmaceuticals Ltd.

COMPLAINT

The complainant had recently been made aware of a

programme being run by Trinity-Chiesi in one of the complainant's practices, which advocated a switch from beclometasone CFC and beclometasone CFC-free to its branded beclometasone CFC-free product, Clenil.

The complainant alleged that this was in breach of Clauses 18.1 and 18.4 of the Code which prohibited switch services paid for and facilitated by the sponsor of the service, Trinity-Chiesi.

When writing to Trinity-Chiesi, the Authority asked it to respond in relation to Clauses 2 and 9.1, as well as Clauses 18.1 and 18.4 referred to by the complainant.

RESPONSE

Trinity-Chiesi stated that it did not operate a switch service for Clenil and as such was unable to respond to the complaint. Following a request from the Panel for information about the services Trinity-Chiesi did provide, the company supplied details about a non-promotional therapeutic review service called the Clinical Support Service (CSS). Trinity-Chiesi noted that the complainant had not complained about the CSS. However, as requested, it would provide the relevant documents pertaining to this service.

The CSS was provided by registered pharmacists who under written instructions from the authorising GP would access individual patient records and carry out a full clinical assessment of each patient's therapy prior to any therapeutic review taking place. The clinical assessments made by the pharmacist, as the recognised professional expert on medicines, included:

- Assessment of each individual patient's medication to ensure any therapeutic review requested and authorised by the GP was appropriate for that patient
- Checking for medication interactions
- Checking for over or under ordering of medicines
- Checking for duplicate therapies
- Assessment of compliance issues
- Checking dosages and strengths were correct
- Checking licensed indications
- Reviewing quantities issued and identifying in-equivalence of quantities
- Checking all clinical investigations were up to date and identifying tests overdue or not recorded
- Assessment of potential side effects
- Assessment of possible strength optimisation

Any of the clinical queries or recommendations emanating or resulting from these assessments, would be detailed on a medication query form and discussed and resolved directly with the authorising GP.

Trinity-Chiesi believed that this non-promotional therapeutic review service complied with the Code and in particular with Clauses 18.1 and 18.4.

Trinity-Chiesi provided copies of the CSS documents which related to the prescribing of beclometasone (with or without CFC). Trinity-Chiesi did not have any service documents which related specifically to the prescribing of Clenil as this was not a product-specific service offering.

In response to a request for further information, Trinity-Chiesi explained that the CSS pharmacist would meet with the authorising GP at the start of the day to agree the therapy reviews which were required. This was documented on the Respiratory Review Authorisation form (TRCSS20070194).

The CSS pharmacist would produce a list of patient cohorts in line with these requirements ready for clinical assessment.

The CSS pharmacist would perform the therapeutic review and clinically assess the therapy of each individual patient. If any changes to therapy were made this was clearly recorded on the patient cohorts list against the relevant individual name and a clinical rationale for the change was annotated by the CSS pharmacist. If a patient was clinically assessed but their therapy was not changed the CSS pharmacist would score through their name on the list and clearly annotate the rationale for this. Whilst any changes to therapy were made at this point, they were only finalised once they had been approved in writing by the GP at the end of the day.

The CSS pharmacist would also Read Code any change to the patients' therapy on the patient records on the GP computer system, detailing the action taken and the date it was done. The rationale for any change made would also be added alongside the Read Code (ie medication changed under direction from Doctor X as part of the transition to CFC-free inhalers).

The CSS pharmacist would meet with the GP at the end of each day in surgery to go through the patient lists. The GP must review the individual patients and the accompanying rationale for change which had been stated by the CSS pharmacist on the lists. The GP must sign each page of the lists to indicate they were happy with the actions taken and they met with their approval. Any clinical queries or recommendations emanating or resulting from the clinical assessments would be detailed on the Medication Review Query forms (TRCSS20070196) and discussed and resolved directly with the GP at this meeting. Any further actions requested by the GP during the meeting were then undertaken by the CSS pharmacist before leaving the surgery.

The process clearly met the requirements of the Code as the decision to change or commence treatment for each individual patient was clearly made and authorised by the prescribing GP and supported by the written evidence on the patient lists which were stored securely within the surgery where the clinical work had taken place. The CSS pharmacist clearly documented the evidence that any changes were made on rational grounds both on the patient lists and on the patients' computer records.

The clinical assessments made by the pharmacists, as the recognised professional experts on medicines, was made using the individual patient records within the surgery.

There were no pre-determined expectations of how many patients a CSS pharmacist would review in a day. There were many variable factors which influenced the time it took to conduct a clinical assessment of each individual patient's medication, such as the number, and complexity, of each individual patient's medication, the availability of the GP during the working day and the type of computer system in the surgery, for any expectation to be set as to the number of reviews to be completed in a day.

Trinity-Chiesi stated that its objective during each review was to ensure the highest level of professional service was delivered to the GP and the patient irrespective of the amount of time taken.

PANEL RULING

The Panel noted that the supplementary information to Clause 18.4, Switch and Therapy Review Programmes, stated, *inter alia*, that Clause 18.1 and 18.4 prohibited switch services paid for or facilitated directly or indirectly by a pharmaceutical company whereby a patient's medicine was simply changed to another without clinical assessment. Companies could promote a simple switch from one product to another but not assist in the implementation of it.

The Panel noted that the complainant had made a very broad allegation that Trinity-Chiesi's programme being run in one of the complainant's practices which advocated a switch to Clenil was in breach of Clauses 18.1 and 18.4. No details had been provided. The complainant was anonymous and non-contactable.

The Panel noted that a document headed 'Prescribing Review Service – Protocol' stated the service, provided by the CSS team, was not linked to the use of any particular products. Briefing material for the representatives clearly explained that the Code prohibited a pharmaceutical company from assisting a health professional with a switch programme. Representatives were thus told that they could not provide any support for a health professional to switch a patient's medicine simply to Trinity-Chiesi's products, although the health professionals were free to do this without support if they wished. The service could only be offered to a practice which required support to undertake a therapeutic review which was a review of patient management which aimed to ensure that patients received optimal treatment following a clinical assessment. There were no criteria listed in the documents as the basis for deciding when patients were not receiving optimal treatment. This was reinforced by the preprinted Respiratory Review Authorization Form (TRCSS20070194) for completion by the GP. The form listed a number of medications, for example 'all beclometasone pmdis', with details of the doses and then a section beneath the heading 'Treatment of choice' which was left blank for the GP to complete as was a box beneath the heading 'Special conditions/patient specific directions'.

The Panel also noted from other documents supplied, that the representatives had no input into the service other than to introduce the service to GPs and liaise between the parties in the early stages to ensure that appointments for CSS pharmacists to go to the practices were made. There was to be little contact between the CSS pharmacist and the representatives although the representatives were expected to meet the CSS pharmacists on their first visit to any surgery to introduce them to the practice staff. No reference to the service being provided or to any Trinity-Chiesi products was to be made at that introductory meeting. Once the CSS pharmacist had been introduced the representative had to leave the surgery.

The Panel noted that the CSS pharmacist and the GP decided which patients to review. Once the patient cohort had been identified the CSS pharmacist reviewed individual patient records to assess interactions/compliance/duplicate therapies etc. Patients were not clinically assessed in person but their individual medical records were reviewed. Any medication changes were noted together with the rationale for such. At the end of the day the authorizing GP had to go through the patient lists generated by the CSS pharmacist and approve all the changes made. The Panel was concerned that medication changes were made by the CSS pharmacist and these were then authorized at the end of the day by the GP even though the meeting at the start of the day would give the CSS pharmacist clear direction of the GPs wishes. The Medication Summary Form stated that the form was a breakdown of the patient numbers on each of the strengths of branded/generic medication that the GP asked the CSS pharmacist to review. It appeared that the review was product led rather than patient led. However patients taking asthma medication would have to be moved to a CFC free medication due to the non availability of CFC containing medication.

The Panel was concerned that some examples of patient letters which had been provided appeared to indicate that it was anticipated that as a result of the CSS patients would be changed onto Trinity-Chiesi's product Clenil Modulite. Nonetheless the Panel considered, on the basis of the information before it, that there was no evidence to show that the CSS acted as a switch service whereby patients were simply switched from one product to another without clinical review. No breach of Clauses 18.1 and 18.4 was ruled. The Panel also considered that there was no breach of Clauses 2 and 9.1 and ruled accordingly.

Complaint received **11 March 2008**

Case completed **15 April 2008**

ANONYMOUS PRIMARY CARE TRUST PHARMACIST v TRINITY-CHIESI

Letter about Clenil

An anonymous primary care trust (PCT) pharmacist alleged that a letter sent by Trinity-Chiesi, promoting Clenil (beclometasone), was misleading and was neither accurate nor balanced. The data for the cost difference between beclometasone 200mcg and Clenil 200mcg was conveniently missed from a cost comparison chart. The complainant questioned why this had been done when the cost difference here was only 2% - compared to the 20 - 35% differences claimed on the other strengths. The heading referred to substantial savings but the chart did not include data where the difference was only 2%.

The Panel noted that there was no way of knowing how the complainant had received the letter which was for health professionals in Scotland only; PCTs did not exist in Scotland. The letter was not sent to addresses in England. Further the representatives based in Scotland, who had been given copies of the letter to distribute, did not cover English territories.

The Panel noted that the complainant had only provided page 2 of the three page letter. Page one of the letter clearly referred, at the outset, to the Scottish Drug Tariff. The Panel considered that this, together with the distribution of the letter only to Scottish health professionals, put the cost comparison chart in context. There was no price in the Scottish Drug Tariff for a beclometasone 200mcg inhaler and so no comparison could be made of the drug tariff price vs Clenil. Although it might have been helpful if the cost comparison chart had explained this rather than just leaving the relevant section blank, the Panel did not consider that the chart was inaccurate, unbalanced or misleading in this regard as alleged. No breach of the Code was ruled.

An anonymous primary care trust (PCT) pharmacist complained about a letter (ref TRCLE20070433) promoting Clenil (beclometasone) received from Trinity-Chiesi Pharmaceuticals Ltd. The complainant provided a page from the letter which featured a chart comparing the cost of Clenil with that of other beclometasone inhalers of various strengths. The chart was headed 'There are now substantial savings to be made in beclometasone metered dose inhaler prescribing costs by changing generic prescribing to Clenil brand'.

COMPLAINT

The complainant alleged that the letter was misleading and was neither accurate nor balanced. The data for the cost difference between beclometasone 200mcg and Clenil 200mcg was conveniently missed from the cost comparison chart. The complainant questioned why this had been done when the cost difference here was only 2% – compared to the 20 – 35% differences claimed on the other strengths. The heading referred to substantial savings but the chart did not include data where the difference was only 2%.

When writing to Trinity-Chiesi, the Authority asked it to respond in relation to Clauses 7.2, 7.3, and 7.4 of the Code.

RESPONSE

Trinity-Chiesi stated that the letter was mailed in October 2007 to primary care organizations in Scotland only. Copies of the letter were also supplied to the sales force in Scotland to give to health professionals in that country only. The 200mcg strength of beclometasone was not included in the cost comparison chart on page 2 because the Scottish Drug Tariff did not feature this strength of beclometasone. A print out of the Scottish Drug Tariff for October-December 2007 was provided. As there was no equivalent 200mcg strength, a comparison with this strength was not possible. Therefore, the cost comparison chart (which consisted of strengths at 50mcg, 100mcg and 250mcg) was accurate, balanced and not misleading.

Trinity-Chiesi also provided a copy of a similar letter which was mailed in October 2007 to primary care organizations in England and Wales (TRCLE20070420). In this letter, the cost comparison chart included the 200mcg strength (in addition to the other three strengths), as all four strengths were featured in the Drug Tariff for England and Wales.

Clenil's UK market share for each strength of the beclometasone metered-dose inhalers in units from November 2007 – January 2008 was as follows: Clenil 50mcg, 3%; Clenil 100mcg, 11%; Clenil 200mcg, 4% and Clenil 250mcg, 2%.

These shares reflected the usage pattern by strength of total beclometasone metered dose inhalers in the market.

In response to a request for further information Trinity-Chiesi noted that its mailing records

showed that the letter in question was not posted to any English addresses. Furthermore, although copies of the letter were also given to representatives in Scotland for distribution to Scottish health professionals, none of the representatives in Scotland covered English territories. A copy of the relevant representatives' briefing material was supplied.

PANEL RULING

The Panel noted that the complainant had stated that they were a PCT pharmacist but had provided no contact details. This was unfortunate because there was no way of asking the complainant how (s)he had received the letter in question. The letter was for health professionals in Scotland only; PCTs did not exist in Scotland and so in that regard the complainant should never have received the letter. Trinity-Chiesi had confirmed that the letter was not sent to English addresses and the representatives based in Scotland, who had been given copies of the letter to distribute, did not cover English territories.

The Panel noted that the complainant had only provided page 2 of the three page letter. Page one of the letter clearly referred, at the outset, to the Scottish Drug Tariff. The Panel considered that this, together with the distribution of the letter only to Scottish health professionals, put the cost comparison chart in context. There was no price in the Scottish Drug Tariff for a beclometasone 200mcg inhaler and so no comparison could be made of the drug tariff price vs Clenil. Although it might have been helpful if the cost comparison chart had explained this rather than just leaving the relevant section blank the Panel did not consider that the chart was inaccurate, unbalanced or misleading in this regard as alleged. No breach of Clauses 7.2, 7.3 and 7.4 was ruled.

Complaint received **17 March 2008**

Case completed **17 April 2008**

CASE AUTH/2107/3/08

BAXTER HEALTHCARE v JOHNSON & JOHNSON WOUND MANAGEMENT

Promotion of Quixil fibrin sealant

Baxter Healthcare alleged that Johnson & Johnson Wound Management's use of a regulatory authority safety alert for Trasylol (aprotinin) in its promotion of Quixil (human fibrin sealant) was misleading.

Baxter explained that in November 2007, worldwide marketing of Trasylol was suspended because of safety concerns – aprotinin was one component of Tisseel Kit fibrin sealant, marketed by Baxter. Immediately following this action, the European Medicines Evaluation Agency (EMEA) issued a statement explaining the reasons for the action, and made it clear that fibrin sealants containing aprotinin were not affected by this alert.

Early in December 2007, Baxter began to receive enquiries regarding the licence status of Tisseel and the appropriateness of its use; Baxter alleged that one customer from a cardiac surgery centre was told by the Johnson & Johnson representative to stop using Tisseel and switch to Quixil because Quixil did not contain aprotinin. Baxter immediately wrote to Johnson & Johnson expressing its dissatisfaction with this turn of events, and asked the company to let Baxter know what action had been taken to ensure this was not repeated. No response was received to this letter.

It subsequently became evident that Johnson & Johnson's salesforce had been officially briefed on the aprotinin withdrawal, however Johnson & Johnson refused to supply a copy of this briefing material – the company offered to show it at a meeting but would not send a copy to Baxter.

Baxter further noted that Johnson & Johnson had written to consultant haematologists informing them that there was a fibrin sealant available that did not contain aprotinin. Given the clear statement from the EMEA that this concern did not relate to fibrin sealants Baxter alleged that this was further misleading promotion of Quixil. Baxter had not got a copy of this letter, and given that use of Quixil was almost exclusively limited to surgical operations Baxter questioned the appropriateness of such a letter to anyone other than a surgeon.

Baxter alleged that it was clear that the briefing and the strategy were global initiatives based on a common theme, namely that fibrin sealants that contained aprotinin were less safe than those that did not. A banner stand for Quixil, used in the UK, included the statement 'Aprotinin free'.

The Panel noted that on 21 November 2007, the EMEA issued a questions and answers document on its recommendation to suspend the marketing authorizations for aprotinin-containing medicines. The first paragraph of the document stated that the Agency's Committee for Medicinal Products for Human Use had concluded that the benefits of systemic formulations of these medicines no longer outweighed their risks and had recommended that all marketing authorizations for these medicines should be suspended throughout Europe. The Agency defined systemic formulations as those which affected the whole body, such as infusions (drips). The document clearly stated in a section headed 'What is Aprotinin?' that 'Aprotinin can also be used locally during surgery, in sealants (glues), to help stop bleeding. These medicines are not affected by this recommendation'.

On 29 November 2007, the MHRA issued a statement entitled 'Aprotinin (Trasylol): Suspension of UK marketing authorisations (licences)'. Unlike the EMEA document the MHRA statement did not differentiate between aprotinin and aprotinin-containing medicines or systemic and local formulations but in that regard the Panel considered that the title of the document made it clear that the statement related solely to Trasylol.

The Panel noted that Johnson & Johnson had acknowledged that there was potential for confusion as to exactly what medicines had been suspended from use. The company had stated that it wanted to ensure that its customers knew that although Trasylol was affected by the suspension of its marketing authorization, there was no effect on Quixil or indeed any fibrin sealant.

