NUMBER 62 NOVEMBER 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 took place from 29 September– 3 October. The week coincided with the 50th anniversary of the Code on 2 October.

During Code Awareness Week, employees from more than 40 companies across the industry united to talk to doctors, nurses, pharmacists and other stakeholders about how the industry can work ethically with the NHS in accordance with the Code.

Code Awareness Week is part of an ongoing campaign to increase understanding of the ethical standards that the industry must meet when dealing with health professionals and others. The aim of the week was to help ensure that as many people as possible know about the Code and its provisions.

During the week health professionals were offered copies of 'The ABPI Code and Health Professionals' leaflet and the 'Quick Guide to the Code for Health Professionals' which clarified the main provisions of the Code. In addition, industry representatives distributed copies of the 50th anniversary leaflet. Copies of all of these documents are available at www.pmcpa.org.uk.

The PMCPA also conducted a targeted media campaign around Code Awareness Week 2008 and a press release was sent to the media on Friday, 26 September. The story was generally covered alongside the debate (see below) in the trade press.

In addition an e-alert about the Code was sent to 53,000 clinicians in the week starting 22 September and a second one, about the 50th anniversary, was sent on 2 October. Approximately 48,000 clinicians viewed these emails and initial figures suggested that about 7% clicked through to the PMCPA website with many others 'bookmarking' the email for future reference. Online advertisements also ran on the BMJ, HSJ, The Pharmaceutical Journal and Nursing Times websites from Monday, 22 September to Friday, 3 October.

A leaflet entitled 'The ABPI Code and Politicians' was sent to MPs and other political stakeholders in advance of the week.

During Code Awareness Week (and throughout the next few months), PMCPA staff were running 'Code Busters!' sessions at pharmaceutical companies. These sessions involved a team quiz about the Code and offered attendees the opportunity to ask questions in a 'myth-busting' surgery session. Nineteen companies initially requested sessions and these requests should be met by the end of the year. Please contact Niamh MacMahon on nmacmahon@pmcpa.org.uk for further details.

PRICE REDUCTIONS

As companies are aware, the revised Pharmaceutical Price Regulation Scheme requires prices of medicines to be reduced with effect from 1 February 2009 so as to achieve an overall reduction for a company of 3.9%.

It is in the interest of advertisers to indicate the new lower prices on promotional material as soon as possible. In the period 1 February to 30 April 2009, however, promotional material will not be considered to be in breach of the Code if it still carries the previous higher price.

Care should be taken, however, to ensure that there is no discrepancy between what representatives say and what is said on written material left with doctors etc by representatives as this could give rise to complaints.

It will not be acceptable at any time to give comparative prices in promotional material if these involve the new lower prices of the advertiser's products and the superseded higher prices of competitor products.

Every effort should be made to ensure that journal advertisements are correct at the time of publication.

FIFTIETH ANNIVERSARY DEBATE

Early in 2008, the PMCPA launched 'The ABPI Code: Still nifty at fifty?' campaign to mark the 50th anniversary of the ABPI Code. The campaign was targeting the pharmaceutical industry, MPs, health professionals, patient organisations and PR and marketing professionals.

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CODE OF PRACTICE TRAINING

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

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

The next Code of Practice seminar dates on which places remain available are:
Tuesday, 13 January
Monday, 23 March

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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As part of this, a 'Question Time' style debate chaired by John Humphrys and entitled 'The ABPI Code: Still nifty at fifty?' took place on the evening of 2 October at the Royal College of Physicians, London. The debate examined what impact the ABPI Code has had on relationships between the industry and health professionals, how these interactions have changed over the past 50 years and where we go from here.

The panel consisted of:
- Chris Brinsmead (President of the ABPI)
- William Harbage QC (Chairman of the Code of Practice Appeal Board)
- Andrew Jack (Journalist, The Financial Times)
- Dr June Raine (Director of Post-Licensing, Medicines and Healthcare products Regulatory Agency)
- Dr Des Spence (GP and regular contributor to the BMJ)

The audience, of approximately 200, was made up of key industry personnel, health professionals, patient representatives, members of the media, political and other relevant stakeholders.

Topics covered during the evening included:
- Whether publicity is the most powerful sanction for Code violations.
- Whether it was appropriate for joint working to take place between the industry and the NHS and the future of industry support for medical education.
- How interactions between the industry and health professionals had changed over the years and where we go from here.
- What information industry should be able to provide to patients.

An audio recording and transcript of the debate can be found on the PMCPA website along with more details about the 50th anniversary.

CASE AUTH/2089/1/08

GENERAL PRACTITIONER v GOLDSHIELD

MacroBid email

A general practitioner complained that Goldshield had sent him, via an agency, an unsolicited email about MacroBid (nitrofurantoin) to his NHS email address. This was a working email address, the utility of which would be rapidly degraded by advertising or infomercial emails. The complainant stated that he had not knowingly signed up to receive any information from Goldshield or any other pharmaceutical company; it was most unwelcome. The ability to be able to unsubscribe did not in any way excuse the activity.

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 MacroBid was clearly promotional material. Whilst it had not been sent directly by Goldshield 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 also noted that health professionals were told by telephone that the agency would, from time to time, send details by email about its affiliates' products and services which might include updates on specialist services, conferences and seminars, diagnostic, medical, pharmaceutical and promotional materials as well as official information. The text did not make it abundantly clear that the company intended to send promotional material from pharmaceutical companies; the text referred to pharmaceutical *and* (emphasis added) promotional materials as if the two were wholly separate. Furthermore, the text referred to 'affiliates' of the agency. In the Panel's view pharmaceutical companies were not affiliates of the agency, and would not be seen as such. Pharmaceutical companies would be purchasing a service from the agency. Similar text appeared in the subsequent confirmatory email.

The Panel considered that the email had been unsolicited. There was no evidence to show that the complainant had given prior, fully informed, consent to receive by email promotional material from a pharmaceutical company. A breach of the Code was ruled which was upheld on appeal by Goldshield.

The Authority subsequently reported Goldshield to the Appeal Board due to its failure to provide the requisite undertaking and assurance in relation to the Appeal Board's ruling of a breach of the Code. An amended signed form of undertaking was subsequently provided by Goldshield.