The Panel disagreed with Johnson & Johnson's submission that, from as early as 13 November 2007, it had made it clear to its representatives that the regulatory status of Trasylol did not affect fibrin sealants. An email to representatives of 13 November stated 'The potential opportunity for Quixil to be used as an alternative [to Trasylol] is due *not necessarily* (emphasis added) to [Tisseel] containing aprotonin but due to the use of Trasylol as a systemic haemostat'. The Panel considered that this statement would lead the representatives to think that the aprotinin contained in Tisseel *might* be a problem. The email did not clearly distinquish between Trasylol and fibrin sealants as submitted.

On 4 December 2007, a further briefing by

Johnson & Johnson to its representatives on the updated guidance from the MHRA with regard to Trasylol, did not differentiate between systemic and local use of aprotinin nor did it distinguish between aprotinin as in Trasylol or aprotinin-containing medicines such as Tisseel. The briefing material did not refer to the EMEA's statement, which pre-dated the MHRA's statement, namely that sealants, or glues, were not affected by the suspension of the Trasylol licences. Representatives were asked to reassure customers that Quixil did not contain bovine aprotinin and if customers asked about other aprotinin-containing products, they were to be reassured that Quixil was the only fibrin sealant on the market that did not contain bovine aprotinin.

The Panel considered that the briefing material implied that because it did not contain aprotinin, there was a benefit for Quixil compared with aprotinin-containing sealants ie Tisseel. No data had been submitted to this effect. The Panel considered that by not explicitly informing representatives that the MHRA statement was Trasylol specific and referring to the EMEA statement that sealants or glues were not affected, the briefing material did not reflect the situation clearly and was misleading by implication and following it was likely to lead to a breach of the Code. The Panel ruled a breach of the Code.

The Panel noted that the letter sent in early January 2008 by Johnson & Johnson, explaining the situation to its customers, was headed 'Quixil Solutions for Sealant (Human Fibrin Sealant)'. This letter emphasised that the marketing suspension and license suspensions of Trasylol were Trasylol specific and did not affect surgical sealants. It also stated that Quixil did not contain aprotinin and there was no implied comparison with sealants which did. The Panel did not consider that the letter was misleading as alleged and no breach of the Code was ruled.

Unlike the letter the exhibition banner did not include information about the current situation with Trasylol. It featured five bullet points about Quixil the final one of which was 'Completely free of animal sourced components – Aprotinin free'. The Panel considered that such a claim implied a benefit for Quixil compared with sealants which contained aprotinin; readers would assume that there was some positive reason for the claim to be made. There was no data to show a clinical benefit for aprotinin- free sealants compared with those that contained aprotinin. The Panel considered that, in the light of the representatives' briefing material discussed above, the balance of probabilities was that the claim would be used to imply a clinical advantage for Quixil which was misleading. A breach of the Code was ruled.

Baxter Healthcare Ltd complained about the promotion of Quixil Solutions for sealant (human fibrin sealant) by Johnson & Johnson Wound Management.

COMPLAINT

Baxter alleged that Johnson & Johnson's use of a regulatory authority safety alert for another product in its promotion of Quixil was misleading in breach of Clause 7.2 of the Code.

Baxter explained that in November 2007, worldwide marketing of Trasylol (aprotinin) was suspended because of safety concerns – aprotinin was one component of Tisseel Kit fibrin sealant, marketed by Baxter. Immediately following this action, the European Medicines Evaluation Agency (EMEA) issued a statement which explained the reasons for the action, and made it clear that fibrin sealants containing aprotinin were not affected by this alert.

Early in December 2007, Baxter began to receive medical information enquiries regarding the licence status of Tisseel and the appropriateness of its use. Baxter alleged that in particular, one customer from a cardiac surgery centre was told by the Johnson & Johnson representative to stop using Tisseel and switch to Quixil because Quixil did not contain aprotinin. Baxter immediately wrote to Johnson & Johnson expressing its dissatisfaction with this turn of events, and asked the company to let Baxter know what action had been taken to ensure this was not repeated. No response was received to this letter.

In subsequent correspondence it became evident that Johnson & Johnson's salesforce had been officially briefed on the aprotinin withdrawal, however Johnson & Johnson refused to supply a copy of this briefing material – the company offered to show it at a meeting but would not send a copy to Baxter.

During this email exchange Baxter found out that Johnson & Johnson had written to consultant haematologists informing them that there was a fibrin sealant available that did not contain aprotinin. This letter came to light at a Baxter haematology advisory board meeting, when a customer mentioned receiving the letter and being rather surprised by it. Given the clear statement from the EMEA that this concern did not relate to fibrin sealants Baxter alleged that this was further misleading promotion of Quixil. Baxter had been unable to obtain a copy of this letter, and given that application of Quixil was almost exclusively limited to surgical operations Baxter questioned the appropriateness of such a letter to anyone other than a surgeon.

Baxter alleged that it was clear that the briefing and the strategy were global initiatives based on a common theme, namely that fibrin sealants that contained aprotinin were less safe than those that

did not. A banner stand for Quixil, used in the UK, included the statement 'Aprotinin free'.

RESPONSE

Johnson & Johnson explained that control of haemostasis was a critical element to ensure successful surgery. Many different approaches to achieving this goal existed including surgical and anaesthetic techniques, local haemostatic devices and pharmacological agents. The health professionals involved in this therapy area included surgeons, other operating theatre staff, pharmacists, haematologists and blood transfusion experts.

The pharmacological agents used as supportive treatments in the control of haemostasis in surgery included fibrin sealants, such as Tisseel and Quixil. Fibrin sealants were not simple chemical entities. Their main components were derived from human plasma. In simple terms, fibrin sealants consisting of a component that was mainly fibrinogen, a component that was mainly thrombin and they might also contain an antifibrinolytic. The antifibrinolytic in Tisseel was bovine aprotinin and that in Quixil was tranexamic acid. When required by the surgeon, these agents were admixed and applied topically to the wound site and formed a stable clot thereby reducing blood loss. Both Tisseel and Quixil were licensed as supportive treatments where standard surgical techniques were insufficient for improvement of haemostasis. Each, in turn, had certain restrictions and warnings on its use but each was effectively licensed for improvement of haemostasis in a range of surgical procedures.

Aprotinin, the active ingredient in Trasylol, was another such medicine which, until its licences were suspended on 7 December 2007 by the MHRA, was licensed to reduce blood loss in certain patients undergoing coronary artery bypass graft surgery. It was also known to be used to reduce blood loss in other unlicensed indications. It was administered intravenously. The MHRA on its website on 29 November 2007 stated, *inter alia*, that a full review of the balance of risks and benefits of aprotinin was underway and that the licences of aprotinin would be suspended from 7 December until further notice. This action had followed results of a study that had been terminated because of an excess of mortality in the aprotinin arm (relative risk of 1.5 compared with both tranexamic acid and aminocaproic acid). Johnson & Johnson noted that the marketing authorization holders for Trasylol, had already voluntarily suspended global marketing of the product (on 6 November 2007) due to safety concerns.

Following the worldwide marketing suspension on 6 November and the MHRA statement on 29 November 2007, health professionals told Johnson & Johnson's representatives about their concerns regarding aprotinin (Trasylol) and of other aprotinin-containing products; Tisseel was specifically mentioned. In many cases, these concerns did not distinguish between aprotinin containing products applied topically in the form of fibrin sealants and aprotinin administered intravenously in the form of Trasylol, a distinction also not made by the MHRA in its statement of 29 November 2007. For example, a consultant surgeon told one of Johnson & Johnson's sales staff that the medical director had emailed all surgeons explaining 'under no circumstances are they to use any product containing aprotinin'. This surgeon viewed this instruction to extend to Tisseel. On 29 November 2007 a cardiac surgeon, who referred to the MHRA alert on aprotinin (Trasylol), told a representative his unit might now have to reconsider the use of fibrin sealants as a supportive treatment.

The potential for confusion of the aprotinin (Trasylol) safety concerns extending to aprotinin containing fibrin sealants was also shown by the EMEA stating in its 'Questions and Answers' document of 21 November 2007 that aprotinin-containing medicines used locally during surgery in sealants were not affected.

Given the confusion concerning the safety of aprotinin in any form and the potential therefore for health professionals to consider that the safety of all fibrin sealants might be affected by the aprotinin (Trasylol) safety concerns, Johnson & Johnson considered it important to reassure its customers that Quixil did not contain bovine aprotinin, especially as Quixil could be an alternative supportive treatment for the improvement of haemostasis in situations where aprotinin (Trasylol) had been used (both in Trasylol's licensed and unlicensed uses). Accordingly Johnson & Johnson felt obliged, firstly, to ensure its staff understood the regulatory situation of aprotinin (Trasylol) and explained the situation to their customers correctly and, secondly, to communicate directly to its customers on the point that the aprotinin (Trasylol) action had no direct effect on Johnson & Johnson's product or indeed on any fibrin sealant.

A copy of the representatives' briefing document was supplied. This gave the regulatory status of aprotinin (Trasylol) and instructed staff to determine how individual hospitals were interpreting this. They were then asked to determine whether this was likely to affect Quixil and to reassure customers that Quixil did not contain bovine aprotinin. They were told not to discuss any aprotinin-containing product other than Trasylol and, should a customer ask about other aprotinin containing products, to refer them to the manufacturer concerned.

In early January 2008, Johnson & Johnson sent a promotional letter to approximately 28,000 of its customers that referred to the aprotinin (Trasylol) safety concerns and the recent regulatory action. These customers consisted mainly of surgeons and pharmacists but included 160 haematologists and 2,100 clinical directors. This letter noted that these regulatory actions were Trasylol specific and did not

affect fibrin sealants, a distinction the company made clear to its sales representatives as early as 13 November 2007.

The email chain referred to by Baxter culminated in an email to Johnson & Johnson dated 15 January 2008 which referred not only to a regulatory safety alert for another product but also to Johnson & Johnson's concerns about possible inappropriate hospitality extended by Baxter staff. Johnson & Johnson would not address this latter matter further in this response.

The email correspondence did continue beyond 15 January 2008. On 16 January 2008, Johnson & Johnson repeated its request for a meeting between the senior medical staff of the companies.

Johnson & Johnson was prepared to show Baxter a copy of its representative' briefing material in order to reassure it of Johnson & Johnson's version of events. Johnson & Johnson did not want to give a hard copy or email copy of this to Baxter as the company was concerned that it would be given to Baxter's marketing and sales departments allowing them to see how Johnson & Johnson addressed its sales staff thereby potentially compromising its commercial competitiveness.

Johnson & Johnson noted that it had repeatedly and unsuccessfully requested the identity of the representative or the hospital concerned. Johnson & Johnson found this surprising since the representative was its member of staff. The effect of this was that Johnson & Johnson was prevented from following up the specifics of Baxter's complaint with the representative concerned.

Johnson & Johnson noted that Baxter had alleged that Johnson & Johnson's use of a regulatory authority safety alert for another product was misleading promotion of Quixil in breach of Clause 7.2. Clause 7.2 stated, *inter alia*, that 'Information, claims and comparisons ... must not mislead either directly or by implication...'.

Johnson & Johnson acknowledged that it used the regulatory authority safety alert to brief its representatives on the issues and the alert was also referred to in a promotional letter sent to appropriate customers. Johnson & Johnson considered that its use of this safety alert was appropriate and was not misleading and it thus denied any breach of Clause 7.2 concerning its use.

Johnson & Johnson noted that although Baxter had referred to the behaviour of one of its staff there was no specific allegation of a breach of the Code in this regard. As stated earlier, Johnson & Johnson was unable to take this aspect of Baxter's complaint further since Baxter would not provide the necessary information. Johnson & Johnson was satisfied that its representatives' briefing material was not misleading and did not advocate a course of action that would bring them into conflict with the Code.

Additionally, Johnson & Johnson noted Baxter's reference to a Quixil banner stand in use in the UK and denied that this banner was misleading in breach of Clause 7.2.

Johnson & Johnson further noted that Baxter referred to activities undertaken in countries outwith the UK. Given the scope of the Code, Johnson & Johnson had not addressed these issues.

PANEL MINUTE

The Panel noted that on 21 November 2007, the EMEA issued a questions and answers document on its recommendation to suspend the marketing authorizations for aprotinin-containing medicines. The first paragraph of the document stated that the Agency's Committee for Medicinal Products for Human Use (CHMP) had concluded that the benefits of systemic formulations of these medicines no longer outweighed their risks and had recommended that all marketing authorizations for these medicines should be suspended throughout Europe. The Agency defined systemic formulations as those which affected the whole body, such as infusions (drips). The document clearly stated in a section headed 'What is Aprotinin?' that 'Aprotinin can also be used locally during surgery, in sealants (glues), to help stop bleeding. These medicines are not affected by this recommendation'.

On 29 November 2007, the MHRA issued a statement entitled 'Aprotinin (Trasylol): Suspension of UK marketing authorisations (licences)'. Unlike the EMEA document the MHRA statement did not differentiate between aprotinin and aprotinin-containing medicines or systemic and local formulations but in that regard the Panel considered that the title of the document made it clear that the statement related solely to Trasylol.

The Panel noted that Johnson & Johnson had acknowledged that there was potential for confusion as to exactly what medicines had been suspended from use. The company had stated that it wanted to ensure that its customers knew that although Trasylol was affected by the suspension of its marketing authorization, there was no effect on Quixil or indeed any fibrin sealant.

The Panel disagreed with Johnson & Johnson's submission that, from as early as 13 November 2007, it had made it clear to its representatives that the regulatory status of Trasylol did not affect fibrin sealants. An email to representatives of 13 November stated 'The potential opportunity for Quixil to be used as an alternative [to Trasylol] is due *not necessarily* (emphasis added) to [Tisseel] containing aprotonin but due to the use of Trasylol as a systemic haemostat'. The Panel considered that this statement would lead the representatives to think that the aprotinin contained in Tisseel *might* be a problem. The email did not clearly make the

distinction between Trasylol and fibrin sealants as submitted. Representatives were instructed to refer questions regarding Tisseel to Baxter as Johnson & Johnson could not comment.

On 4 December 2007, Johnson & Johnson further briefed its representatives on the updated guidance from the MHRA with regard to Trasylol. The powerpoint presentation did not differentiate between systemic and local use of aprotinin nor did it distinguish between aprotinin as in Trasylol or aprotinin-containing medicines such as Tisseel. The briefing material did not refer to the EMEA's statement, which pre-dated the MHRA's statement, namely that sealants, or glues, were not affected by the suspension of the Trasylol licences. Representatives were asked to reassure customers that Quixil did not contain bovine aprotinin and if customers asked about other aprotinin-containing products, they were to be reassured that Quixil was the only fibrin sealant on the market that did not contain bovine aprotinin. A slide headed 'Your briefing instructions' stated that representatives should be prepared to engage on this topic with appropriate customers and should be familiar with the MHRA guidance on Trasylol. Representatives then had to establish whether the customer expected this to affect Quixil, and if so why, and then reassure customers that Quixil did not contain bovine aprotinin. Representatives could not discuss other aprotinin-containing products except Trasylol. If customers asked about such products representatives were to reassure them that Quixil was the only fibrin sealant on the market which did not contain bovine aprotinin.

The Panel considered that the briefing material implied that because it did not contain aprotinin, there was a benefit for Quixil compared with aprotinin-containing sealants ie Tisseel. No data had been submitted to this effect. The Panel considered that by not explicitly informing representatives that the MHRA statement was Trasylol specific and referring to the EMEA statement that sealants or glues were not affected, the briefing material did not reflect the situation clearly and was misleading by implication and following it was likely to lead to a breach of the Code. The Panel noted that Baxter had not alleged a breach of Clause 15.9 of the Code which related to briefing material although this was not surprising as Baxter had not seen the briefing material. Although Clause 15.9 would have been more relevant, given that the briefing material was misleading, the Panel ruled a breach of Clause 7.2 of the Code.

The Panel noted that the letter sent in early January 2008 by Johnson & Johnson, explaining the situation to its customers, was headed 'Quixil Solutions for Sealant (Human Fibrin Sealant)'. This letter emphasised that the marketing suspension and license suspensions of Trasylol were Trasylol specific and did not affect surgical sealants. It also stated that Quixil did not contain aprotinin and there was no implied comparison with sealants which did. The Panel did not consider that the letter was misleading as alleged and no breach of Clause 7.2 of the Code was ruled.

Unlike the letter the exhibition banner did not include information about the current situation with Trasylol. It featured five bullet points about Quixil the final one of which was 'Completely free of animal sourced components – Aprotinin free'. The Panel considered that such a claim implied a benefit for Quixil compared with sealants which contained aprotinin; readers would assume that there was some positive reason for the claim to be made. There was no data to show a clinical benefit for aprotinin- free sealants compared with those that contained aprotinin. The Panel considered that, in the light of the representatives' briefing material discussed above, the balance of probabilities was that the claim would be used to imply a clinical advantage for Quixil which was misleading. A breach of Clause 7.2 the Code of was ruled.