The Appeal Board was very concerned that Goldshield had not provided the requisite undertaking within the time set out in the Constitution and Procedure. The Appeal Board noted that the company was not a member of the ABPI but it had agreed to comply with the Code and accept the jurisdiction of the Authority. The Appeal Board decided that as in effect Goldshield had not continued to use material in breach of the Code it would not take further action at this stage. It expected the company to comply with the Constitution and Procedure in the future otherwise it could no longer be included on the list of non members that complied with the Code.

A general practitioner complained about an unsolicited email about MacroBid (nitrofurantoin) received from Goldshield Pharmaceuticals via an agency

COMPLAINT

The complainant explained that the email was sent to his NHS email address. This was a working email address, the utility of which would be rapidly degraded by advertising or infomercial emails if the industry took up this practice. The complainant stated that he had not knowingly signed up to receive any information from Goldshield or any other pharmaceutical company; it was most unwelcome.

The complainant submitted that if the sending of SPAM emails was not already contrary to the Code then he thought it should be. The complainant was astonished that Goldshield allowed its name to be associated with this behaviour as sending SPAM was associated with the seedier side of the Internet and was a practice frowned upon by most reputable organisations which wished to preserve a good name. The ability to be able to unsubscribe did not excuse the activity.

When writing to Goldshield the Authority asked it to respond in relation to Clause 9.9 of the Code.

RESPONSE

Goldshield submitted that an agency with over fifteen years' experience of working with the NHS had asked it to sponsor of its electronic medical education services for health workers. As a result Goldshield agreed to sponsor four educational emails which were produced by the agency and these were sent to a range of health workers on their database (including GPs, hospital pharmacists, nurses and hospital specialists) who might have an

interest in a range of disease areas. The disease areas sponsored by Goldshield were pain management and urinary tract infection.

The main section of each educational email was written by an independent writer. Two emails had been sent – the first in September 2007 on pain management and the other in January 2008 on urinary tract infection in the community (the email in question).

Goldshield was assured by the agency that the educational email conformed to the Code in the way in which it had both obtained permission from health workers to send information and its strict opt-out policy. Permission to contact health workers was obtained in a two-step process:

Firstly, each health worker was telephoned and the services provided explained as follows:

'Good morning Doctor. We are [the agency], we publish the [agency] NHS directory, you are probably familiar with it – it is known as the [named] book. We also own and regularly update our NHS Online personnel directory service which can be found at [a website] which currently contains details of over 500,000 NHS personnel.

This is a secure facility, accessible after we have verified your status. Then after you have completed the registration process the system will send you your user name and password. Of course any information you give us will not be shared with third parties.

[The agency] will from time to time send details by email about our affiliates' products and services relevant to your area of specialization, such as educational [emails] on disease areas, along with information from certain government agencies, such as the DVLA, Royal College of Nursing and other professional bodies. These may include updates on specialist services, conferences and seminars, medical, pharmaceutical and promotional materials as well as official information. Is this OK? Good, what is your email address and would you confirm your job title'.

A follow-up email then re-iterated the telephone conversation and asked the health worker to confirm that they would like to access data held on the website through an access code. This was verified yearly and a copy of the email was provided.

Goldshield submitted that an unsubscribe/opt-out response option was provided at the bottom of each educational email by the agency. The agency assured Goldshield that this was received and checked daily and usually implemented within forty-eight hours (except weekends). A copy of the opt-out response was provided.

The complainant was first telephoned in September 2007 and emailed shortly after. Since then, the complainant had received nine electronic transmissions – seven educational emails from pharmaceutical companies (including an earlier one sponsored by Goldshield in September 2007), one from the DVLA and another from NHS Choices. Throughout this period, although provided with the option to opt out of the services provided by the agency the complainant had declined to do so. In addition to this, the agency had told Goldshield that 179 requests were received during this period to unsubscribe from their services; less than 1% of the emails sent.

Goldshield submitted that it had acted responsibly in this matter and therefore was not in breach of the Code, however it regretted any distress and inconvenience caused to the complainant.

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 MacroBid was clearly promotional material. Whilst it had not been sent directly by Goldshield 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 also noted the script used on the telephone: health professionals were told that the agency would, from time to time, send details by email about its affiliates' products and services which might include updates on specialist services, conferences and seminars, diagnostic, medical, pharmaceutical and promotional materials as well as official information. The text did not make it abundantly clear that the company intended to send promotional material from pharmaceutical companies; the text referred to pharmaceutical **and** (emphasis added) promotional materials as if the two were wholly separate. Furthermore, the text referred to 'affiliates' of the agency. In the Panel's view pharmaceutical companies were not affiliates of the agency, and would not be seen as such. Pharmaceutical companies would be purchasing a service from the agency. Similar text appeared in the subsequent confirmatory email.

The Panel considered that the email had been unsolicited. There was no evidence to show that the complainant had given prior, fully informed, consent to receive by email promotional material from a pharmaceutical company. A breach of Clause 9.9 was ruled.

APPEAL BY GOLDSHIELD

Goldshield submitted that the complainant was telephoned and emailed by the agency in September 2007 about his interest in the services it provided. Both forms of communication clearly stated that the agency would from time to time

email details on its 'affiliates' products and services and that these might include updates on pharmaceutical and promotional materials. The wording 'pharmaceutical and promotional materials' made abundantly clear the type of services provided by the agency.

Goldshield disagreed with the Panel's comments that the text referring to pharmaceutical companies as 'affiliates' of the agency was incorrect. Webster's dictionary defined affiliate as being 'closely associated with another typically in a dependent or subordinate position' and although Goldshield had sponsored the material sent to the complainant, it was in a 'subordinate position' in that the material was written independently by writers provided by the agency.

Goldshield further submitted that not only did the complainant give his permission on two different occasions – in the first instance when he gave the agency his email address and secondly by email, when he logged onto the agency database site using a verification code before registering – he was provided with nine opportunities between September and December 2007 to opt out of the services provided by the agency, all of which he declined.

Goldshield noted that Clause 9.9 of the Code stated that 'the telephone, text message, email, telemessage, facsimile, automated calling systems and other electronic data communications should not be used for promotional purposes except with prior permission from the recipient'. Goldshield submitted that it had acted within the Code (both by telephone and email) and had not contacted the complainant without his permission.