Complaint received **18 March 2008**

Case completed **30 April 2008**

ORPHAN EUROPE v SPECIAL PRODUCTS and CHEMICAL DEVELOPMENTS

Promotion of unlicensed medicines

Orphan Europe complained about the promotion of N-carbamyl-L-glutamic acid powder and anhydrous betaine powder by Special Products and Chemical Developments. Neither product was licensed anywhere in Europe

Orphan Europe stated that in November 2007 both websites, www.specialproducts.biz and www.chemicaldevelopments.com, provided the same and similar information on the products which the site stated, to any visitor to the site, were available to 'buy'. Both websites provided printed materials and the website data sheets for each product, with sections headed 'Therapeutic Indications', listed the medical conditions and patients for which these products were indicated for use. Further information regarding dosages, adverse events, etc was also provided.

As of 19 March 2008, the information was still freely available on the Chemical Developments' website, despite Special Products' letter of 7 January 2008 stating that 'this site has been temporarily removed since December 2007 while we make the appropriate changes'. On the Special Products' website, information regarding N-carbamyl-L-glutamic acid powder appeared to have been removed. However, full prescribing information, advice, indications etc, was still available with regard to anhydrous betaine powder.

Despite inter-company correspondence both Special Products and Chemical Developments continued to proactively make such information openly available. Furthermore, the bold highlighted strapline on Special Products' homepage proclaimed: '"Specials" are unlicensed medicinal products prescribed by doctors when a licensed product for a particular illness does not exist'. Licensed products did exist in the same presentation for the same indications, Carbaglu and Cystadane, for which Orphan Europe SARL was the marketing authorization holder, and which both benefited from special orphan drug status in the EU. The Special Products website was thus misleading to the detriment of Orphan Europe's licensed portfolio.

In Case AUTH/2108/3/08 the Panel noted the submission that Chemical Developments was a chemicals only supplier. The Code applied to the activities of pharmaceutical companies and so the question arose as to whether Chemical Developments could be considered to be a pharmaceutical company subject to the Code.

The Panel noted that the pages of the Chemical Developments' website provided were headed with the picture of, *inter alia*, someone who appeared to be a doctor in that he had a stethoscope around his neck. Text in the heading read 'Our products can be used as Active Pharmaceutical Ingredients (API) to manufacture pharmaceuticals'. It thus appeared that the company did not view its products as pharmaceuticals in their own right. The product description, however, referred to the medical use of the compounds. The Panel considered that the boundary between a chemical supplier and a pharmaceutical company had become blurred. On balance the Panel decided that given the depiction of a health professional and inclusion of medical information for each product, Chemical Developments, via its website, was acting as a pharmaceutical company and was thus subject to the Code.

The website provided information about N-carbamyl-L- glutamic acid and betaine including indications. The Panel considered that the material provided by the complainant dated 19 March 2008 amounted to promotion of medicines which were not the subject of marketing authorizations and ruled a breach of the Code.

The Panel noted the alleged breach of the prohibition in the Code on the use of abbreviated advertisements on the Internet. The advertisements at issue did not include prescribing information. This would not be possible in any event as the products did not have marketing authorizations and thus no summaries of product characteristics (SPCs) upon which to base the prescribing information. In the circumstances the Panel considered the matter was covered by its ruling above.

In Case AUTH/2109/3/08, the Panel noted that on its website, Special Products described itself as a wholesale pharmaceutical company; it had a wholesale dealer's licence issued by the MHRA. The company worked to convert 'specials' into licensed products. Inasmuch as the company was thus working towards selling medicines with marketing authorizations, the Panel considered that Special Products was a pharmaceutical company subject to the Code.

The Panel noted the company's comments in relation to the MHRA guidance about promoting specials. It did not accept Special Products' submissions that the use of a password before being able to access product information meant that Special Products was responding to requests.

The Panel was concerned that the full prescribing information, advice, indications etc was still available for anhydrous betaine powder. Further the statement that specials were unlicensed medicines prescribed when a licensed product did not exist confused matters given there was a licensed product, that of the complainant. The Panel considered that the material in effect promoted a product that did not have a marketing authorization. A breach of the Code was ruled.

The Panel noted the alleged breach of the prohibition in the Code of the use of abbreviated advertisements on the Internet. The advertisements at issue did not include prescribing information. This would not be possible in any event as anhydrous betaine powder did not have a marketing authorization and thus no SPC upon which to base the prescribing information. In the circumstances the Panel considered the matter was covered by its ruling of a breach above.

Orphan Europe complained about the Internet promotion of unlicensed medicines by Special Products Limited and Chemical Developments Ltd. Orphan Europe stated that inter-company correspondence had failed to resolve the issues.

COMPLAINT

Orphan Europe stated that in November both websites, www.specialproducts.biz and www.chemicaldevelopments.com, provided the same and similar information on N-carbamyl-L-glutamic acid powder and anhydrous betaine powder which the site stated, to any visitor to the site, were available to 'buy'. Neither was licensed anywhere in Europe. Breaches of Clauses 3 and 5.2 of the Code were alleged.

In both websites, the printed materials and the website data sheets for each product were provided, each with a section headed 'Therapeutic Indications', under which Special Products and Chemical Developments listed the medical conditions and patients for which these products were indicated for use in treatment. Further information regarding dosages, adverse events, etc was also provided.

As of 19 March 2008, all such information referred to above with regard to each of these products was still freely available on the Chemical Developments' website, despite Special Products' letter of 7 January 2008 stating that 'this site has been temporarily removed since December 2007 while we make the appropriate changes'.

On the Special Products' website, information regarding N-carbamyl-L-glutamic acid powder appeared to have been removed. However, full prescribing information, advice, indications etc, was still available with regard to anhydrous betaine powder, by simply clicking a button that indicated that you desired this information.

Despite inter-company correspondence both Special Products and Chemical Developments were evidently continuing to proactively make such information openly available.

Furthermore, the bold highlighted strapline on Special Products homepage proclaimed: '"Specials" are unlicensed medicinal products prescribed by doctors when a licensed product for a particular illness does not exist'.

With regard to N-carbamyl-L-glutamic acid powder and anhydrous betaine powder being openly promoted by Special Products and Chemical Developments, licensed products did in fact exist in the same presentation for the same indications, namely Carbaglu and Cystadane respectively, for which Orphan Europe SARL held the marketing authorizations; both benefited from a special orphan drug status in the EU.

Therefore, Orphan Europe alleged that the current website of Special Products was misleading to the detriment of its licensed portfolio, and that the continued actions of both Special Products and Chemical Developments represented the advertising and promotion of unlicensed medicines.

RESPONSE

Special Products stated that it would keep Chemical Developments separate from Special Products as it was a chemicals only supplier rather than a specials manufacturer.

Case AUTH/2108/3/08 Chemical Developments Ltd

When Orphan Europe originally complained, Special Products instructed the Malaysian Internet service provider hosting its site to remove it from the web while Special Products corrected the issues that caused the problem – this it did and notified Special Products: 'ChemicalDevelopments.com website was disabled on Thu, Dec 13, 2007 at 11:32PM'.

Special Products tested the website uniform resource locator (URL) and found that it came back with a message: 'This website is temporarily closed for maintenance' and was therefore inaccessible via the www.chemicaldevelopments.com URL to potential viewers.

Unfortunately, and unbeknown to Special Products, the online store could still be accessed through searches on the Internet for a specific product listed in this store if, like Orphan Europe, one knew where to find it. The website was not freely available as alleged. This loophole was closed as soon as Special Products was notified of this complaint and on testing again on 9 April the URL example sent by Orphan Europe could not be accessed. Special Products would review the whole Chemical Developments site to ensure that when it did go online again, it made no medical claims.

Special Products apologised for this oversight.

Case AUTH/2109/3/08 Special Products Ltd

Special Products specialized in the manufacture of 'specials' in accordance with the exemption contained within the Medicines for Human Use (Marketing Authorisation) Regulations 1994.

Guidance from the Medicines and Healthcare products Regulatory Agency (MHRA) on the manufacture and supply of specials stated that 'A specials manufacturer, importer or wholesaler may advertise the service he provides but in particular, "specials" must not be advertised. He may, however, respond to requests for information on specific products'.

Special Products submitted that it adhered to this guidance.

As stated previously, the Special Products website www.specialproducts.biz described the services provided by the company. In order to request information about specific products, a user must be a health professional and register with the website. Only following vetting by Special Products to gain a user name and password could a user access product information. Requests for information on products required a double opt-in approach so that any medical information had to be requested, in compliance with MHRA guidance.

PANEL RULING

Case AUTH/2108/3/08 Chemical Developments Ltd

The Panel noted Special Products' submission that Chemical Developments was a chemicals only supplier. The Code applied to the activities of pharmaceutical companies and so the question arose as to whether Chemical Developments could be considered to be a pharmaceutical company subject to the Code.

The Panel noted that the pages of the Chemical Developments' website provided were headed with the picture of, *inter alia*, someone who appeared to be a doctor in that he had a stethoscope around his neck. Text in the heading read 'Our products can be used as Active Pharmaceutical Ingredients (API) to manufacture pharmaceuticals'. It thus appeared that the company did not view its products as pharmaceuticals in their own right. The product description, however, referred to the medical use of the compounds. The Panel considered that the boundary between a chemical supplier and a pharmaceutical company had become blurred. On balance the Panel decided that given the depiction of a health professional and inclusion of medical information for each product, Chemical Developments, via its website, was acting as a pharmaceutical company and was thus subject to the Code.

The Panel noted that the website provided information about two products, N-carbamyl-L-glutamic acid and betaine. Indications were included. The Panel considered that the material provided by the complainant dated 19 March 2008 amounted to promotion of the medicines which were not the subject of marketing authorizations. Thus the Panel ruled a breach of Clause 3.1.

The Panel noted the alleged breach of Clause 5.2 which, *inter alia*, prohibited the use of abbreviated advertisements on the Internet. The advertisements at issue did not include prescribing information. This would not be possible in any event as the products did not have marketing authorizations and thus no summaries of product characteristics (SPCs) upon which to base the prescribing information. In the circumstances the Panel considered the matter was covered by its ruling of a breach of Clause 3.1.

Case AUTH/2109/3/08 Special Products Ltd

The Panel noted that on its website, Special Products Limited described itself as a wholesale pharmaceutical company; it had a wholesale dealer's licence issued by the MHRA. The company worked to convert 'specials' into licensed products. Inasmuch as the company was thus working towards selling medicines with marketing authorizations, the Panel considered that Special Products was a pharmaceutical company subject to the Code.

The Panel noted the company's comments in relation to the MHRA guidance about promoting specials. It did not accept Special Products' submissions that the use of a password before being able to access product information meant that Special Products was responding to requests.

The complainant stated that this website was similar to that of Chemical Developments.

The Panel was concerned that the full prescribing information, advice, indications etc was still available for anhydrous betaine powder. Further the statement that specials were unlicensed medicines prescribed when a licensed product did not exist confused matters given there was a licensed product, that of the complainant. The Panel considered that the material in effect promoted a product that did not have a marketing authorization. A breach of Clause 3.1 was ruled.

The Panel noted the alleged breach of Clause 5.2 which, *inter alia*, prohibited the use of abbreviated advertisements on the Internet. The advertisements at issue did not include prescribing information. This would not be possible in any event as anhydrous betaine powder did not have a marketing authorization and thus no SPCs upon which to base the prescribing information. In the circumstances the Panel considered the matter was covered by its ruling of a breach of Clause 3.1.

Complaint received	**25 March 2008**
Cases completed	**5 June 2008**

GENERAL PRACTITIONER v PROCTER & GAMBLE AND SANOFI-AVENTIS

Promotion of Actonel Combi by email

A general practitioner complained about an email he had received in March 2008 relating to Actonel Combi (risedronate sodium tablets plus calcium and vitamin D effervescent granules). The product was co-promoted by Procter & Gamble and Sanofi-Aventis and the matter was taken up with both companies.

The complainant stated that the email was singularly inappropriate and a breach of ABPI guidelines. The practice manager who forwarded the complaint stated that the email was unsolicited.

The Panel considered that the email on Actonel Combi was clearly promotional material. Whilst it had not been sent directly by Procter & Gamble or Sanofi-Aventis it was nonetheless an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel noted that an agency had emailed the complainant in February 2008 stating that it would, from time to time, send emails which might include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information. The email thus made it clear that the company intended to send promotional material from pharmaceutical companies. The Panel thus considered that the Actonel Combi email had not been unsolicited. The complainant had given prior, fully informed, consent to receive promotional emails on behalf of pharmaceutical companies. No breach of the Code was ruled.

A general practitioner complained about an unsolicited email (ref ACT 3811) received in March 2008 relating to Actonel Combi (risedronate sodium tablets plus calcium and vitamin D effervescent granules). The product was co-promoted by Procter & Gamble Pharmaceuticals UK Limited and Sanofi-Aventis and the matter was taken up with both companies.

COMPLAINT

The complainant stated that the email was singularly inappropriate and a breach of ABPI guidelines. The practice manager who forwarded the complaint stated that the email was unsolicited.

When writing to the companies, the Authority asked them to respond in relation to Clause 9.9 of the Code.

RESPONSE

Procter & Gamble and Sanofi-Aventis submitted a joint response as The Alliance for Better Bone Health.

The Alliance noted that the email had been sent by an agency which operated a permission-based database requiring physicians to 'opt-in' to receiving information. Procter & Gamble gave the agency a list of GPs who had an interest in osteoporosis and the agency cross referenced this to its own online directory to establish which GPs were also on its database and had therefore completed opt-in consents to receive promotional emails. Subsequently, the agency distributed the email to only the GPs from whom an opt-in statement had been received.

The GPs on the mailing list had therefore opted-in to receive promotional materials and also had an interest in osteoporosis so the material in question was appropriate for the audience with respect to both content and distribution.

Doctors' details were added to the online directory on a clear opt-in basis. In the first instance the doctor would be asked, by telephone, for an e-mail address so that a sign up code for the online directory service could be emailed to them. During the call, doctors were informed that if they signed up, the agency would from time to time email them about their affiliates' product and services which might include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information.

After the telephone call the sign up code would be emailed to the doctor's previously provided personal email address (thus preventing the possibility of a colleague registering on their behalf). This email reiterated that doctors who signed up by registering their details might be sent promotional material: '[the agency] will from time to time send information by e-mail about our affiliates' products and services which may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information'.

In summary, doctors' contact details were only added to the database via a sign up process in which it was clear that doctors who registered might be sent emails promoting pharmaceutical

products. As such there was no unsolicited distribution of a promotional email by The Alliance or any company acting on its behalf and thus no breach of Clause 9.9 of the Code.

In response to a request for further information, and having been told the identity of the complainant, The Alliance stated that the agency reviewed the wording for the validation process on a regular basis (at least six monthly). The wording on the email that the information to be sent '….. may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information.' was added in January 2008 and implemented in mid-February 2008, both in the telephone script and the confirmation email. Following an initial telephone call using the enclosed telephone script, the agency gained verbal agreement from the doctor or contact in surgery to receive a confirmation email that would include a registration form and access code.

The telephone script and confirmation email that were used in a call and sent to the complainant were implemented in mid-February 2008. The confirmation email was sent to the complainant in late February 2008, this email included a web address and access code. The complainant used the web address and code to complete a registration form in early March. A copy of the email that was sent to the complainant in late February 2008 was provided.

PANEL RULING

The Panel noted Clause 9.9 prohibited the use of email for promotional purposes except with the prior permission of the recipient. The Panel considered that the email on Actonel Combi was clearly promotional material. Whilst it had not been sent directly by Procter & Gamble or Sanofi-Aventis it was nonetheless an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel noted that the complainant had been emailed by the agency in late February 2008. The email stated that the agency would, from time to time, send emails which might include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information. The email thus made it clear that the company intended to send promotional material from pharmaceutical companies. The Panel thus considered that the Actonel Combi email sent in mid-March had not been unsolicited. The complainant had given prior, fully informed, consent to receive promotional emails on behalf of pharmaceutical companies. No breach of Clause 9.9 was ruled.

Complaint received **25 March 2008**

Cases completed **20 May 2008**

GENERAL PRACTITIONER v NORGINE

Invitation to a meeting

A general practitioner alleged that the £250, along with hospitality and transport, offered to him by Norgine to attend a 'Managing Constipation Movicol Regional Advisory Forum' was excessive. It simply did not seem tenable that the meeting was necessary or even conceivably of any business value to the company. In the complainant's view this was merely an attempt to pay doctors to promote Movicol using a loophole in the Code.

The Panel noted that the invitation to the meeting in question stated that the honorarium was in recognition of 'your time and input at the meeting'. The invitation stated that Norgine wanted to hear the views of health professionals on the management of chronic constipation and faecal impaction. The company would review current prescribing patterns and discuss any relevant local issues. The Panel considered that the invitation could have been clearer as to the exact nature of the meeting.

The agenda was sent once the invitation was accepted. The meeting would start at 6.30pm with a buffet dinner and then run from 7pm to 9pm. It included an introduction to Norgine (10 minutes), the evidence base for treating constipation (30 minutes) and a review of the therapy area and the laxative market (20 minutes). The latter two sessions included a facilitated group discussion. The final session 'Developing a local action plan: what do Norgine need to be doing?' was a group discussion of 45 minutes.