COMMENTS FROM THE COMPLAINANT

The complainant alleged that in essence Goldshield submitted that its communication was reasonable because it had been told by the agency that he had 'opted in' to receive promotional material. The complainant had not done so, and the agency had never telephoned him to ask if it could send him educational/promotional material. The reason he had protested about being sent unsolicited promotional emails was exactly because it was unsolicited. The agency had telephoned the complainant stating that its records showed he had been telephoned and had consented to this information being sent, however this was incorrect.

The complainant submitted that Goldshield did not have to simply accept his word that the agency had sent unsolicited commercial promotional emails, one of his medical colleagues confirmed that she had been receiving unsolicited educational emails from the agency. She also denied that she had been telephoned by the agency to consent to receive this information. (The other doctor emailed the Authority separately to confirm these facts).

The complainant stated that Goldshield could believe either its agent (which clearly had a vested interest in denying its behaviour was unacceptable) or the account from two GPs with no vested interests in this matter at all, other than the hope that the agency would be instructed to desist.

APPEAL BOARD RULING

The Appeal Board noted that the parties' accounts differed; it was difficult in such cases to know exactly what had transpired. A judgement had to be made on the available evidence and the balance of probabilities.

The Appeal Board noted that no documentation specific to the complainant was provided by Goldshield to support its position that he was telephoned and had given his fully informed and explicit permission for pharmaceutical promotional material to be sent to his email address.

The Appeal Board noted Goldshield's submission that on nine occasions the complainant had declined to opt out of the service. The Appeal Board disagreed with the company's view that this implied a positive action on the complainant's part to ensure continued receipt of emails.

The Appeal Board noted that the complainant alleged that he had received an unsolicited email promoting MacroBid. His colleague's submission did not refer to Goldshield but lent some support to his position given that she stated that she had also received unsolicited emails from the agency.

The Appeal Board considered that on the balance of probability the email received by the complainant had been unsolicited. The complainant had not given prior permission to receive the promotional material by email. The Panel's ruling of a breach of Clause 9.9 was upheld. The appeal was thus unsuccessful.

* * * * *

The Authority subsequently reported Goldshield to the Code of Practice Appeal Board in accordance with Paragraph 11 of the 2006 Constitution and Procedure because the company failed to provide the requisite undertaking and assurance in relation to the Appeal Board's ruling of a breach of the Code.

COMMENTS ON THE REPORT FROM GOLDSHIELD

Goldshield stated that it had some serious manufacturing issues with respect to a range of products and had to spend a huge amount of time resolving these with the Department of Health and the Medicines and Healthcare products Regulatory Agency. This had placed considerable strain on the whole company.

Goldshield stated that its reservations about the findings related to the issue about whether the email was unsolicited. As the sign up process had included telephone contact and an online sign-up which included the words 'pharmaceutical and promotional' in the statement to which the doctor had agreed and the doctor had had several opportunities to opt out and had not taken these, then Goldshield found it very difficult to understand how the email could have been considered as SPAM. Goldshield was happy to accept that the wording could be made even clearer.

In addition, Goldshield also felt very frustrated as it had gone to some lengths to check that all the proper sign up procedures were being used when it selected the agency.

Goldshield submitted that as it had always endeavoured to comply with the Code it had given an instruction that the company should not use the agency until such time as it had a statement that could be considered clear and acceptable. This had now been undertaken.

Goldshield stated it would always make the best efforts to comply with the Code and it had had an internal review to strengthen its procedures in this respect. An amended form of undertaking had been signed.

APPEAL BOARD CONSIDERATION

The Appeal Board was very concerned that Goldshield had not provided the requisite undertaking within the time set out in the Constitution and Procedure (Paragraph 10.2). The form should have been provided by 16 May. Goldshield had stopped the activity in question but had not provided the undertaking until 14 July 2008. The Appeal Board noted that the company was not a member of the ABPI but it had agreed to comply with the Code and accept the jurisdiction of the Authority. The Appeal Board decided that as in effect Goldshield had not continued to use material in breach of the Code it would not take further action at this stage. It expected the company to comply with the Constitution and Procedure in the future otherwise it could no longer be included on the list of non members that complied with the Code.

Complaint received	**25 January 2008**
Undertaking received	**14 July 2008**
Case completed	**16 July 2008**

CASE AUTH/2115/4/08

ROCHE v GLAXOSMITHKLINE

Press releases for Tykerb/Tyverb on corporate website

Roche complained about two press releases for Tykerb/Tyverb (lapatinib) posted on GlaxoSmithKline's corporate website (www.gsk.com). Tykerb was already licensed in the US. Tyverb was the registered brand name for lapatinib in Europe and the proposed trade name in certain other markets pending regulatory approval. Lapatinib was used in the treatment of advanced or metastatic breast cancer.

Roche alleged that a press release titled 'GlaxoSmithKline reviews positive EMEA opinion for a conditional approval of Tyverb', dated 14 December 2007, was promotional, unbalanced and did not accurately and fairly reflect available evidence, in breach of the Code. In particular Roche was concerned at the selective representation of lapatinib efficacy data, and misleading downplaying of adverse events.

Roche was concerned that a quotation from Piccart, '… this is just the beginning given the ongoing clinical programme investigating the potential use of lapatinib in earlier stages of the disease' implied an unsubstantiated claim for activity of lapatinib in early breast cancer.

Roche alleged that the press release implied that lapatinib was effective for the treatment of brain metastases and that additional data to be presented at an international meeting would substantiate this. GlaxoSmithKline claimed that the use of words such as 'potential' made this acceptable. Roche considered that this did not make the section balanced and fair in that it was speculative and implied lapatinib activity where there was no substantiation. Roche noted that on one hand, GlaxoSmithKline argued that the press release solely concerned the data relevant to the conditional positive opinion from the European Medicines Evaluation Agency (EMEA), and used this as a justification for not including a full and balanced picture of lapatinib's data in brain metastases.

Conversely, however, the press release unduly emphasised data from a retrospective brain metastases analysis and advertised the fact that further data would be presented. This was not relevant to the purpose of the press release and constituted promotion prior to licence. Furthermore, a full and balanced picture of the brain metastases data (ie that studies in this area had failed to meet their primary endpoints) had not been provided.

Roche alleged that the statement 'The majority of adverse events were mild to moderate in severity and were not significantly higher than those seen with capecitabine' was misleading and did not give a fair and balanced impression of the additional side effects associated with lapatinib. The press release inaccurately implied that toxicity with lapatinib was negligible. It was important to provide information about the additional toxicity attributable to lapatinib (ie a significant increase in diarrhoea, dyspepsia and rash) to provide balance alongside claims of additional efficacy. Roche further noted that this was not a straight comparison since a lower dose of capecitabine was used in the combination arm of the study compared with the capecitabine monotherapy arm. The company was also concerned at the lack of reference to more serious adverse events, such as cardiac toxicity. Roche alleged that downplaying of serious adverse events potentially prejudiced patient safety.

Roche also considered that it was inappropriate to place the press release on an open-access UK website; it was on GlaxoSmithKline's homepage not the investors' section of the website. GlaxoSmithKline had claimed that the intended audience for the press release was business journalists, but Roche considered that this was ambiguous in terms of both content and placement of the press release.

The Panel noted that the press release had been issued in the UK and that it referred to Tyverb, the proposed brand name for lapatinib in the UK. The Panel thus considered that the press release came within the scope of the Code.

The press release was principally about the positive opinion given by the EMEA with regard to the use of lapatinib, in combination with capecitabine, in the treatment of patients with advanced or metastatic breast cancer whose tumours over-expressed HER2. The EMEA had recommended that a conditional marketing authorization be granted. Patients had to have progressive disease despite prior therapy with other antineoplastic agents. Piccart had welcomed the positive opinion and stated that lapatinib represented an important new treatment option for a group of patients in real need of alternative therapies. Piccart further stated 'Not only that, but this is just the beginning given the ongoing clinical programme investigating the potential use of lapatinib in earlier stages of the disease'. The Panel did not consider that, within the context in which it appeared, the statement implied activity of lapatinib in early breast cancer as alleged. No breaches of the Code were ruled.

The press release gave details of the data upon

which the EMEA had based its positive opinion. Readers were then told that, in addition to the achievement of the primary endpoint, results had demonstrated the associated potential to reduce the incidence of brain metastases as the first site of recurrence in metastatic breast cancer. The Tyverb summary of product characteristics (SPC) was cited in support of a statement that progression of brain metastases was 2% in the combination arm compared with 6% in the capecitabine alone arm. It was further noted that central nervous system metastases were a major burden for breast cancer patients and that the latest data on the use of lapatinib and capecitabine in brain metastases would be presented at a major breast cancer symposium on 16 December 2007 (two days after the press release was issued).

The press release explained that a conditional marketing authorization was granted to a medicine that fulfilled an unmet medical need when the benefit to public health of immediate availability outweighed the risk inherent in the fact that additional data were still required. In the case of lapatinib, GlaxoSmithKline was to provide further data from the pivotal study and also additional demonstration of decreased incidence of relapse in the central nervous system, for which a study would be conducted. It was further explained that the conditional marketing authorization would be valid for one year and thereafter might be renewed annually.

The Panel did not consider that undue emphasis had been given to the brain metastases data as alleged. The press release was factual and low key in this regard. The data was topical, given that it was about to be discussed at a major breast cancer symposium, and was not irrelevant to the conditional marketing authorization recommended by the EMEA. It was clear that the results were preliminary and were the basis of ongoing research. The data was included in the draft Tyverb SPC. No breaches of the Code were ruled. The Panel did not consider that the press release constituted promotion of lapatinib prior to the grant of a marketing authorization as alleged. No breaches of the Code were ruled.

The Panel noted that the press release stated that the most common adverse events during therapy with lapatinib plus capecitabine were gastrointestinal (diarrhoea, nausea and vomiting) or skin disorders (rash and hand and foot syndrome). It was further stated that the majority of adverse events were mild to moderate in severity and were not significantly higher than those seen with capecitabine monotherapy. There was no reference to more serious adverse events such as cardiac toxicity. In that regard the Panel noted that decreased left ventricular ejection fraction (LVEF) was listed in the draft Tyverb SPC as a common cardiac disorder adverse reaction associated with therapy. The SPC further stated that LVEF should be evaluated in all patients prior to initiation of treatment and that it should continue to be evaluated during treatment to ensure that it did not decline to an unacceptable level.

The Panel considered that the brief reference to adverse effects in the press release was misleading as alleged and did not reflect the available evidence. In that regard the risk benefit profile of lapatinib had not been presented fairly. Breaches of the Code were ruled.

The Panel noted that the material at issue was a press release specifically aimed at business journalists and analysts/investors. In that regard the Panel did not consider that the press release constituted an advertisement to the public for lapatinib. No breach of the Code was ruled.

Despite undertakings in inter-company dialogue from GlaxoSmithKline that it would remind its corporate colleagues not to use names excessively in press releases, Roche was concerned that a press release dated 18 March 2008 and titled 'Tyverb (lapatinib) European regulatory update' had been posted on the www.gsk.com website which breached the Code by using the stylized brand name more than ten times in the opening five paragraphs.

The Panel noted that the press release had been issued in the UK and that it referred to Tyverb, the proposed brand name for lapatinib in the UK. The Panel thus considered that the press release came within the scope of the Code.

The Panel noted that Tyverb was referred to ten times in the first five paragraphs of text. There were, however, twelve paragraphs of text and in all Tyverb was referred to twelve times. Although each reference to the product name was in italics the Panel noted that the text was not emboldened; the product name did not appear in logo type. Lapatinib was referred to seven times. The press release was about a delay in the regulatory procedure for Tyverb due to reports of hepatotoxicty. The Panel considered that although it would have been preferable not to have mentioned Tyverb so frequently, taking all the circumstances into account, it did not consider that the references to Tyverb were excessive or in a style such as to make the press release promotional as alleged. No breach of the Code was ruled which was upheld on appeal by Roche.

Roche Products Ltd complained about two press releases for Tykerb/Tyverb (lapatinib) posted on GlaxoSmithKline's corporate website (www.gsk.com). Tykerb was already licensed in the US. Tyverb was the registered brand name for lapatinib in Europe and the proposed trade name in certain other markets pending regulatory approval. Lapatinib was used in the treatment of advanced or metastatic breast cancer.