The report for a similar meeting showed that the event had been interactive. Attendees had identified Issues which would be relevant to Norgine on a national basis. The report included a number of action points for the local Norgine team to follow up.

The Panel noted that the feedback form for the meeting at issue seemed at odds with the purpose of the advisory board. In the Panel's view the main benefit of an advisory board should be to the sponsoring company and not to the delegates. Feedback was requested to ensure that Norgine had met the attendee's needs and expectations. It included questions on the educational content of the meeting and the relevance and interest of the sessions. Delegates were asked whether their management of chronic constipation and faecal impaction was likely to change as a result of the meeting and to identify key take home messages. The Panel considered that in the context of an advisory board such questions might be inappropriate. The context in which the form was presented to the attendees would be important.

Nonetheless the Panel did not consider that the form on its own rendered the meeting inappropriate.

On balance the Panel considered that the arrangements for the meeting were not unacceptable. It was acceptable to pay doctors to attend advisory board meetings. The Panel ruled no breaches of the Code.

The Panel did not accept that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and ruled accordingly.

A general practitioner complained about an invitation (ref MO/07/1118 March 2007) to a 'Managing Constipation Movicol Regional Advisory Forum' to take place in Scotland on 30 May, sent by Norgine Pharmaceuticals Ltd.

COMPLAINT

The complainant alleged that the fees offered to attend the advisory board were excessive at £250, along with hospitality and transport. It simply did not seem tenable that the meeting was necessary or even conceivably of any business value to the company.

In the complainant's view this was merely an attempt to pay doctors to promote Movicol using a loophole in the Code.

When writing to Norgine, the Authority asked it to respond in relation to Clauses 2, 9.1 and 18.1 of the Code.

RESPONSE

Norgine explained that Movicol (macrogol 3350 plus sodium chloride, sodium bicarbonate, and potassium chloride) was a product for chronic constipation and faecal impaction. Despite overwhelming evidence that had accumulated over the past few years, showing that macrogol laxatives like Movicol were more effective and better tolerated than older laxatives, such as lactulose and ispaghula husk, the older laxatives still dominated the market, and Movicol had less than half the market share of lactulose.

In addition, pharmacoeconomic studies showed that Movicol was a dominant treatment compared to lactulose ie not only was Movicol more effective than lactulose, but it also reduced costs. Norgine

decided to convene a number of regional advisory boards primarily to assess if there were any local issues that prevented Movicol achieving a market share commensurate with the current evidence base.

It was clearly essential for Norgine to present the current evidence at the meeting so that all the delegates had the same level of knowledge in order for them to contribute optimally to the meeting.

According to Norgine's advisory board guidelines (copy provided), the advisory board should have a clear objective in relation to the advice required, and should be set up to allow the objective to be met. The objective of any individual meeting determined: the selection of members, who were selected individually on the basis of their knowledge and experience; the number of members, who should represent the different groups managing the disease of interest, and was limited to allow each member to make a meaningful contribution and the number of meetings, dependent on the different management of the disease in different regions.

In practice, the regional manager asked their local sales representatives and NHS liaison managers to nominate possible delegates. Norgine had invited 32 delegates from the local area and planned to have 10 attendees on the night. This relatively small number was designed to ensure that all delegates had a chance to make a significant contribution to the meeting. Lists of the invitees' and attendees' names and addresses would be available after the meeting had taken place. This was the only regional advisory forum planned to be held in Scotland.

The invitations were all sent directly from head office: representatives were not given letters to hand out.

The delegates were a mix of GPs managing the disease of interest, consultants from the local hospitals, PCT representatives (eg pharmacists) and one or two continence advisors who were experienced in managing constipation and faecal incontinence. It was important that all the delegates were knowledgeable in the area, as Norgine was seeking their advice on local prescribing guidelines for constipation (if any), the reason that Movicol was not prescribed first line, what Norgine could do to change prescribing habits in line with the current evidence and any other issues considered important.

In terms of Norgine's advisory board guidelines, it was acceptable to pay advisory board members an honorarium, which should appropriately reflect the amount of time and effort required, and was in keeping with usual professional rates. For the meeting in question £250 (ie £125/hour) was very reasonable and certainly not excessive compared with BMA rates of over £200/hour for private consultation or report writing. Similarly Norgine would pay less per mile than the BMA currently stated. The same fee was payable irrespective of the professional standing of the delegate ie consultants were paid the same as GPs. The invitation made it clear that the honorarium was in recognition of the individual's time spent on, and input to, the meeting. No work prior to the meeting was asked for. The honorarium did not include any travelling time, nor did it account for the fact that the meeting took place outside of normal working hours. The advisory board was run for the benefit of the company, with advice on local prescribing practices provided as a professional service, in the same way that professional advice and services were provided to patients on health matters. The meetings were very interactive. The delegates participated in every session, asking questions, giving their opinions, and offering advice.

The hospitality for the forum would consist of a buffet dinner, which would last half an hour. No alcohol would be provided. If delegates required overnight accommodation because they had far to travel, this would be provided at the hotel by Norgine. The venue would be a local 4 star hotel.

Norgine stated that two national advisory boards were held in England in 2006 and one in 2007.

Copies were provided of the presentations used at the Movicol regional advisory forum in Ireland in April, which would be adapted for the meeting in Scotland. As the Scotland meeting was scheduled for May, Norgine had not yet finalised the presentations for the meeting. The meeting in Ireland would not be identical to the meeting in Scotland, as it referred to Irish market shares and Irish products, but it gave a reasonable idea as to what would be presented in Scotland.

Norgine submitted that the meeting summary report of a previous Movicol regional advisory forum held in England in February, clearly illustrated the level of lengthy and interesting discussions, as well as the sound advice and feedback on the local situation that was provided to the company. The actions noted clearly demonstrated that these regional advisory forums were of significant advisory value to Norgine. In addition to a meeting summary report, an audio recording was also made of all advisory meetings which reinforced the genuine advisory nature of these meetings.

In conclusion, Norgine believed that the regional advisory forum to be held in Scotland was a genuine advisory meeting of real business value to Norgine, and did not amount to offering a pecuniary advantage to induce the prescription of a medicine. It was made clear that the honorarium offered was for the input into the meeting expected from the delegates, and the amount was reasonable for providing input to a meeting held outside normal working hours.

Norgine also believed that the arrangements for the meeting were of a high standard. This was reflected

inter alia by the fact that a limited number of delegates were invited, and all invitations were personal invitations from the medical director of Norgine. Also Norgine believed that appropriate subsistence was to be provided to delegates, and the venue was not a lavish hotel, which would in itself be attractive to delegates.

Norgine regretted that the GP in question would not be attending the meeting. If he or she were to attend, Norgine was confident that they would be reassured about the genuine advisory nature of the meeting, and that the honorarium was commensurate with the input expected from them.

In response to a request for further information Norgine stated that it had already held one Movicol regional advisory forum this year and two others were planned, including the meeting that was the subject of this complaint. Approximately ten delegates were expected to attend each meeting, giving a total of thirty for the three meetings.

The success of the Movicol national advisory boards was measured by the qualitative outputs from these three meetings (see below) as reflected in the meeting summary reports. Direct quotes from these meeting reports were as follows:

> 'The multidisciplinary group provided a well rounded discussion and valuable insight in to the different issues effecting each of the delegates' specialities'. (April 2006)
>
> 'The meeting was a great success with some lengthy and interesting discussion, and the delegates offering sound advice and feedback to Norgine'. (July 2006)
>
> 'This was a highly successful meeting, with good discussion and a well engaged group….. The second Movicol National Advisory Board centred around updating the delegates on the progress of recommendations made in the first meetings, as well as discussion around the key challenges in patient management and the development of constipation in patient management and the development of constipation care pathways in both primary and secondary care'. (December 2006).

It was also inevitable that the Norgine personnel present at the advisory board meeting formed their own views as to how beneficial the meeting had been to the company. Further meetings would not have taken place had senior managers not been convinced that these national meetings were a success in respect of the value of the advice they delivered to Norgine. No other metrics, including quantitative measures, were used to evaluate these meetings, nor would they be for the two further meetings planned.

Delegates to the national meetings were drawn from all parts of the UK. Participants were recruited on the basis of their expertise and experience rather than their geographic location.

As far as the specific recommendations which led to the plan to have regional advisory boards was concerned, the following statement appeared in the meeting summary report of the meeting in July 2007:

> '[A named person] updated the group on the progress Norgine has made with the recommendations from the group, including the Regional Advisory Forums, patient and professional group liaison, and educational materials and meetings'.

PANEL RULING

The Panel considered that there was a difference between holding a meeting for health professionals and employing them to act as consultants. It was acceptable for companies to arrange advisory board meetings and the like and to pay health professionals and others for advice on subjects relevant to the products they promoted. Nonetheless the arrangements for such meetings had to comply with the Code. The requirements as to hospitality being of a reasonable standard etc, as set out in Clause 19 of the Code had to be followed. The company must be able to justify the number of meetings held. The choice and number of delegates should stand up to independent scrutiny; each should be chosen according to their expertise such that they would be able to contribute meaningfully to the purpose and expected outcomes of the meeting. The number of delegates at a meeting should be limited so as to allow active participation by all. The agenda must allow sufficient time for feedback and input by the delegates. Invitations to participate in an advisory board meeting should clearly state the purpose of the meeting, the expected role of the invitees and the amount of work to be undertaken; it should be clear that any honorarium offered was a payment for such work and advice.

The invitation to the meeting in question stated that the honorarium was in recognition of 'your time and input at the meeting'. The invitation stated that Norgine wanted to hear the views of health professionals on the management of chronic constipation and faecal impaction. The company would review current prescribing patterns and discuss any relevant local issues. The Panel considered that the invitation could have been clearer as to the exact nature of the meeting.

The agenda was sent once the invitation was accepted. The meeting would start at 6.30pm with a buffet dinner and then run from 7pm to 9pm. It included an introduction to Norgine (10 minutes), the evidence base for treating constipation (30 minutes) and a review of the therapy area and the laxative market (20 minutes). The latter two sessions included a facilitated group discussion. The final session 'Developing a local action plan:

what do Norgine need to be doing?' was a group discussion of 45 minutes. The slides for the meeting held in Ireland gave a breakdown of the laxative market as well as comparing Movicol, Lactulose and Fybogel.

From the report for a recent Regional Advisory Forum it appeared that the meeting had been interactive with comments in the report attributed to various attendees. Issues had been identified by the attendees which would be relevant to Norgine on a national basis. The Panel noted that the meeting report included a number of action points for the local Norgine team to follow up.

The Panel noted that the feedback form for the meeting at issue seemed at odds with the purpose of the advisory board which was to provide Norgine with information. In the Panel's view the main benefit of an advisory board should be to the sponsoring company and not to the delegates. Feedback was requested to ensure that Norgine had met the attendee's needs and expectations. It included questions on the educational content of the meeting and the relevance and interest of the sessions. Delegates were asked whether their management of chronic constipation and faecal impaction was likely to change as a result of the meeting and to identify key take home messages. The Panel considered that in the context of an advisory board such questions may be inappropriate. The context in which the form was presented to the attendees would be important. Nonetheless the Panel did not consider that the form on its own rendered the meeting inappropriate.

On balance the Panel considered that the arrangements for the meeting were not unacceptable. It was acceptable to pay doctors to attend advisory board meetings. The Panel ruled no breach of Clause 18.1 of the Code and thus no breach of Clause 9.1.

The Panel did not accept that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and ruled accordingly.

Complaint received **26 March 2008**

Cases completed **25 May 2008**

CASE AUTH/2114/4/08

PRACTICE PHARMACIST v RECKITT BENCKISER HEALTHCARE

Gaviscon Advance journal advertisement

The practice pharmacist at a medical centre complained about the strapline 'Reflux super-suppressant' in an advertisement for Gaviscon Advance (sodium alginate/potassium bicarbonate), issued by Reckitt Benckiser Healthcare, which had appeared in the BMJ. The complainant considered that 'super' implied either a comparison to other reflux suppressants, yet this was not justified or referenced in the advertisement, or that the product was of a higher quality than alternative, again this was not qualified or referenced.

The Panel considered that describing Gaviscon Advance as a super-suppressant implied that it had qualities/properties well beyond those associated with other reflux suppressants. This was a very strong and broad claim for general superiority. The question was, could such a claim be substantiated?

The advertisement referred to the use of Gaviscon Advance in hoarseness, cough and sore throat associated with laryngopharyngeal reflux. In that regard the Panel noted that Gaviscon Advance was the only reflux suppressant to be so licensed. Further, data submitted by Reckitt Benckiser showed that in terms of raft strength and resilience and duration of action Gaviscon Advance was better than other products tested. The Panel noted, however, that not all the available reflux suppressants had been examined. The Panel also noted, *inter alia*, some of the features of Gaviscon Advance which Reckitt Benckiser submitted were unique were only unique inasmuch as relevant data had not been generated for the other products. For instance, although the company stated that Gaviscon Advance did not affect the bioavailability of proton pump inhibitors, no data was provided to show the converse for all other alginates – it appeared that Gaviscon Advance was the only product for which there was relevant data.

On balance the Panel considered that the strapline 'reflux super-suppressant' was a claim for general superiority which could not be substantiated. The Panel also considered that the claim was misleading. Breaches of the Code were ruled.

Although noting its rulings above, the Panel did not consider that high standards had not been maintained.

The practice pharmacist at a medical centre complained about an advertorial for Gaviscon Advance (sodium alginate/ potassium bicarbonate) issued by Reckitt Benckiser Healthcare (UK) Limited, which had appeared In the BMJ on 5 April. Below the depiction of a bottle of Gaviscon Advance was the strapline 'Reflux super-suppresant'.

COMPLAINT

The complainant considered that 'super' implied one of two things. Either there was a comparison to other reflux suppressants, yet this was not justified or referenced elsewhere in the advertisement, or the product was of a higher quality than alternative, again this was not qualified or referenced.

The complainant alleged breaches of Clauses 7 and 9 of the Code.

When writing to Reckitt Benckiser to inform it of the complaint, the Authority asked it to consider the requirements of Clauses 7.2, 7.4, 7.10 and 9.1.

RESPONSE

Reckitt Benckiser considered that both of the complainant's concerns related to 'super-suppressant' being a comparative claim. Reckitt Benckiser disagreed; the term 'super' was not itself a comparative claim, in this context it was merely a statement about the efficacy of the product in the same way that numerous products claimed 'great' and 'excellent' efficacy. This was supported by the new licensed indication covering 'symptoms of laryngopharyngeal reflux such as hoarseness and other voice disorders, sore throats and cough' which complemented the existing indication for 'gastro-oesophageal reflux'. In addition, the licence now also covered use along with acid suppression therapy. All of these licence extensions were clearly stated on the advertisement. As such Gaviscon Advance presented a comprehensive or 'super' treatment for the symptoms of reflux. Hence, the use of term 'super' in this advertisement was a statement about the product's comprehensive efficacy and not a comparative claim.

Despite the above, even if 'super-suppressant' was considered a comparative claim, the licensed particulars, the method of action and the clinical and *in vitro* data for Gaviscon Advance would still support and justify it. The term 'super' did not mean the best, it was not an exaggeration, nor an all embracing claim, it simply meant very good. Gaviscon Advance could justify 'super' and 'very good' since it had the most comprehensive indications for the treatment of the symptoms of reflux, with the 'treatment of the symptoms of

laryngopharyngeal reflux such as hoarseness and other voice disorders, sore throats and cough' being unique to the product. 'Super' was also supported by both clinical and *in vitro* data where Gaviscon Advance had demonstrated superior properties to other available reflux suppressants.

Reckitt Benckiser explained that Gaviscon Advance was a 'second generation' alginate reflux suppressant indicated for the symptomatic relief of gastro-oesophageal reflux. Gaviscon Advance contained the active ingredients, per 10ml dose, sodium alginate (1000mg) and potassium bicarbonate (200mg), which was double the concentration of sodium alginate compared with other available alginates such as Liquid Gaviscon.

Gaviscon Advance did not work via systemic absorption; it had a physical mode of action, whereby on contact with the gastric contents sodium alginate reacted to form an alginic acid gel. The gel then entrapped carbon dioxide, produced by reaction of potassium bicarbonate with acid in the stomach, forming a buoyant aerated raft that floated on top of the stomach contents and prevented gastric reflux into the oesophagus. The raft might also be refluxed preferentially into the oesophagus where, by virtue of its neutral pH, it protected the oesophageal mucosa from corrosive attack. Gaviscon Advance also contained calcium carbonate as an excipient which provided calcium ions that strengthened the alginate raft by cross-linking within it.