GlaxoSmithKline noted that the corporate press releases at issue were available on www.gsk.com

via the 'Media Centre', which was aimed at business journalists and the investor/analyst community. The following statement on the 'Media Centre' home page (available at www.gsk.com/media/index.htm) made it very clear the audience for which the information was intended: 'These press releases are intended for business journalists and analysts/investors. Please note that these releases may not have been issued in every market in which GSK operates.' In addition, each press release bore the following explicit wording at the top: 'This press release is intended for business journalists and analysts/investors. Please note that this release may not have been issued in every market in which GlaxoSmithKline operates.'

GlaxoSmithKline acknowledged that links to latest press releases appeared on the GlaxoSmithKline home page but under the heading 'Corporate press releases'. Clicking the title of a particular release opened the release itself within the 'Media Centre' with the header described above. Thus, whilst the content of www.gsk.com, including the 'Media Centre', could be accessed by the public, GlaxoSmithKline considered that the intended audience of these releases was clear and unambiguous.

1 Press release dated 14 December 2007: 'GlaxoSmithKline receives positive EMEA opinion for a conditional approval of Tyverb'

COMPLAINT

Roche alleged that the press release was promotional, unbalanced and did not accurately and fairly reflect available evidence, in breach of Clauses 3.1, 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 9.1 and 20.2. In particular Roche was concerned at the selective representation of lapatinib efficaty data, and misleading downplaying of adverse events:

- **Use of a quotation from Piccart:** Roche was concerned about the language used in this quotation, particularly the sentence '… this is just the beginning given the ongoing clinical programme investigating the potential use of lapatinib in earlier stages of the disease'. Clause 7.10 of the Code clearly stated that 'Claims should not imply that a medicine or an active ingredient has some special merit, quality or property unless this can be substantiated'. The quotation implied activity of lapatinib in early breast cancer – a claim which could not be substantiated. Roche further alleged a breach of Clause 7.4.

- **Data on progression with brain metastases:** Roche alleged that the information presented implied that lapatinib was effective for the treatment of brain metastases and that additional data to be presented at an international meeting would substantiate this. GlaxoSmithKline claimed that the use of words such as 'potential' made this acceptable. Roche considered strongly that this did not make the section balanced and fair, but in fact constituted a further breach of Clause 7.10 in that it was speculative and implied lapatinib activity where there was no substantiation. Roche noted that on one hand, GlaxoSmithKline argued that the press release solely concerned the data relevant to the conditional positive opinion from the EMEA, and used this as a justification for not including a full and balanced picture of lapatinib's data in brain metastases. Conversely, however, the press release unduly emphasised the retrospective brain metastases analysis from the EGF 100151 trial and advertised the fact that further data would be presented at an international meeting. By GlaxoSmithKline's own admission, this was not relevant to the purpose of the press release and Roche alleged that this constituted promotion prior to licence, in breach of Clauses 3.1 and 3.2. Furthermore, Roche alleged that a full and balanced picture of the brain metastases data (ie that specific studies in this area had failed to meet their primary endpoints) had not been provided, in breach of Clauses 7.2, 7.10, 9.1 and 20.2.

- **Adverse event data:** Roche considered that the statement 'The majority of adverse events were mild to moderate in severity and were not significantly higher than those seen with capecitabine' was misleading and did not give a fair and balanced impression of the additional side effects associated with lapatinib. The press release inaccurately implied that toxicity with lapatinib was negligible. It was important to provide information about the additional toxicity attributable to lapatinib (ie a significant increase in diarrhoea (60% vs 39%, $p<0.001$), dyspepsia (11% vs 3%, $p=0.014$) and rash (27% vs 15%, $p=0.011$)) to provide balance alongside claims of additional efficacy. Roche further noted that this was not a straight comparison since a lower dose of capecitabine was used in the combination arm of the study compared with the capecitabine monotherapy arm. Roche alleged breaches of Clauses 7.2, 7.3, 7.4 and 7.9. The company was also concerned at the lack of reference to more serious adverse events, such as cardiac toxicity, with lapatinib in the press release. The Code required information to be fair and balanced (Clause 7.2) and reflect available evidence (Clause 7.10) and so it was not sufficient to simply list the most common adverse events, as this ignored less common adverse events which might be more serious or clinically significant. This general principle was supported by Clause 4.2 which stated that information should include common side-effects, serious side-effects and precautions and contraindications. Since cardiac safety was an important clinical issue in breast cancer management Roche considered that it was inappropriate to downplay the cardiac toxicity seen with lapatinib. Since the US prescribing information for lapatinib (ie available evidence) referred to the need for regular cardiac monitoring, decreases in left ventricular ejection

fraction (LVEF) and prolongation of the QT interval under 'Warnings and Precautions' (and in light of the warning letter from the Food and Drug Administration (FDA) to GlaxoSmithKline regarding the company's omission of the most serious and important risk information in the lapatinib-related literature) Roche considered that the UK company should include such important information. Roche alleged that downplaying of serious adverse events breached Clauses 7.2 and 7.9 and potentially prejudiced patient safety.

Roche also considered that it was inappropriate to place the press release on an open-access UK website; it was placed on GlaxoSmithKline's homepage not on the investors' section of the website. Roche noted that GlaxoSmithKline claimed that the intended audience for the press release was business journalists, but considered that this was ambiguous in terms of both content and placement of the press release.

Roche considered that the press release fell within the scope of the Code since it was freely accessible to the UK public, related to a prescription only medicine, had been placed on the Internet by a UK company (issued in London) and referred to the availability or use of lapatinib in Europe, which included the UK (see Case AUTH/2046/9/07). Roche alleged a breach of Clause 20.1.

RESPONSE

GlaxoSmithKline explained that the purpose of the press release was to highlight positive European Medicines Evaluation Agency (EMEA) opinion for the conditional approval of lapatinib (in combination with capecitabine). Communication of such business-important information was expected and appropriate for the business/financial audience for which this release was intended.

Use of the Piccart quotation: GlaxoSmithKline noted that the sentence referred to by Roche was the last in a four-sentence quotation by Piccart, and should not therefore be considered in isolation. The full quotation was:

'This positive opinion is fantastic news for eligible women with ErbB2-positive [HER2-positive] breast cancer across the European Union. Thousands of women are diagnosed every year in Europe with ErbB2-positive breast cancer and are at a greater risk of disease progression and death compared to women with tumours that do not over-express this protein,' said Dr Martine Piccart, Professor of Oncology, Université Libre de Bruxelles and Department Head, Medicine, Jules Bordet Institute, Brussels. *'Lapatinib represents an important new treatment option for a group of patients in real need of alternative therapies and I look forward to the day that I can prescribe lapatinib. Not only that, but this is just the beginning given the ongoing clinical programme investigating the potential use of lapatinib in earlier stages of the disease.'*

GlaxoSmithKline considered that the sentence highlighted by Roche was acceptable and balanced when read in the context of the whole quotation and the preceding paragraphs of the press release. Indeed, the opening paragraph of the release clearly and explicitly referred to the indication for lapatinib (ie patients with advanced or metastatic breast cancer whose tumours overexpressed HER2 and who had progressive disease following prior therapy with anthracyclines, taxanes and therapy with trastuzumab in the metastatic setting) so that there was no ambiguity as to which patients it would be licensed for and therefore had demonstrated activity in.

GlaxoSmithKline did not accept that this final sentence of the quotation suggested definitive activity or efficacy for lapatinib in earlier stages of breast cancer. It most certainly did not imply that lapatinib had some special merit, quality or property. It was a statement of fact that trials evaluating lapatinib in earlier stages of breast cancer were ongoing. This reflected the usual sequence of oncology medicine development, in which efficacy was established in advanced/metastatic disease before progressing to trials in earlier stages of disease. The sentence was accurate and fair in acknowledging that the clinical development was *'ongoing'* and was investigating the *'potential'* for lapatinib in this setting.

In summary, GlaxoSmithKline firmly considered that this closing sentence was fair and balanced in the context of the whole quotation, which was primarily concerned with welcoming the good news regarding the positive opinion for lapatinib as a new treatment option for women with HER2-positive advanced breast cancer who had progressed on trastuzumab, an area of unmet clinical need for which there were currently no specifically licensed treatment options. It was entirely appropriate, given the intended audience, to highlight that not only had a positive opinion been reached for lapatinib in a late-stage setting but that further development work in earlier settings was ongoing. GlaxoSmithKline denied breaches of Clauses 7.4 and 7.10 of the Code.

Data on progression with brain metastases: As stated in the opening paragraph of the release, the indication for which lapatinib had received positive opinion for a conditional approval was for use in combination with capecitabine for patients with advanced or metastatic breast cancer whose tumours overexpressed HER2. Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes, and therapy with trastuzumab in the metastatic setting. Thus, GlaxoSmithKline emphasised that any patient with advanced/metastatic breast cancer, including those with brain metastases from breast cancer, would be eligible to receive lapatinib in combination with capecitabine providing they had received the specified pre-treatments in the correct settings.

GlaxoSmithKline noted Roche's allegation that undue emphasis was given to the retrospective brain metastases analysis from the EGF100151 trial, the pivotal study supporting this indication. In addition, the company had asserted that the use of the word *'potential' ('associated potential to reduce the incidence of brain metastases as first site of recurrence .....')* was speculative and implied lapatinib activity where there was no substantiation, in breach of Clause 7.10.

GlaxoSmithKline did not accept that these data were overly emphasised. They were germane to the positive opinion from the EMEA for the use of lapatinib in combination with capecitabine and therefore appropriate to include in the press release. Further, given that the management of breast cancer with brain metastases was a major clinical challenge for which few treatments were available and new options were urgently required, any new data in this area was of high clinical and scientific interest and relevant to the business/investor community to whom the release was directed. GlaxoSmithKline had taken great care to represent the data in a balanced and transparent manner. The information was presented separately from and following the study's primary endpoint results. The word *'potential'* was deliberately included to accurately reflect the volume of evidence to date and, as discussed in a later paragraph of the release, a requirement of lapatinib's conditional marketing authorization was additional demonstration of reduced incidence of relapse in the central nervous system. In addition, it was fairly acknowledged that these data were *'preliminary'* and were the *'basis of ongoing research in this area'*. Nevertheless, the inclusion of these data in section 5.1 of the lapatinib draft summary of product characteristics (SPC) surely indicated some evidence of activity in this regard, as well as evidence of the clinical importance of such data in this area of high unmet medical need. GlaxoSmithKline therefore did not accept that the statements were misleading and incapable of substantiation and denied the alleged breaches of Clauses 7.2 and 7.10.

GlaxoSmithKline disagreed with Roche's allegation that these data were not relevant to the purpose of the press release and therefore constituted promotion prior to licence in breach of Clauses 3.1 and 3.2. As explained above, the data on brain metastases provided in the release were from the pivotal EGF100151 trial underpinning the registration of lapatinib plus capecitabine and were therefore pertinent to the positive opinion that formed the prime focus of the release. It was entirely appropriate to give the business/investor community this information given the high level of interest and unmet medical need in this area.

Finally, GlaxoSmithKline noted that Roche had alleged that the press release did not provide a full and balanced picture of data regarding lapatinib in brain metastases by not referring to two studies in this area that had failed to meet their primary endpoint, constituting breaches of Clauses 7.2, 7.10, 9.1 and 20.2.

The studies in question were both by Lin *et al* (CTEP 6969 and EGF 105084); they evaluated lapatinib monotherapy as treatment for patients with progressive brain metastases following trastuzumab and cranial radiotherapy, and hence, were not relevant to the press release which was concerned with the positive opinion for the lapatinib plus capecitabine combination. However, in the extension phase of EGF105084, some patients went on to receive the same lapatinib plus capecitabine combination with which the press release was concerned, and therefore, GlaxoSmithKline considered that it was appropriate to refer to the fact that latest data for this combination were to be presented at the forthcoming international meeting. For the above reasons, GlaxoSmithKline denied the alleged breaches. In particular, since the press release was not directed to the public the company strongly refuted the alleged breach of Clause 20.2.

Adverse event data: Roche had asserted that the statement *'The majority of adverse events were mild to moderate in severity and were not significantly higher that those on capecitabine monotherapy'* was misleading and gave an inaccurate impression of the additional side effects associated with lapatinib. Roche further stated that the important information to provide was what additional toxicity was attributable to lapatinib.