Gaviscon Advance was proven to form a stronger and more resilient raft than other alginates and that it was effective in suppressing acid reflux to relieve the symptoms of gastro-oesophageal reflux. Gaviscon Advance was also proven to reside in the stomach for longer than some other alginates; 4 hours compared with 2 hours for Peptac and Acidex. The unique qualities of Gaviscon Advance included the indications for symptomatic relief of laryngopharyngeal reflux and the concomitant prescribing with proton pump inhibitors, Gaviscon Advance was also the only alginate proven to protect the oesophagus from damage by bile and pepsin.

Reckitt Benckiser therefore believed that there were no breaches of Clauses 7.2, 7.4 or 7.10, since there was no unfair comparison, the claim was fair, balanced and capable of substantiation, there was no undue exaggeration, and there was no information that would have a negative effect on rational prescribing. As such there had also not been any breach of Clause 9.1, since high standards had been maintained and this was further confirmed by the fact that this was an isolated complaint, and that other professionals viewing this advertisement had understood the meaning and intent of the claim.

PANEL RULING

The Panel considered that describing Gaviscon Advance as a super-suppressant implied that it had qualities/properties well beyond those associated with other reflux suppressants. This was a very strong and broad claim for general superiority. The question was, could such a claim be substantiated?

The advertisement in question referred to the use of Gaviscon Advance in hoarseness, cough and sore throat associated with laryngopharyngeal reflux. In that regard the Panel noted that Gaviscon Advance was the only reflux suppressant to be so licensed. Further, data submitted by Reckitt Benckiser showed that in terms of raft strength and resilience, Gaviscon Advance was better than other products tested. The Panel noted, however, that not all the available reflux suppressants had been examined. Similarly, although the duration of action of Gaviscon Advance was longer than other products it had only been compared with four other agents. The Panel also noted Reckitt Benckiser's submission that Gaviscon Advance was the only alginate indicated for treatment of the symptoms of gastro-oesophageal reflux during concomitant treatment with or following withdrawal of acid suppressing therapy. There was no specific mention in the summary of product characteristics (SPC) of proton pump inhibitors in this regard. Some of the features of Gaviscon Advance which Reckitt Benckiser submitted were unique were only unique inasmuch as relevant data had not been generated for the other products. For instance, although the company stated that Gaviscon Advance did not affect the bioavailability of proton pump inhibitors, no data was provided to show the converse for all other alginates – it appeared that Gaviscon Advance was the only product for which there was relevant data.

On balance the Panel considered that the strapline 'reflux super-suppressant' was a claim for general superiority which could not be substantiated. Breaches of Clauses 7.10 and 7.4 were ruled. The Panel also considered that the claim was misleading. A breach of Clause 7.2 was ruled.

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

Complaint received **7 April 2008**

Case completed **28 May 2008**

CASE AUTH/2116/4/08

GENERAL PRACTITIONER v RECKITT BENCKISER HEALTHCARE

Unsolicited email about Gaviscon Advance

A general practitioner who had complained previously about receiving unsolicited emails (Cases AUTH/2083/1/08, AUTH/2088/1/08 and AUTH/2089/1/08) further complained that he continued to receive spam emails despite having opted-out of the email service.

The Panel noted that the Code prohibited the use of email for promotional purposes except with the prior permission of the recipient. The Panel considered that the email on Gaviscon Advance was clearly promotional material. Whilst it had not been sent directly by Reckitt Benckiser it was nonetheless an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel noted that, following previous complaints by the complainant about unsolicited promotional emails, he had asked for his details to be removed from the agency's database. The agency failed to do this and thus as a result of retaining his details, and presumably unbeknown to Reckitt Benckiser, the email promoting Gaviscon Advance was sent, unsolicited, to the complainant. The Panel noted the circumstances of this case and considered that Reckitt Benckiser had been badly let down by the third party working on its behalf. A breach of the Code was ruled.

A general practitioner, who had complained previously about unsolicited promotional emails (Cases AUTH/2083/1/08, AUTH/2088/1/08 and AUTH/2089/1/08), further complained that despite opting-out of the email service offered by an agency he had continued to receive spam emails. The email now in question promoted Gaviscon Advance and had been sent on behalf of Reckitt Benckiser Healthcare.

When writing to Reckitt Benckiser to inform it of the complaint the Authority asked it to consider the requirements of Clause 9.9 of the Code.

RESPONSE

Reckitt Benckiser submitted that it had sent the email in question via an agency that provided education and pharmaceutical industry sponsored promotional material to prescribers in the NHS. All material sent to prescribers by the agency by an opt-in system. Prior permission of the recipient was sought before promotional material was sent electronically. The agency's policy in this regard was provided.

Reckitt Benckiser discussed the proposed email with the agency. In January 2008, after checking that only health professionals who had opted-in would be emailed, Reckitt Benckiser decided to work with the agency. Material provided by the agency to Reckitt Benckiser when the company decided to use the agency to email promotional material to opted-in prescribers was supplied.

The agency advised Reckitt Benckiser that it sent out a number of different emails which were considered to be educational and diagnostic tools by clinicians. Some of these communications involved a sponsorship element, and Reckitt Benckiser sponsored the email in question.

Reckitt Benckiser noted that although it supplied the information for the section of the email dealing with Gaviscon Advance, it did not sponsor the entire email. The major proportion of the content, including the independent article, was written and wholly managed by the agency which had full editorial control and copyright for same.

On 29 January 2008, the agency was notified of a complaint by the complainant who had given instructions to unsubscribe him from the electronic database and mailing list. The complainant had previously opted-in to receive emails from the agency, but since 29 January had requested that his details be removed from the database. The agency assured him it would do so. However, the individual who usually headed up the data division was on leave and a much junior person was asked to remove the complainant's name from the database. To clarify the opt-out position, the individual telephoned the complainant's group practice to establish whether all the doctors wished to be removed from the database. This junior individual was confused by the instructions received as all the other doctors at the practice wanted to remain on the recipient list. The complainant's name was therefore not removed from the database list and it was unfortunate that he received further emails from the agency which included a sponsored element about Gaviscon Advance.

When this was raised with the agency, it sent a letter of apology and explanation to the complainant. The agency also stated that it should take full responsibility for this misunderstanding and not Reckitt Benckiser.

Reckitt Benckiser submitted that this had been a genuine misunderstanding and error by the agency. Reckitt Benckiser had carried out the necessary due

diligence to establish that the agency had prior agreement from clinicians to receive the email in question.

Reckitt Benckiser therefore believed that in this instance, it had not breached Clause 9.9 of the Code.

PANEL RULING

The Panel noted that Clause 9.9 prohibited the use of email for promotional purposes except with the prior permission of the recipient. The Panel considered that the email on Gaviscon Advance was clearly promotional material. Whilst it had not been sent directly by Reckitt Benckiser it was nonetheless an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel noted that, following previous complaints by the complainant about unsolicited promotional emails, he had asked for his details to be removed from the agency's database. That task was given to a junior member of staff who became confused and, in error, left the complainant's details on the database. As a result of retaining these details, and presumably unbeknown to Reckitt Benckiser, the email promoting Gaviscon Advance was sent to the complainant.

The Panel noted that the complainant had stated that he did not want to receive promotional emails; the email in question was thus unsolicited. The Panel noted the circumstances of this case and considered that Reckitt Benckiser had been badly let down by the third party working on its behalf. A breach of Clause 9.9 was ruled.

Complaint received **21 April 2008**

Case completed **30 May 2008**

CASE AUTH/2118/4/08

LIFEBLOOD: THE THROMBOSIS CHARITY v BOEHRINGER INGELHEIM

Pradaxa press release

Lifeblood: The Thrombosis Charity complained about a press release about Pradaxa (dabigatran etexilate) which it stated had been issued by a media advisor acting for Boehringer Ingelheim.

Lifeblood stated that the press release appeared to have come from it. Lifeblood did not, nor would it, its trustees or its medical director, ever issue any press release which endorsed or appeared to endorse a specific product.

In other press releases concerning Pradaxa, Lifeblood discussed the area generally and did not endorse the product directly.

It was the policy of Lifeblood to remain independent. When there were advances in the prevention and treatment of thromboembolic disease, the trustees including the medical director took great care not to give specific endorsements. Any statements sought from the trustees, or the medical director, were deliberately couched in neutral terms to welcome the advance but not to endorse the product. No payment was accepted for participating in any press releases, and all releases were vetted to ensure that the neutrality was preserved. Lifeblood, and in particular its medical director, were not given sight of the press release in question, the opportunity to comment on its content or asked for consent to publish the press release.

Three trustees of Lifeblood were health professionals who were active on the National Institute for Health and Clinical Excellence (NICE) committees. NICE was in the midst of determining what the NHS best practice should be in this field.

The impartiality of those trustees, and of Lifeblood, was of paramount importance, for without it the charity's credibility as a lobbying force, and any research it commissioned would be tainted. This was of particular concern when dealing with any of the multinational pharmaceutical companies which were competitively and aggressively pursuing an alternative to warfarin.

Lifeblood's medical director was invited by Boehringer Ingelheim to participate in media interviews, the day that Pradaxa (the new oral anticoagulant) was launched in April 2008. Boehringer Ingelheim was fully aware of the necessity for Lifeblood to remain impartial.

Boehringer Ingelheim offered to pay Lifeblood and its medical director for the time she spent participating in media interviews, but this was declined.

The press release at issue had placed Lifeblood in a very difficult position, for it compromised its apparent integrity and impartiality. Reputation and trust were very hard won, and very easy to lose. In this instance the irresponsible publication of an unauthorised press release had placed its reputation in jeopardy.

This press release was not known about, or sanctioned, by Lifeblood. Its content was completely unacceptable and appeared designed to cynically manipulate public opinion and market forces – at the expense of Lifeblood and its medical director – for the benefit of those promoting Pradaxa.

The Panel noted that it was a clearly established principle under the Code that a company was responsible for the actions of third parties employed on the company's behalf even if that third party acted outside the instructions from the pharmaceutical company.

The Panel considered that Boehringer Ingelheim had been very badly let down by a subcontractor to its agency who had not followed the agreed procedures regarding prior approval of material. This was of serious concern. The agency had subcontracted the media advisor. Neither the agency nor Boehringer Ingelheim knew why the approved press release had been amended without reference or approval from either the agency or Boehringer Ingelheim.

The effect of the actions of the consultant to the agency were extemely serious. Quotations were used in an inappropriate manner ie the quotations did not reflect the meaning of the author and formal permission had not been obtained. Thus the Panel ruled breaches of the Code. The Panel also considered that the quotation attributed to Lifeblood's medical director was not in line with the authorized indications for Pradaxa as it did not state that it was for use after elective surgery; the material was thus misleading and inaccurate in this regard. A breach of the Code was ruled.

The Panel considered that it was particularly important when working with third parties such as patient organisations that all materials were in accordance with the Code. This was even more important when working on a new product as all such materials had to be prevetted by the Medicines and Healthcare Products Regulatory Agency (MHRA).

The Panel noted the circumstances of this case. Boehringer Ingelheim had a procedure for approving press releases and its contract with the agency stated that material had to be submitted to the company for written approval before release. The contract further stated that the agency should comply with all codes of practice. According to Boehringer Ingelheim's submission the agency had used an experienced subcontractor, trained on the Code, who had acted entirely outside the contract and without the knowledge of either the agency or Boehringer Ingelheim. It was difficult to see what more Boehringer Ingelheim could have done. The Panel considered that as Boehringer Ingelheim had procedures and processes in place to ensure compliance with the Code and had been so very badly let down by a third party there was no breach in relation to the requirements to maintain high standards and not to bring discredit upon the pharmaceutical industry.

Lifeblood: The Thrombosis Charity complained about a press release about Pradaxa (dabigatran etexilate) which it stated had been issued by a media advisor acting for Boehringer Ingelheim Limited.

Paraxa was indicated for the primary prevention of venous thromboembolic events in adult patients who had undergone elective total hip replacement surgery or total knee replacement surgery.

COMPLAINT

Lifeblood stated that the press release appeared to have come from it. Lifeblood did not, nor would it, its trustees or its medical director, ever issue any press release which endorsed or appeared to endorse a specific product.

In other press releases concerning Pradaxa, Lifeblood discussed the area generally and did not endorse the product directly. For example, in one of the press releases from Boehringer Ingelheim the following was stated:

> '[A named] Consultant Haematologist and Medical Director of the UK thrombosis charity, Lifeblood commented,
>
> "The prevention of blood clots with blood thinners after orthopaedic surgery is not done well in the UK. One of the problems is that the current blood thinners can only be given as an injection. We therefore very much welcome the arrival of a tablet for adults undergoing elective hip and knee surgery. The need for, and the potential impact of a generally well tolerated oral anticoagulant that does not require monitoring is profound"'.

Lifeblood was an independent charity founded just over five years ago; its objectives were to increase awareness of thrombosis among the public, and health professionals, and to raise research funds to improve patient care through improved prevention and treatment of venous thromboembolic disease. Lifeblood worked closely with the National Institute for Health and Clinical Excellence (NICE), an All Party Parliamentary Health Select Committee, the Department of Health, the Government, the Scottish and Welsh Assemblies, National Health trust hospitals and primary care trusts in the furtherance of these aims.

It was the policy of Lifeblood to remain independent. When there were advances in the prevention and treatment of thromboembolic disease, the trustees including the medical director took great care not to give specific endorsements. Any statements sought from the trustees, or the medical director, were deliberately couched in neutral terms to welcome the advance but not to endorse the product. No payment was accepted for participating in any press releases, and all releases were vetted to ensure that the neutrality was preserved. Lifeblood, and in particular its medical director, were not given sight of the press release in question, the opportunity to comment on its content or asked for consent to publish the press release.

Three trustees of Lifeblood were health professionals who were active on NICE committees. NICE was in the midst of determining what the NHS best practice should be in this field.

The impartiality of those trustees, and of Lifeblood, was of paramount importance, for without it the charity's credibility as a lobbying force, and any research it commissioned would be tainted. This was of particular concern when dealing with any of the multinational pharmaceutical companies who were competitively and aggressively pursuing an alternative to warfarin.

Lifeblood's medical director, was invited by Boehringer Ingelheim to participate in media interviews, the day that Pradaxa (the new oral anticoagulant) was launched in April 2008. Boehringer Ingelheim was fully aware of the necessity for Lifeblood to remain impartial.

Boehringer Ingelheim offered to pay Lifeblood's medical director for the time she spent participating in media interviews, but this was declined for it would cause a conflict of interest which would compromise her status as an independent consultant haematologist within NICE and as medical director of Lifeblood. Boehringer Ingelheim had offered to make payments direct to Lifeblood, but this offer would also be declined, for it would compromise the integrity of the charity.

The press release at issue had placed Lifeblood in a very difficult position, for it compromised its apparent integrity and impartiality. Reputation and trust were very hard won, and very easy to lose. In this instance the irresponsible publication of an unauthorised press release had placed its reputation in jeopardy.

This press release was not known about, or sanctioned, by Lifeblood. Its content was completely unacceptable and appeared designed to cynically manipulate public opinion and market forces – at the expense of Lifeblood and its medical director – for the benefit of those promoting Pradaxa.

When writing to Boehringer Ingelheim the Authority asked it to respond in relation to Clauses 2, 9.1, 11.2, 11.3 and 20.2 of the Code.

RESPONSE

Boehringer Ingelheim stated that it planned a media awareness campaign at the time of launch of Pradaxa and contracted an agency, to provide media contact and implement the campaign.

Two press releases, one for the medical profession (ref DBG1128) and one for the public (ref DBG1129) were the core items of this campaign and Boehringer Ingelheim additionally produced disease awareness (ref DBG1130) and Pradaxa related fact sheets (ref DBG1131) to be distributed alongside the press releases to provide additional information if needed. Within the two press releases quotations from Lifeblood's medical director, for which she had given her prior approval to the agency, were faithfully reproduced.

All of these press materials were factual and presented in a balanced way and were approved by Boehringer Ingelheim according to the standard operating procedure (SOP) Approving Communication Materials. In addition, all press materials were pre-vetted by the MHRA and its comments were incorporated into the final versions.

Approved press releases were released to the agency on headed Boehringer Ingelheim paper and it was clear that the two press releases were issued by Boehringer Ingelheim.

The contract between Boehringer Ingelheim and the agency clearly stated the agency's responsibility in activities undertaken on behalf of Boehringer Ingelheim. Specifically, the contract stated in:

> 'Clause 4.2: All campaign materials are to be submitted by the Agency for Boehringer Ingelheim approval. Such approval is the Agency's authority to proceed.'
>
> 'Clause 4.5: The Agency commits to comply with all relevant legislation and codes of practice.' (The codes were defined to include the ABPI Code, amongst others).
>
> 'Clause 5.4: The Agency warrants that it will use due skill and a professional standard of care.'

The agency subcontracted a media advisor to conduct this media activity on its behalf. The media advisor had worked for many years as a healthcare media relations consultant and was previously public relations director at another pharmaceutical company. The media advisor was not directly employed by Boehringer Ingelheim.

The media advisor, for reasons that were entirely unclear to Boehringer Ingelheim and to the agency, changed the approved press release without reference to Boehringer Ingelheim or the agency, without seeking any form of approval for the amended release. This altered press material was the subject of the complaint and was sent to the Daily Telegraph, the Daily Express, the Daily Mail and the BBC. The Daily Mail received material headed 'from thrombosis charity Lifeblood' and the BBC received material headed 'from Lifeblood'. This altered material was neither created nor approved by Boehringer Ingelheim. Other news organisations received the approved press release. At no stage during the creation and finalisation of the approved press releases did Boehringer Ingelheim alter or ask the agency to alter Lifeblood's medical director's quotation, without her permission.

Therefore, in relation to clause 4.2 of the contract referred to above, no approval was issued by Boehringer Ingelheim for the agency, or its subcontractor, to proceed with disseminating this unauthorised press material.

Boehringer Ingelheim disagreed that the material was issued by '[a named media advisor] acting on behalf of Boehringer Ingelheim', when the media advisor and/or the agency were acting totally outside the scope of their authority and instructions. Boehringer Ingelheim was extremely disappointed by these events and could not understand why an experienced consultant such as the media advisor would have changed the approved release, or issued an amended version without seeking the approval of Boehringer Ingelheim.

Since Boehringer Ingelheim was made aware of this situation the following actions had been taken:

- The agency required to remove the media advisor from PR activity.
- The agency asked for records of the media advisor to ascertain to whom the press material was sent.
- Meeting between Lifeblood's medical director, the agency and Boehringer Ingelheim to fully understand events.
- Meeting with Lifeblood trustees, the agency and Boehringer Ingelheim to understand their concerns.
- Communication with Lifeblood, sharing with it an internal Boehringer Ingelheim statement to be used to address enquiries regarding relationship of Boehringer Ingelheim and Lifeblood.
- The agency directed to have no direct contact with Lifeblood during the complaint process.
- Lifeblood informed about the agency's investigation.
- Boehringer Ingelheim took initial steps to contact the ABPI itself, because of concerns about the unauthorised materials.

Boehringer Ingelheim strongly believed that throughout the process of preparation, approval and release of its press releases it had maintained high standards and that through its procedures had complied with the Code. If, which was not admitted, there was found to have been a breach of the Code, Boehringer Ingelheim did not accept that it was party to any act, omission or default which led to such a breach.

In spite of robust internal approval processes for these press releases and a clear contractual requirement that the agency get all materials approved, and an explicit requirement that it comply with the Code, a press release was issued that had been subsequently amended after final certification by Boehringer Ingelheim.

In the ordinary course, if a pharmaceutical company instructed an agency to issue a press release, knowing that it did not comply with the Code, one would fully expect a breach of the Code to be found. However, the facts of this case were materially different. In this case, Boehringer Ingelheim did everything to comply with the legal and regulatory requirements. It was therefore difficult to see how Boehringer Ingelheim could have prevented this irresponsible and totally unexpected activity.

In light of these events Boehringer Ingelheim would undertake an internal review to investigate if and how contracts etc with agencies could be amended, or if other action could be taken to reduce the risk of a similar situation ever arising again.

Boehringer Ingelheim submitted that, if a breach of the Code occurred, it was due to the agency and/or its sub-contractor acting totally beyond the scope of their or his authority and brief, effectively being 'on a frolic of their or his own'. In such circumstances, Boehringer Ingelheim should not be found to be in breach of the Code.

If, which was not admitted, a breach of the Code was found to have occurred, despite the absence of fault on the part of Boehringer Ingelheim, the company trusted that it would be treated in the most lenient manner possible, having regard to the mitigating factors referred to above.

In relation to Clause 2, Boehringer Ingelheim submitted that it had not brought discredit to, or reduced confidence in the pharmaceutical industry. The unauthorised press materials were issued without any reference to, or knowledge of, Boehringer Ingelheim and without the knowledge of the agency, by an experienced person who was thought to be (and given their background and recent compliance training with the agency should have been) fully aware of the Code. As soon as Boehringer Ingelheim knew of the circumstances it investigated the matter and apologised to Lifeblood for what had occurred. Indeed, Boehringer Ingelheim had already made a preliminary contact with the ABPI before the complaint was received.

Boehringer Ingelheim held Lifeblood, its trustees and medical director in the highest regard and would not wish to do anything to affect their impartiality and integrity. Boehringer Ingelheim had been scrupulous in ensuring that all necessary approvals were obtained and was satisfied that the authorised press releases complied with the Code and all other requirements. Since the matter came to light, Boehringer Ingelheim had acted promptly and in the best interests of Lifeblood and the industry.

In this regard, Boehringer Ingelheim felt it must deal with two particular points made by Lifeblood in its complaint.

The first was where Lifeblood referred to the 'irresponsible publication of an unauthorised article'. Boehringer Ingelheim objected to the reference of 'irresponsible' being used in relation to a complaint against Boehringer Ingelheim. As it hoped it had shown, Boehringer Ingelheim had behaved in a very responsible manner throughout and deeply regretted the media advisor's actions which were taken without Boehringer Ingelheim's knowledge or authority.

Secondly, Lifeblood referred to the content of the press materials as appearing to be 'designed to cynically manipulate public opinion and market forces – at the expense of Lifeblood and its [medical director] – for the benefit of those promoting Pradaxa'. Boehringer Ingelheim had no such intention or design and it almost went without saying that the actions of the agency and/or the media advisor, far from benefiting Boehringer Ingelheim, had caused significant damage.

As regards Clause 9.1, Boehringer Ingelheim's actions, both in relation to the approval process for the authorised press releases and once it became aware of the unauthorised press materials, demonstrated its commitment to high standards. If, having done everything possible to ensure that the highest standards were maintained, Boehringer Ingelheim was badly let down by a trusted agency and/or its sub-contractor, who had acted without authority and out of character, Boehringer Ingelheim suggested that it would not be appropriate to find that it had failed to maintain high standards.

Boehringer Ingelheim took great care to comply with the requirements of Clauses 11.2 and 11.3, aware of the importance of only using accurate quotations from an accredited source, as was reflected in the authorised press releases. It was not clear to Boehringer Ingelheim what more it could have been done to ensure that only the quotations, as stated, were used, in the form presented, but it had to acknowledge that, due to the wholly unauthorised actions of the media advisor, quotations were used in an inappropriate manner.

In relation to Clause 20.2, Boehringer Ingelheim took great care to prepare two distinct press releases, one

for the public and the other for the medical profession. Boehringer Ingelheim was scrupulous to ensure that the requirements of the Code were met regarding information provided to the public. However, it acknowledged that, despite its best efforts, unauthorised actions resulted in inappropriate information being made available for use.

* * * * *

Following receipt of the complaint, an email from the media advisor to the complainant (dated 17 May) was forwarded to the Authority.

This email referred to the the complaint and encouraged withdrawal of the complaint. It referred to helping Lifeblood and its medical director achieve the best possible coverage for National Thrombosis Week. The author referred to himself as a media advisor and that he would be contacting other parties about the matter.

A copy of this email was provided to Boehringer Ingelheim Limited.

* * * * *

FURTHER COMMENTS FROM THE COMPLAINANT

In response to a request from the Panel the complainant confirmed that neither the agency nor the media advisor worked for Lifeblood independently of any work for Boehringer Ingelheim. The original press release came to the complainant's attention via a friend who knew how hard Lifeblood worked to remain independent of any possibility of being influenced by pharmaceutical companies and had been surprised to see it, and assumed Lifeblood had not authorised it.

FURTHER COMMENTS FROM THE RESPONDENT

Boehringer Ingelheim confirmed it was not aware that the media advisor had emailed Lifeblood's medical director until Lifeblood's medical director sent it a copy of the correspondence on 19 May 2008. Immediately Boehringer Ingelheim's lawyers sent a letter to the media advisor by email and hard copy on 20 May 2008 stating that 'Boehringer Ingelheim Limited totally disassociates itself from the email and its contents'. The letter also stated 'Our client will not comment on the contents of your email other than to say it is wholly inappropriate and unprofessional, particularly given your apparent experience in the medical and pharmaceutical areas'. Furthermore, Boehringer Ingelheim required an undertaking from him that he would neither explicitly nor implicitly state that he acted on behalf of Boehringer Ingelheim. The agency had no prior knowledge of the media advisor's email to Lifeblood's medical director, although a copy had been forwarded to it by Boehringer Ingelheim. Since 26 April 2008 the media advisor had not acted on behalf of the agency and in no way represented that company's views.

A copy of the letter to the media advisor was also sent to Lifeblood's medical director and the Chairman of the Board of Trustees of Lifeblood by email on 21 May 2008. This was acknowledged by Lifeblood's medical director. The letter was sent to the media advisor on 20 May 2008, but no response had been received. Boehringer Ingelheim was therefore unable to include any comments from the media advisor within this response.

Boehringer Ingelheim continued to be extremely disappointed by these events and could not understand why an experienced consultant such as the media advisor communicated with Lifeblood's medical director in this way.

In relation to the question whether the agency also worked separately for Lifeblood, the agency had responded thus:

> 'We confirm that [the agency] has never worked separately with Lifeblood and has no contract with Lifeblood the charity.
>
> In early April 2008, [the agency] was contacted by [Lifeblood's medical director] who asked whether it would be able to assist Lifeblood with public relation services for National Thrombosis Week. [The agency] made it clear to Lifeblood that it would not be able to take on any separate project for Lifeblood without consent of its existing client, Boehringer Ingelheim (BI). BI confirmed its approval to [the agency] undertaking work for Lifeblood, however, no contract has been entered into with Lifeblood with [the agency] for the provision of such services and no work undertaken'.

PANEL RULING

It was a clearly established principle under the Code that a company was responsible for the actions of third parties employed on the company's behalf even if that third party acted outside the instructions from the pharmaceutical company. Clause 20.6 of the Code made it clear that companies were responsible for information about products issued by their public relations agencies.

The Panel considered that Boehringer Ingelheim had been very badly let down by a subcontractor to its agency who had not followed the agreed procedures regarding prior approval of material. This was of serious concern. The agency had subcontracted the media advisor. Neither the agency nor Boehringer Ingelheim knew why the approved press release had been amended without reference or approval from either the agency or Boehringer Ingelheim.

The effect of the actions of the consultant to the agency were extemely serious. Quotations were used in an inappropriate manner ie the quotations did not reflect the meaning of the author and formal permission had not been obtained. Thus the Panel ruled breaches of Clauses 11.2 and 11.3 of the Code. The Panel also considered that the quotation attributed to Lifeblood's medical director was not in line with the authorized indications for Pradaxa as it did not state that it was for use after elective surgery; the material was thus misleading and inaccurate in this regard. A breach of Clause 20.2 was ruled.

The Panel considered that it was particularly important when working with third parties such as patient organisations that all materials were in accordance with the Code. This was even more important when working on a new product as all such materials had to be prevetted by the Medicines and Healthcare Products Regulatory Agency (MHRA).

The Panel noted the circumstances of this case. Boehringer Ingelheim had a procedure for approving press releases and its contract with the agency stated that material had to be submitted to the company for written approval before release (clause 4.2). The contract further stated (clause 4.5) that the agency should comply with all codes of practice. According to Boehringer Ingelheim's submission the agency had used an experienced subcontractor, trained on the Code, who had acted entirely outside the contract and without the knowledge of either the agency or Boehringer Ingelheim. It was difficult to see what more Boehringer Ingelheim could have done. The Panel considered that as Boehringer Ingelheim had procedures and processes in place to ensure compliance with the Code and had been so very badly let down by a third party there was no breach of Clauses 9.1 and 2 of the Code.

Complaint received **25 April 2008**

Case completed **27 June 2008**

CASE AUTH/2119/4/08

ALLERGAN v MERZ PHARMA

Promotion of Xeomin

Allergan complained about the promotion of Xeomin (*clostridium botulinum* neurotoxin type A, free of complexing proteins) by Merz Pharma. The materials at issue were a BMJ advertisement, a leavepiece and stand panels used at the Association of British Neurologists (ABN) conference in Ireland in March 2008. Allergan supplied Botox (botulinum toxin (from *clostridium botulinum*) type A).

Allergan believed the claim 'Neurotoxin you need – complexing proteins you don't' in the journal advertisement made a bold statement of fact regarding the relevance of complexing proteins. It clearly implied that complexing proteins present in botulinum toxin type A products, *per se*, were not required and played no role in a product's efficacy or safety profile. While this might be true for Xeomin, this was not the case for all botulinum toxin type A products, including Allergan's product Botox.

Allergan did not accept, as submitted by Merz, that the claim made no comment concerning the role of complexing proteins. There was a comparison between Xeomin and other botulinum toxin type A products. It was disingenuous to suggest that the claim would be considered to apply only to Xeomin.

Allergan submitted that the role of complexing proteins was still one of scientific debate. The size of the botulinum toxin complex was thought likely to account for some of the clinical differences seen when comparing botulinum toxin molecules. The potential role of the accessory (complexing) proteins might confer an advantage in persistency in the target muscle versus naked neurotoxin. The issue had not been resolved in favour of one generally accepted viewpoint as indicated in the Xeomin advertisement.

Allergan alleged that the claim was not an accurate, balanced or objective evaluation of the scientific evidence.

The Panel noted that Xeomin was free from complexing proteins whilst Allergan's product, Botox, was not. The two products had been compared in a parallel group study which demonstrated non-inferiority of Xeomin (n=232) vs Botox (n=231) across various endpoints in the treatment of cervical dystonia. The authors concluded that complexing proteins were dispensable for clinical efficacy (Benecke *et al*). A similar study compared the two products in the treatment of belpharospasm. The results demonstrated the non-inferiority of Xeomin to Botox in terms of efficacy and a comparable safety profile for the two products (Roggenkämper *et al*).

The Panel noted that the role and clinical significance of the complexing proteins was one of scientific debate. The claim at issue appeared above the picture of a horse chestnut emerging from its spiky shell. The Panel considered that there was an implied comparison of Xeomin with other botulinum products. Furthermore the Panel considered that the claim at issue implied a proven clinical disadvantage for those products associated with complexing proteins for which there was no supporting data. This impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of the Code was ruled.

Allergan alleged that the claim 'In addition, Xeomin does not require refrigeration (prior to reconstitution) – reducing the risk of therapy failure or product wastage due to a gap in the cold chain' in the journal advertisement disparaged its product, Botox, which required refrigeration, and Allergan's cold chain supply procedures. This alleged 'risk' was based on speculation not fact. Allergan was not aware of any evidence of this 'reduced risk' with Xeomin and there was a clear implication of 'reduced risk' vs another botulinum toxin type A. All products if not stored correctly were at equal 'risk' of therapy failure or wastage.

The Panel considered that the claim at issue '… Xeomin does not require refrigeration (prior to reconstitation) – reducing the risk of therapy failure or product wastage due to a gap in the cold chain' was not unreasonable given the Xeomin Summary of Product Characteristics (SPC) which stated that the unopened vial had a shelf life of 3 years and the reconstituted solution had demonstrated chemical and physical in-use stability for 24 hours at 2 to 8oC. This was different to other unopened botulinum toxin products which required storage in a refrigerator or freezer.

The Panel did not accept that the claim disparaged either Allergan's cold chain procedures or its product Botox. The Panel considered that gaps in the cold chain might occur once a product was delivered to a customer – they might not be the fault of the supplier. The Panel noted that there was a difference between Botox and Xeomin in relation to the storage of an unopened vial which would have important practical implications for the customer. No breach of the Code was ruled.

Allergan noted that the claims 'Neurotoxin you

need – complexing proteins you don't' and 'Therapeutic efficacy is solely a characteristic of the Botulinum neurotoxin – complexing proteins have no therapeutic effect' both appeared in the leavepiece and the first board of the stand panels. The second, even more definitive claim, was in a section of the leavepiece entitled 'What is the role of complexing proteins?' This section discussed the role of complexing proteins in the context of all botulinum toxins. As outlined previously, this issue had not been resolved in favour of one generally accepted viewpoint as would seem to be clearly indicated in the leavepiece. Therefore, Allergan did not believe the claims to be an accurate, balanced or objective evaluation of the scientific evidence.

The Panel considered that the first claim had been dealt with above. The Panel considered its ruling above was relevant to the second claim 'Therapeutic efficacy is solely a characteristic of the botulinum neurotoxin – complexing proteins have no therapeutic effect'. The exact clinical role, if any, of complexing proteins had yet to be determined. Aoki *et al* stated that it was proposed that complexing proteins affected tissue distribution of botulinum toxins and although it appeared that this had yet to be proven the claim 'complexing proteins have no therapeutic effect' did not represent the current scientific and clinical debate. The Panel thus considered that the claim was misleading and a breach of the Code was ruled.

Allergan referred to a number of claims on the leavepiece and stand panels: 'Xeomin: Comparable efficacy and safety profile to [Botox] … when compared at 1:1 dosing ratio'; 'Clinical studies have demonstrated a comparable unit 1:1 dosing ratio with [Botox]'. The Xeomin SPC stated that 'Unit doses recommended for Xeomin are not interchangeable with those for other preparations of botulinum toxin'. A similar statement was included in the SPCs for all botulinum toxins. The requirement for such a statement was to ensure that physicians knew about the lack of interchangeability between botulinum toxins to minimise the risk of adverse events, ensure good clinical practice and enhance patient safety. The claims which suggested interchangeability were alleged to be misleading and not consistent with the SPC for Xeomin.