GlaxoSmithKline disagreed. The company considered that it was more important and relevant to highlight the safety profile of the lapatinib plus capecitabine combination that patients would receive in clinical practice rather than focus on that of lapatinib *per se*. Indeed, the preceding sentence in the press release appropriately described the most common adverse events associated with this combination as being *'gastrointestinal (diarrhoea, nausea and vomiting) or skin disorders (rash and hand and foot syndrome)'*.

The sentence at issue correctly referred to the *'majority'* of adverse events not being significantly higher in the combination arm versus capecitabine alone. Indeed, the adverse event table presented in the Geyer publication listed 18 adverse events, of which only 3 (diarrhoea, rash, dyspepsia) were significantly greater with the combination. This amounted to 15 of 18 events (the great majority) for which there was not a significant difference between the combination and capecitabine monotherapy.

In addition, whilst the total incidence of diarrhoea, rash and dyspepsia (ie at any grade) was higher in the combination arm, the difference was mainly accounted for by an increase in grade 1 and 2 events; for each, the incidence of grade 3 or 4 events was very similar between treatment groups.

Thus, GlaxoSmithKline continued to believe that the paragraph in the press release correctly and fairly

reflected the adverse event profile reported for lapatinib plus capecitabine compared with capecitabine alone in the pivotal EGF100151 study. The company strongly denied breaches of Clauses 7.2, 7.3, 7.4 and 7.9 of the Code.

GlaxoSmithKline noted Roche's concern at the lack of reference to more serious events, such as cardiac toxicity.

As discussed earlier, the purpose of the release was to communicate positive EMEA opinion for conditional approval of lapatinib (in combination with capecitabine) to the business/investor community. It was not intended to provide comprehensive safety information on the product for clinicians/prescribers. The release therefore listed only those adverse events that were most commonly observed with lapatinib plus capecitabine therapy in the pivotal registration study.

GlaxoSmithKline accepted that cardiac safety was an important clinical issue in breast cancer management and believed that it was relevant to discuss such events and cardiac monitoring requirements in materials directed at health professionals once the product was licensed and commercially available.

In conclusion, GlaxoSmithKline did not accept that the press release was misleading with respect to the safety information provided, given its focus on the positive EMEA opinion, and the company denied breaches of Clauses 7.2, 7.9 and 7.10. GlaxoSmithKline strongly refuted the allegation that the press release potentially prejudiced patient safety given the audience for which it was intended and the fact that lapatinib was currently only available in the UK through a clinical trials programme with guidance on cardiac monitoring; it was not commercially available.

PANEL RULING

The Panel noted that the press release had been issued in the UK and that it referred to Tyverb, the proposed brand name for lapatinib in the UK. The Panel thus considered that the press release came within the scope of the Code.

The press release was clearly marked as being intended for business journalists and analysts/investors and not for distribution to US media. The press release also stated that it might not have been issued in every market in which GlaxoSmithKline operated. The supplementary information to Clause 20.2, Financial Information, stated that information made available in order to inform shareholders, the Stock Exchange and the like by way of annual reports and announcements etc, might relate to both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. Business press releases should identify the business importance of the information.

The press release was principally about the positive opinion given by the EMEA with regard to the use of lapatinib, in combination with capecitabine, in the treatment of patients with advanced or metastatic breast cancer whose tumours over-expressed HER2. The EMEA had recommended that a conditional marketing authorization be granted. Patients had to have progressive disease despite prior therapy with other antineoplastic agents. Piccart had welcomed the positive opinion and stated that lapatinib represented an important new treatment option for a group of patients in real need of alternative therapies. Piccart further stated 'Not only that, but this is just the beginning given the ongoing clinical programme investigating the potential use of lapatinib in earlier stages of the disease'. The Panel did not consider that, within the context in which it appeared, the statement implied activity of lapatinib in early breast cancer as alleged. No breaches of Clauses 7.4 and 7.10 were ruled.

The Panel was concerned that the press release referred to the positive opinion being '… fantastic news …' as this might not meet the requirements of the Code with regard to balance etc. Nevertheless there was no specific complaint on this point. It requested that GlaxoSmithKline be advised of its concerns in this regard.

The press release gave details of the data upon which the EMEA had based its positive opinion. Readers were then told that, in addition to the achievement of the primary endpoint, results had demonstrated the associated potential to reduce the incidence of brain metastases as the first site of recurrence in metastatic breast cancer. The Tyverb SPC (GlaxoSmithKline data on file) was cited in support of a statement that progression of brain metastases was 2% in the combination arm compared with 6% in the capecitabine alone arm. It was further noted that central nervous system metastases were a major burden for breast cancer patients and that the latest data on the use of lapatinib and capecitabine in brain metastases would be presented at a major breast cancer symposium on 16 December 2007 (two days after the press release was issued).

The press release explained that a conditional marketing authorization was granted to a medicine that fulfilled an unmet medical need when the benefit to public health of immediate availability outweighed the risk inherent in the fact that additional data were still required. In the case of lapatinib, GlaxoSmithKline was to provide further data from the pivotal study and also additional demonstration of decreased incidence of relapse in the central nervous system, for which a study would be conducted. It was further explained that the conditional marketing authorization would be valid for one year and thereafter might be renewed annually.

The Panel did not consider that undue emphasis

had been given to the brain metastases data as alleged. The press release was factual and low key in this regard. The data was topical, given that it was about to be discussed at a major breast cancer symposium, and was not irrelevant to the conditional marketing authorization recommended by the EMEA. It was clear that the results were preliminary and were the basis of ongoing research. The data was included in the draft Tyverb SPC. No breaches of Clauses 7.2, 7.10, 9.1 and 20.2 were ruled. The Panel did not consider that the press release constituted promotion of lapatinib prior to the grant of a marketing authorization as alleged. No breaches of Clauses 3.1 and 3.2 were ruled.

The Panel noted that the press release stated that the most common adverse events during therapy with lapatinib plus capecitabine were gastrointestinal (diarrhoea, nausea and vomiting) or skin disorders (rash and hand and foot syndrome). It was further stated that the majority of adverse events were mild to moderate in severity and were not significantly higher than those seen with capecitabine monotherapy. There was no reference to more serious adverse events such as cardiac toxicity. In that regard the Panel noted that decreased LVEF was listed in the draft Tyverb SPC as a common cardiac disorder adverse reaction associated with therapy. Under special warnings and precautions for use (section 4.4 of the SPC) it was stated that LVEF should be evaluated in all patients prior to initiation of treatment and that it should continue to be evaluated during treatment to ensure that it did not decline to an unacceptable level.