Both claims noted above appeared in the leavepiece. The Panel noted the prominent statement in the SPC that unit doses for Xeomin were not interchangeable with those for other preparations of Botulinum toxin. The Panel considered that it was misleading and inconsistent with the SPC not to make it clear that, although in the studies cited a 1:1 dosage ratio was used, unit doses were not interchangeable. The Panel ruled breaches of the Code.

Allergan Ltd complained about the promotion of Xeomin (*clostridium botulinum* neurotoxin type A, free of complexing proteins) by Merz Pharma UK Ltd.

The materials at issue were a BMJ advertisement (ref 1012a/XEO/NOV/2007/BB), a leavepiece (ref 10/10/XEO/NOV/2007/BB) and stand panels used at the Association of British Neurologists (ABN) conference in Dublin 26-28 March 2008.

Inter-company contact had failed to resolve the issues. Allergan supplied Botox (botulinum toxin (from *clostridium botulinum*) type A).

Xeomin was indicated for the symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults.

Merz confirmed that the materials used in Dublin came under the scope of the Code. They were provided by Merz for the 2008 ABN conference and were over-stickered to reflect the licensed status in Ireland. The leavepiece without the aforementioned modification had been employed in the UK whereas the only additional use of the exhibition panels had been at a UK launch meeting.

1 Claim 'Neurotoxin you need – complexing proteins you don't'

COMPLAINT

Allergan believed this claim in the journal advertisement made a bold statement of fact regarding the relevance of complexing proteins. It clearly implied that complexing proteins present in botulinum toxin type A products, *per se*, were not required and played no role in a product's efficacy or safety profile. While this might be true for Xeomin, this was not the case for all botulinum toxin type A products, including Allergan's product Botox.

Allergan did not accept, as submitted by Merz, that the claim made no comment concerning the role of complexing proteins in the safety and efficacy profile of any other botulinum toxin, type A product. In the advertisement at issue and throughout the Xeomin campaign, including the leavepiece and stand panels also at issue, there was comparison between Xeomin and other botulinum toxin type A products on the market. It was disingenuous to suggest that the claim would be considered to apply only to Xeomin.

Allergan submitted that the role of complexing proteins was still one of scientific debate. The size of the botulinum toxin complex was thought likely to account for some of the clinical differences seen when comparing botulinum toxin molecules. The potential role of the accessory (complexing) proteins might confer an advantage in persistency in the target muscle versus naked neurotoxin (Aoki *et al* 2006; Foster *et al* 2006 and Johnson and Bradshaw 2001). Certainly, Allergan did not believe this issue had been resolved in favour of one generally accepted viewpoint as seemed to be indicated in the Xeomin advertisement.

Allergan did not believe the claim was an accurate, balanced or objective evaluation of the scientific evidence. Therefore, it alleged that the claim 'Neurotoxin you need – complexing proteins you don't' was in breach of Clause 7.2 of the Code.

RESPONSE

Merz stated that this claim reflected the marketing authorization for Xeomin based on its proven efficacy without the presence of complexing proteins and was consistent with the product's summary of product characteristics (SPC). It was factually accurate, balanced and reflected the up-to-date information for Xeomin. It made no comment concerning the role of complexing proteins in the safety and efficacy profile of any other botulinum toxin type A product.

Allergan supported its submission that the role of complexing proteins was one of scientific debate by suggesting that the size of the botulinum toxin complex was thought likely to account for some of the clinical differences seen when comparing botulinum toxin molecules and that accessory (complexing) proteins might confer an advantage in persistency in the target muscle versus the naked neurotoxin. To support these suggestions it had drawn evidence from three articles which were reviews and opinions. Two of these articles were published in 2006 and the authors included Allergan employees (Aoki *et al* and Foster *et al*) and the third was published seven years ago (Johnson and Bradshaw).

The opinions used to substantiate the allegations were based on animal and studies that referred to Botox, Dysport, Myobloc and Neurobloc rather than Xeomin. Johnson and Bradshaw pre-dated the introduction of Xeomin and as such the opinions expressed were made without knowledge available e of Merz's complexing protein free product. Such views could not reflect the current available information.

Aoki *et al* implied that the size of the complex in different formulations might account for some of the preclinical and clinical differences. However, the evidence was again centred on studies which preceded the introduction of Xeomin.

Foster *et al* utilised comparisons between the older botulinum products which contained complexing proteins, namely Botox, Dysport and Neuroblox and failed to include Xeomin in the comparisons.

Unlike the articles cited by Allergan, Merz's claims were supported by randomised, controlled clinical trials involving over 750 patients (Benecke *et al* 2005 and Roggenkämper *et al* 2006). Whilst the authors included Merz personnel they were based on non-refutable endpoints. Furthermore, the evidence for Xeomin had been accepted by the regulatory authorities and was included in the product's European Public Assessment Report (EPAR).

Benecke *et al* compared [Xeomin] with Botox in cervical dystonia in over 460 patients and concluded that '… noninferiority of [Xeomin] vs Botox across various endpoints. We thus conclude that the complexing proteins contained in currently marketed [botulinum type A] preparations are dispensible for clinical efficacy. The safety and tolerability profiles for both treatments were similar…'.

Such statements were clearly consistent with the concept that Xeomin demonstrated the efficacy required without the presence or need for complexing proteins.

Merz robustly contested the allegation that 'Neurotoxin you need – complexing proteins you don't' was in breach of Clause 7.2. It was based on randomised controlled clinical evidence for Xeomin which had been accepted by regulatory authorities and was consistent with the SPC. Furthermore, the evidence supplied by Allergan to support the allegation of a breach of Clause 7.2 was based on opinion centred on older studies and failed to consider the information available for Xeomin and therefore could not be considered an up-to-date evaluation of evidence.

PANEL RULING

The Panel noted that Xeomin was free from complexing proteins whilst Allergan's product, Botox, was not. The two products had been compared in a parallel group study which demonstrated non-inferiority of Xeomin (n=232) vs Botox (n=231) across various endpoints in the treatment of cervical dystonia. The authors concluded that complexing proteins were dispensable for clinical efficacy (Benecke *et al*). A similar study compared the two products in the treatment of belpharospasm. The results demonstrated the non-inferiority of Xeomin to Botox in terms of efficacy and a comparable safety profile for the two products (Roggenkämper *et al*).

The Panel noted that the role and clinical significance of the complexing proteins was one of scientific debate. The supplementary information to Clause 7.2 in relation to emerging clinical or scientific opinion stated that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint particular care must be taken to ensure that it was treated in a balanced manner in promotional material.

The claim at issue 'Neurotoxin you need – complexing proteins you don't' appeared above the picture of a horse chestnut emerging from its spiky shell. The Panel considered that there was an implied comparison of Xeomin with other botulinum products. Furthermore the Panel considered that the claim at issue 'Neurotoxin you need – complexing proteins you don't' implied a proven clinical disadvantage for those products

associated with complexing proteins for which there was no supporting data. This impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

2 Claim 'In addition, Xeomin does not require refrigeration (prior to reconstitution) – reducing the risk of therapy failure or product wastage due to a gap in the cold chain'

COMPLAINT

Allergan alleged that this claim in the journal advertisement disparaged its product, Botox, which required refrigeration, and Allergan's cold chain supply procedures. This alleged 'risk' was based on speculation not fact.

This claim would clearly be considered by the reader within the context of the advertisement and the wider Xeomin campaign, where Xeomin was compared with other botulinum toxin type A products.

Allergan agreed that if medicines were not stored according to their licensed recommendations then there was a risk of loss of efficacy and associated wastage due to stability issues. However, the claim clearly stated 'reducing the risk' of therapy failure or product wastage due to a gap in the cold chain. Allergan was not aware of any evidence of this 'reduced risk' with Xeomin and there was a clear implication of 'reduced risk' vs another botulinum toxin type A. All products if not stored correctly were at equal 'risk' of therapy failure or wastage.

Allergan alleged a breach of Clause 8.1.

RESPONSE

Merz stated that the claim that Xeomin (prior to reconstitution) did not require refrigeration was factually accurate. Botox required refrigeration.

If any medicine was not stored according to licensed recommendations then there was a risk of loss of efficacy and associated wastage due to stability issues or even a safety risk. If there was not a risk of therapy failure or product wastage from the product not being refrigerated the regulatory authorities would not have required that this be included on the SPC.

Merz contested that it disparaged Botox in breach of Clause 8.1 as the claim was factually accurate for Xeomin and no other product was mentioned. In addition, should one choose to compare this factual property of Xeomin with Botox then it would still be fair and balanced.

PANEL RULING

The Panel considered that the claim at issue '… Xeomin does not require refrigeration (prior to reconstitution) – reducing the risk of therapy failure or product wastage due to a gap in the cold chain' was not unreasonable given the Xeomin SPC. Section 6.3 stated that the unopened vial had a shelf life of 3 years and the reconstituted solution had demonstrated chemical and physical in-use stability for 24 hours at 2 to 8°C. From a microbiological point of view the product should be used immediately. Section 6.4 stated that the unopened vial should not be stored above 25°C. This was different to other unopened botulinum toxin products which required storage in a refrigerator or freezer.

The Panel did not accept that the claim disparaged either Allergan's cold chain procedures or its product Botox. The Panel considered that gaps in the cold chain might occur once a product was delivered to a customer – they might not be the fault of the supplier. The Panel noted that there was a difference between Botox and Xeomin in relation to the storage of an unopened vial which would have important practical implications for the customer. The Panel considered the claim was not disparaging as alleged and no breach of Clause 8.1 was ruled.

3 Claims 'Neurotoxin you need – complexing proteins you don't' and 'Therapeutic efficacy is solely a characteristic of the Botulinum neurotoxin – complexing proteins have no therapeutic effect'

COMPLAINT

Allergan stated that both claims appeared in the leavepiece and the first board of the stand panels. The second, even more definitive claim, was in a section of the leavepiece entitled 'What is the role of complexing proteins?' This section discussed the role of complexing proteins in the context of all botulinum toxins and not just Xeomin, as Merz stated in inter-company dialogue. As outlined previously, with respect to the BMJ advertisement in point 1 above, Allergan did not believe this issue had been resolved in favour of one generally accepted viewpoint as would seem to be clearly indicated in the leavepiece.

Therefore, Allergan did not believe the claims to be an accurate, balanced or objective evaluation of the scientific evidence on this matter and alleged a breach of Clause 7.2.

RESPONSE

Merz submitted that its response regarding the claim 'Neurotoxin you need – complexing proteins you don't' had been addressed in point 1 above.

The claim 'Therapeutic efficacy is solely a characteristic of the Botulinum neurotoxin – complexing proteins have no therapeutic effect' was supported by clinical studies involving Xeomin which was free from complexing proteins and commercially available toxin which contained complexing proteins. The results demonstrated that Xeomin was non-inferior in terms of efficacy with no difference in side effects compared with Botox, a fact acknowledged by the article supplied by Allergan (Aoki *et al*).

Merz did not believe that the claim was in breach of Clause 7.2 as it reflected the current evidence from clinical trials and was not based on inappropriate comparisons between toxins containing complexing proteins, animal studies or opinions based on evidence which did not consider all the currently available information for Xeomin.

PANEL RULING

The Panel considered that the first claim had been dealt with in point 1 above. The second claim appeared in the leavepiece. Merz had provided one page showing the stand panel and the second claim did not appear on that.

The Panel considered its ruling in point 1 was relevant to the claim 'Therapeutic efficacy is solely a characteristic of the botulinum neurotoxin – complexing proteins have no therapeutic effect'. The exact clinical role, if any, of complexing proteins had yet to be determined. Aoki *et al* stated that it was proposed that complexing proteins affected tissue distribution of botulinum toxins and although it appeared that this had yet to be proven the claim 'complexing proteins have no therapeutic effect' did not represent the current scientific and clinical debate. The Panel thus considered that the claim was misleading and a breach of Clause 7.2 was ruled.

4 Interchangeability between botulinum toxins

COMPLAINT

Allergan referred to a number of claims on the leavepiece and stand panels:

'Xeomin: Comparable efficacy and safety profile to [Botox] in spasmodic torticollis and blepharospasm when compared at 1:1 dosing ratio'

'Clinical studies have demonstrated a comparable unit 1:1 dosing ratio with [Botox]'

In Section 4.2 of the Xeomin SPC (Posology and method of administration) it was stated that 'Unit doses recommended for Xeomin are not interchangeable with those for other preparations of botulinum toxin'. A similar statement was included in the SPCs for all botulinum toxins. The requirement by the regulatory authorities for such a statement was to ensure that physicians knew about the lack of interchangeability between botulinum toxins to minimise the risk of adverse events, ensure good clinical practice and enhance patient safety.

The claims at issue, without appropriate reference to a lack of interchangeability, were of concern and raised potential safety issues.

The claims which suggested interchangeability were alleged to be misleading and not consistent with the SPC for Xeomin, in breach of Clauses 3.2 and 7.2 of the Code.

RESPONSE

Merz stated that the claims in question were clearly referenced to the cited clinical studies (Benecke *et al* and Roggenkämper *et al*) and as might be expected referred to the dosing ratios used. This was to ensure that prescribers knew that the dosages of Botox and Xeomin employed were the same. No statement suggesting interchangeability was made.

Whilst this was the case, the EPAR (page 6) expressed the opinion that '… the data from the non-clinical and clinical development program… provided sufficient evidence that a 1:1 dose ratio between Xeomin and Botox with respect to efficacy and safety can be concluded…'.

As the statements were factually accurate and framed in the context of the cited clinical trials, balanced by additional statements with no suggestion of interchangeability, Merz contested the claim that the data presented was inconsistent with the SPC and that the information presented from the cited clinical studies was factually inaccurate. Merz denied breaches of Clauses 7.2 or 3.2.

PANEL RULING

The Panel noted that the stand panel provided by Merz made no mention of the 1:1 dosing ratio comparison. Both claims noted above appeared in the leavepiece.

The Panel noted the prominent statement in the SPC that unit doses for Xeomin were not interchangeable with those for other preparations of Botulinum toxin. The Panel considered that it was misleading and inconsistent with the SPC not to make it clear that, although in the studies cited a 1:1 dosage ratio was used, unit doses were not interchangeable. The Panel ruled a breach of Clauses 3.2 and 7.2 of the Code.

Complaint received **30 April 2008**

Case completed **2 July 2008**

ANONYMOUS v BAYER SCHERING PHARMA

Promotion of Nebido

An anonymous ex-employee complained that an advertisement for Nebido (long-acting testosterone injection) implied that the product would enable men to become sexually attractive to younger women which was not a licensed indication. The complainant noted in particular a photograph in the advertisement of a gentleman of advancing years, apparently hailing a taxi and accompanied by a woman who looked significantly younger than him clutching his arm.

The Panel did not consider that the advertisement promoted Nebido for an unlicensed indication as alleged. The advertisement reflected the positive effects of treating hypogonadism leading to, *inter alia*, restoration of libido. No breach of the Code was ruled.

An anonymous ex-employee of Bayer Schering Pharma complained about an advertisement for Nebido (long-acting testosterone injection) published in the BMJ 3 May 2008.

COMPLAINT

The complainant stated that the advertisement in question included a picture of a gentleman of advancing years who appeared to be hailing a taxi with a woman who looked significantly younger than him clutching his arm. This picture implied that taking Nebido would enable men to become sexually attractive to younger women. This was not a licensed indication for Nebido.

The complainant alleged the advertisement was in breach of Clauses 2, 3.2 and 9.1 of the Code.

RESPONSE

Bayer Schering submitted that the advertisement in question was a fair, accurate and balanced representation of the effects of the treatment of male hypogonadism using Nebido therapy and did not contravene any clause of the Code.

Nebido was indicated for male hypogonadism when testosterone deficiency had been confirmed by clinical features and biochemical tests. The accepted features of hypogonadism were described in a consensus statement of the International Society of Andrology, International Society of the Study of the Aging Male and the European Association of Urology as a syndrome characterised by decrease in cognitive functions, fatigue, diminished sexual desire (libido) and depressed mood. Furthermore the Klinefelter's Syndrome Association recognised that patients with hypogonadism might experience body image issues and a lessened capacity for enjoyment which led to some untreated hypogonadal patients leading relatively sedentary and insular lives.

In the hypogonadal man, Nebido restored serum testosterone levels to the physiological range which led to the normalisation of hypogonadal symptoms such as improved feeling of wellbeing, improved emotional stability, restoration of libido and increases in muscle mass.

There were also data to demonstrate that Nebido achieved therapeutic effects without the peaks and troughs in serum testosterone levels associated with shorter-acting testosterone injections. More importantly Nebido achieved these effects following the administration of three to five injections per year which was fewer than short-acting preparations which required approximately seventeen injections per year, affording Nebido patients fewer visits to the clinic to receive their treatment, which was the subject of the advertisement in question.

The advertisement importantly depicted the symptomatic improvement to patients when their testosterone levels were restored and maintained within the normal physiological range. The patient was able to conduct typical, normal activities demonstrating restoration of positive mood, concentration, energy and sexual interest. The man and women featured in the advertisement were aged 57 and 45 years old respectively; the man's age was entirely appropriate for a patient with late-onset hypogonadism.

The advertisement in question was therefore balanced and accurate. It did not suggest that treated patients were more attractive to younger women.

Bayer Schering totally refuted the complainant's allegations that the advertisement was in breach of Clauses 2, 3.2 and 9.1 of the Code. The advertisement presented a fair, balanced and accurate view of the symptomatic improvements which hypogonadal patients experienced when their serum testosterone levels were restored to and maintained within the accepted physiological range. The claims were factually correct, consistent with the summary of product characteristics (SPC) and current international guidelines and were fully referenced to well-respected publications. The pictures were in good taste and depicted a man and woman who were of an appropriate age carrying out typical, normal activities.

PANEL RULING

The Panel noted that the advertisement included four photographs. The one commented on by the complainant was of a man apparently hailing a taxi. He was accompanied by a woman, clutching his arm, who was half turned away from the camera. Her face could not be seen. The other three photographs were of the same man alone in different situations.

The Panel noted that Nebido was authorized for testosterone replacement therapy for male hypogonadism when testosterone deficiency had been confirmed by clinical features and biochemical tests.

The Panel did not consider that the advertisment promoted an unlicensed indication as alleged. Nor had the advertisement failed to maintain a high standard. The four photographs reflected the positive effects of treating hypogonadism such as improvements in well-being and restoration of libido.

No breach of Clauses 3.2 and 9.1 was ruled. Given its ruling of no breach the Panel did not consider the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure.

Complaint received	**6 May 2008**
Case completed	**23 May 2008**

ANONYMOUS v ROCHE

MabThera symposium

An anonymous consultant rheumatologist complained that Roche had attracted delegates to a satellite symposium of a national meeting by having a celebrity (a newsreader on national television) co-chair the meeting. The complainant noted that the main attraction of a meeting should be the speakers/educational content and everything else should be secondary. The complainant further alleged that as the co-chair was a lay person they were not qualified to attend the meeting and by being there Roche had thus promoted MabThera (rituximab) to the public. The complainant considered that high standards had not been maintained and that Roche's activities had the potential to bring discredit upon the whole pharmaceutical industry.

The Panel noted that the one and a half hour symposium, attended by approximately 100 health professionals, had been co-chaired by a television newsreader. The written brief stated 'Your main responsibilities as chair are to keep a positive atmosphere during the meeting, to ensure that it runs to time and that as many delegates as possible are actively involved in the meeting'. The brief stated that the aim of the newsreader's presentation was to welcome delegates and offer a short introduction to the meeting and to discuss why it was so important to hold meetings like this. Background information on MabThera was provided with the brief. The printed materials promoting the meeting did not mention the newsreader's role. The Panel noted that the newsreader had been employed by Roche to deliver a professional service. In the Panel's view, given her role the newsreader, although not a health professional, qualified as a participant in her own right. It was thus not inappropriate for her to receive hospitality. No breach of the Code was ruled.

The Panel noted that of the ways in which potential delegates might find out about the symposium only the invitation and online registration site referred to the newsreader. The invitation included a thumbnail photograph. The flyer and the congress banner made no reference to the newsreader. Only the speaker biographies made it clear that the newsreader was the co-chair. The Panel considered that delegates had not been attracted to the meeting on the basis of there being a celebrity co-chair as alleged. No breach of the Code was ruled.

Given the newsreader's professional role as the co-chair the Panel did not consider that in these circumstances Roche had promoted MabThera to the general public as alleged. The meeting was aimed at and attended by health professionals to who MabThera could be promoted. No breach was ruled.

The Panel did not consider that the arrangements for the meeting were unreasonable. Roche had not failed to maintain high standards. No breach was ruled.

An anonymous consultant rheumatologist complained about a MabThera (rituximab) symposium held by Roche Products Limited.

COMPLAINT

The complainant stated that he attended a promotional meeting organised by Roche on 23 April 2008. The complainant noted Roche called it a symposium, but out of five presentations, most were focussed on rituximab; two even had rituximab in their title. Copies of the invitation and the speakers' biographies were provided.

The complainant was concerned that a lay person/celebrity co-chaired the meeting (this was what the biography said). Clause 19 clearly stated that only persons qualified to attend should attend meetings. Inviting a lay person/celebrity to attend/co-chair a promotional meeting and offering hospitality to such unqualified lay people (breakfast was available from 6.30am) was, in the complainant's opinion, a breach of Clause 19.

The complainant further noted that Clause 19 implied that the main attraction of a meeting should be the speakers/educational content and everything else should be secondary. Why print a picture of a lay person/celebrity on an invitation of a promotional meeting organised by a pharmaceutical company? Attracting attendees by printing a picture of the co-chair on the invitation in the complainant's opinion gave the wrong impression, was in bad taste and purely a selling exercise. The complainant alleged a breach of Clause 19. If this activity was allowed to take place, other companies would invite even bigger celebrities, give them a five minute slot, ask them to co-chair (like this person), print their pictures and attract attendees on this basis rather than the educational content!

By printing the picture of a celebrity and for the reasons cited above, the complainant alleged that Roche had failed to maintain the high standards expected from an ethical industry in breach of Clause 9.1.

This was a promotional meeting as evident from the agenda and the invitation. At least one inappropriate lay person was present at this meeting. Giving promotional messages in front of a member of the general public, the complainant believed was prohibited by the Code. A breach of

Clause 20.1 was alleged.

The complainant believed that Roche's activities had the potential of bringing discredit to the entire pharmaceutical industry and should be stopped altogether.

RESPONSE

Roche explained that it had sponsored the meeting at issue which was a breakfast satellite symposium at the annual meeting of the British Society of Rheumatology (BSR) in Liverpool. The symposium, entitled 'Passport to RA [rheumatoid arthritis] Management', was an opportunity for the audience to hear a review of the current and future challenges in the management of refractory RA and for UK rheumatologists to have the benefit of receiving expert evaluations of potential treatment options. Roche noted the world class scientific faculty for the symposium and provided the written briefs and biographies for the scientific/medical co-chair and the other four speakers. Given the seniority of the faculty a strong and proven moderator was required to ensure that each speaker kept to both the strict timelines set out by the BSR and the overall objective of the meeting.

This was the rationale for seeking a co-chair with the capability and experience to moderate and manage this potentially challenging setting. Supplementary to this was the requirement of the co-chair to be able to initiate and manage the debate. The person contacted to perform this role was a newsreader on national television.

The newsreader co-chair was to moderate the symposium. She was contracted to attend in her professional capacity as a skilled journalist/expert facilitator/interviewer. In contrast to the other co-chair's scientific role, her main responsibilities were to introduce the meeting, to explain why it was important to 'set your sights high', maintain a positive atmosphere, probe the speakers' views and opinions and to facilitate audience participation. Her role also required her to direct and link questions to individual speaker's presentations.

The newsreader received a comprehensive written brief (provided) which was reviewed with her by Roche.

The symposium was held on 23 April at 7am, with a simple breakfast of juice, coffee, pastries and fruit, available to all attendees, including the faculty, from 6.30am. Full agenda details contained in the invitation were provided and logistical details were contained in the briefing documents which were also provided. Approximately 100 health professionals attended.

Health professionals were informed of the symposium by one of three means: a 'save-the-date' flyer, invitation and a banner in the congress centre (all provided). For further information, there was also an online registration site and speaker biographies (both provided).

In summary, Roche believed that this was a *bona fide* forum for the exchange of scientific and educational opinion, challenge, questions and debate. Furthermore, Roche believed that all arrangements regarding the meeting were wholly appropriate.

PANEL RULING

The Panel noted that the one and a half hour symposium, attended by approximately 100 health professionals, had been co-chaired by a television newsreader. The written brief stated 'Your main responsibilities as chair are to keep a positive atmosphere during the meeting, to ensure that it runs to time and that as many delegates as possible are actively involved in the meeting'. The brief stated that the aim of the newsreader's presentation was to welcome delegates and offer a short introduction to the meeting and to discuss why she felt it was so important to hold meetings like this. Background information on MabThera was provided with the brief. The printed materials promoting the meeting did not mention the newsreader's role. The Panel noted that the newsreader had been employed by Roche to deliver a professional service ie co-chair the meeting. In the Panel's view, given her role the newsreader, although not a health professional, qualified as a participant in her own right. It was thus not inappropriate for her to receive hospitality provided that hospitality met the requirements of the Code. No breach of Clause 19.1 was ruled.

The Panel noted that of the ways in which potential delegates might find out about the symposium (flyer, invitation, congress banner and online registration site) only the invitation and online registration site referred to the newsreader. The invitation included a thumbnail photograph. The flyer and the congress banner made no reference to the newsreader. Only the speaker biographies made it clear that the newsreader was the co-chair. The Panel considered that delegates had not been attracted to the meeting on the basis of there being a celebrity co-chair as alleged. No breach of Clause 19.1 was ruled.

Given the newsreader's professional role as the co-chair the Panel did not consider that in these circumstances Roche had promoted MabThera to the general public as alleged. The meeting was aimed at and attended by health professionals to whom MabThera could be promoted. No breach of Clause 9.1 was ruled.

The Panel did not consider that the arrangements for the meeting were unreasonable. Roche had not failed to maintain high standards. No breach of Clause 9.1 was ruled.

Complaint received **9 May 2008**

Case completed **29 May 2008**

CASE AUTH/2134/6/08

PHARMACIST v JANSSEN-CILAG

Lyrinel XL journal

A pharmacist complained about a Janssen-Cilag advertisement for Lyrinel XL (oxybutynin hydrochloride).

The advertisement was headed 'Gets our vote' followed by details from Diokno *et al* 2002 that '1,067 patients enrolled in an open-label study of extended-release oxybutynin. Three quarters of these (795) remained in the study by 3 months, of which 88% indicated that they would recommend extended-release oxybutynin to others.' Beneath the claim was an illustration of an audience most of which were holding up a card with a photograph of a camel on it. One woman in the front row was not holding up her card. The complainant stated that in the illustration there were 24 clearly distinguishable cards with only one woman clearly not holding her card up. This equated to 4% rather than 12% who would not recommend this product before taking into account any drop out rate! The complainant alleged that the pictorial representation misrepresented the data presented at the top of the page.

The Panel did not consider that the illustration was a fair reflection of the total data. The patients who had discontinued by three months were not represented at all. The illustration implied that only 4% (1/24) of patients would not recommend the product to others and this was not so. The illustration together with the prominent heading 'Gets our vote' implied that almost everyone who took Lyrinel XL would be happy to stay on it. This was not so. Diokno *et al* reported that after 3 months 25% (272) of patients discontinued therapy mainly due to adverse events (166) or lack of efficacy (52). Those who stayed on therapy after 3 months were thus a selected group of patients who could tolerate therapy and for whom it was effective. Even out of this group 12% (95) would not recommend the product to others. In effect, after 3 months' therapy approximately 29% of patients who originally started therapy (313/1067) would presumably not recommend the product to others. This was not consistent with the illustration which was misleading and exaggerated. The Panel did not consider that the inclusion of some of the data from the study as a heading to the advertisement was sufficient to negate the effect of the illustration. The Panel ruled breaches of the Code.

A pharmacist complained about an advertisement (ref LYR/08-0036) for Lyrinel XL (oxybutynin hydrochloride) placed by Janssen-Cilag Ltd in GP, 6 June. The product was indicated in adults for the symptomatic treatment of urge incontinence and/or increased urinary frequency associated with urgency as may occur in patients with unstable bladder. In children over six years of age Lyrinel could be used for the symptomatic treatment of detrusor hyperreflexia secondary to a neurogenic condition.

The advertisement was headed 'Gets our vote' followed by details from Diokno *et al* 2002 that '1,067 patients enrolled in an open-label study of extended-release oxybutynin. Three quarters of these (795) remained in the study by 3 months, of which 88% indicated that they would recommend extended-release oxybutynin to others.' Beneath the claim was an illustration of an audience most of which were holding up a card with a photograph of a camel on it. One woman in the front row was not holding up her card.

COMPLAINT

The complainant stated that in the illustration there were 24 clearly distinguishable cards with only one woman clearly not holding her card up. This equated to 4% rather than 12% who would not recommend this product before taking into account any drop out rate!

The complainant alleged that the pictorial representation mis-represented the data presented at the top of the page.

RESPONSE

Janssen-Cilag stated that the advertisement was published in Pulse, 4 June 2008.

The heading at the top of the advertisement 'Gets our Vote' was followed by a brief synopsis of one aspect of the study involving extended release oxybutynin (Lyrinel XL). This synopsis was well substantiated by Diokno *et al*. Janssen-Cilag submitted that the picture of a group of women 'voting' for Lyrinel XL was fair and balanced and did not mislead or misrepresent the facts as stated in the text, and so was not in breach of Clauses 7.2 or 7.8 of the Code.

The synopsis in the advertisement refered to 795 patients remaining in the quoted study at 3 months. Of these 795 patients, 88% indicated they would recommend their study medication to others. The figure of 88% was clearly displayed in the strapline in large font print. In the image only 6 individuals could be clearly seen (although 24 cards could be seen to be held up).

It was not appropriate to derive a precise

percentage response based on the picture as it was not possible to discern the total number of women represented. In mathematical terms, as only the numerator (the number of visible cards) and not the denominator (the total number of women) of the fraction was known, a precise percentage could not be calculated. For this reason, the imagery could not be described as misrepresenting the data presented, especially as the study-derived figure of 88% appeared prominently within the text.

If one followed the logic of the complainant and extrapolated that the individuals seen in the imagery represented the percentage of study patients who would recommend the product, only six individuals could clearly be seen in the foreground and of these only five were holding up cards. Therefore at most only 83% of the individuals actually seen could be interpreted as voting for the product. This was a lower figure than that described in the synopsis but was consistent with a clear majority expressing satisfaction with the medication. Further of the most prominent individuals in the front row of the image (and the clear focus of the imagery), only two of the three were holding up cards (67% voting for). A deliberate decision was made to avoid the implication that all individuals would endorse the product by ensuring that one of the three most prominent individuals seen in the front row was not holding up a card. In addition there were also several distinct gaps in the background where cards had not been held up (though these individuals could not be seen themselves).

PANEL RULING

The Panel noted that the advertisement was headed with the results from Diokno *et al*. Of the 1067 patients enrolled in the open-label study three quarters (795) remained in the study by three months of whom 88% indicated that they would recommend their study medication (extended-release oxybutynin) to others. Diokno *et al* stated that of the 272 patients who discontinued therapy at 3 months, 166 did so because of adverse events, 52 for lack of efficacy and 49 for other reasons.

The illustration showed a number of people sitting in a theatre or similar. All but one were holding up a card which had on it a picture of a camel (twenty four cards in total). The one women who had not held up her card was smiling broadly.

The Panel did not consider that the illustration was a fair reflection of the total data. The patients who had discontinued by three months were not represented at all. The illustration implied that only 4% (1/24) of patients would not recommend the product to others and this was not so. The illustration together with the prominent heading 'Gets our vote' implied that almost everyone who took Lyrinel XL would be happy to stay on it. This was not so. Diokno *et al* reported that after 3 months 25% (272) of patients discontinued therapy mainly due to adverse events (166) or lack of efficacy (52). Those who stayed on therapy after 3 months were thus a selected group of patients who could tolerate therapy and for whom it was effective. Even out of this group 12% (95) would not recommend the product to others. In effect, after 3 months' therapy approximately 29% (166+52+95 = 313) of patients who originally started therapy (313/1067) would presumably not recommend the product to others. This was not consistent with the illustration which was misleading and exaggerated. The Panel did not consider that the inclusion of some of the data from the study as a heading to the advertisement was sufficient to negate the effect of the illustration. The Panel ruled a breach of Clauses 7.2 and 7.8 of the Code.

Complaint received **16 June 2008**

Case completed **2 July 2008**

CODE OF PRACTICE REVIEW – AUGUST 2008

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

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2095/2/08	Actelion v Encysive	Pilot study with Thelin	No breach	Appeal by respondent Report from Panel to Appeal Board Suspension of pilot study At issue pending final outcome of case required by Panel	Page 18
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2099/2/08 and 2100/2/08	**Ex-employee and Media/Director v Roche**	**Supply of Xenical and support for a slimming clinic**	**Two breaches Clause 2 in each case** **Two breaches Clause 9.1 in each case** **Breach Clause 18.1 in each case** **Public reprimand by Appeal Board** **ABPI Board suspended Roche from membership for a minimum of six months**	**Appeal by respondent** **Report from Panel to Appeal Board** **Report from Appeal Board to ABPI Board**	**Page 37**
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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.