The Panel considered that the brief reference to adverse effects in the press release was misleading as alleged and did not reflect the available evidence. In that regard the risk benefit profile of lapatinib had not been presented fairly. Breaches of Clauses 7.2, 7.3, 7.4, 7.9 and 7.10 were ruled.

The Panel noted that the material at issue was a press release specifically aimed at business journalists and analysts/investors. In that regard the Panel did not consider that the press release constituted an advertisement to the public for lapatinib. No breach of Clause 20.1 was ruled.

2 Press Release – 18 March 2008: 'Tyverb (lapatinib) European regulatory update'

COMPLAINT

Despite receiving undertakings in inter-company dialogue from GlaxoSmithKline that it would remind its corporate colleagues not to use names excessively in press releases, Roche was concerned that the press release of 18 March had subsequently been posted on the www.gsk.com website which again breached Clause 3.1 by using the stylized brand name more than ten times in the opening five paragraphs.

Again, Roche considered that this press release fell within the scope of the Code since it was freely accessible to the UK public, related to a prescription only medicine, had been placed on the Internet by a UK company (issued in London) and referred to the availability or use of the medicine in Europe, which included the UK, again Clause 3.1.

RESPONSE

GlaxoSmithKline accepted that the frequent use of the brand name was regrettable and this had been addressed with its corporate colleagues. However, the intent of this corporate press release was not promotional but to provide an update on the regulatory status for lapatinib in Europe. Marketing authorization for lapatinib in combination with capecitabine had been expected from the EU Commission between 22 February and 8 March 2008. However, the provision of new data by GlaxoSmithKline (arising from a standard pharmacovigilance review) relating to possible hepatotoxicty during treatment with lapatinib had prompted the Commission to refer lapatinib back to the Committee for Medicinal Products for Human Use (CHMP) for further discussion, thereby delaying the marketing authorization.

GlaxoSmithKline did not believe that any pharmaceutical company would set out to communicate a potential safety issue associated with its product in a promotional manner. GlaxoSmithKline put out a press release to be transparent about these new data and the reason for the regulatory delay. The company considered it entirely appropriate to keep the business community and investors appraised of such important information on a medicine in which they might have a material interest. The coverage that was generated from the release was confined to the business/financial media.

In summary GlaxoSmithKline submitted that intent of the press release was not promotional but to communicate the reason for lapatinib's regulatory delay. In addition, there was no doubt as to the intended audience for the item given the explicit statement on www.gsk.com's 'Media Centre' homepage and on the top of the item.

PANEL RULING

The Panel noted that the press release had been issued in the UK and that it referred to Tyverb, the proposed brand name for lapatinib in the UK. The Panel thus considered that the press release came within the scope of the Code.

The press release was clearly marked as being intended for business journalists and analysts/investors and not for distribution to US media. The press release also stated that it might not have been issued in every market in which GlaxoSmithKline operated. The supplementary

information to Clause 20.2, Financial Information, stated that information made available in order to inform shareholders, the Stock Exchange and the like by way of annual reports and announcements etc, might relate to both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. Business press releases should identify the business importance of the information.

The Panel noted that Tyverb was referred to ten times in the first five paragraphs of text. There were, however, twelve paragraphs of text and in all Tyverb was referred to twelve times. Although each reference to the product name was in italics the Panel noted that the text was not emboldened; the product name did not appear in logo type. Lapatinib was referred to seven times. The press release was about a delay in the regulatory procedure for Tyverb due to adverse data regarding hepatotoxicty. The Panel considered that although it would have been preferable for the press release not to mention Tyverb so frequently, taking all the circumstances into account, it did not consider that the references to Tyverb were excessive or in a style such as to make the press release promotional as alleged. No breach of Clause 3.1 was ruled.

APPEAL BY ROCHE

Roche noted that the Code clearly stated that 'the brand name of the product may be included in moderation but it should not be stylized or used in excess'. Roche submitted that it had raised similar concerns to GlaxoSmithKline twice before and on both occasions received an undertaking to address this with its corporate colleagues. Whilst Roche accepted that the subject of the press release was a safety issue with lapatinib, this did not negate the requirement to comply with the Code. Roche alleged that the press release breached Clause 3.1 by using italics which stylized the brand name 'Tyverb' and it was unnecessary and a breach of the Code to use the brand name ten times in the first five paragraphs and twelve times in total. Roche considered that the current ruling would set a precedent that was in conflict with the Code.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline submitted that the press release at issue was not intended to be promotional but to provide an update on the regulatory status for lapatinib in Europe. The marketing authorization for lapatinib in combination with capecitabine had been expected from the EU Commission between 22 February and 8 March 2008. However the provision of new data by GlaxoSmithKline arising from a standard pharmacovigilance review relating to possible hepatotoxicty during lapatinib treatment had prompted the Commission to refer lapatinib back to the CHMP for review of these data, thereby delaying the marketing authorization. Clause 20.2 of the Code allowed information to be made available in order to inform shareholders and the like about both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. The press release should identify the business importance of the information. The press release clearly met these requirements.

GlaxoSmithKline submitted that the press release itself was clearly aimed at business journalists and analysts/investors (it was headed with: 'This press release is intended for business journalists and analysts/investors'). In addition, the press release was placed in the 'Media Centre' on www.gsk.com, the home page of which also clearly stated the nature of the audience for which the information was intended.

GlaxoSmithKline submitted that it was entirely appropriate and responsible to have informed the business/financial/investor community of new data relating to possible hepatotoxicity associated with lapatinib and the impact on its regulatory status, a medicine from a company in which they might have had a material interest, particularly in an environment where there was increased interest in understanding the risks as well as the benefits of new medicines. In this context, GlaxoSmithKline strongly refuted the implication that this activity amounted to promotion prior to the grant of marketing authorization, particularly as communicating these adverse safety data might have a potentially negative impact on future sales of lapatinib and hence shareholder return. GlaxoSmithKline issued the press release to be transparent about these new data and the reasons for the regulatory delay.

As discussed above, the press release was clearly not aimed at health professionals who might have been responsible for the prescription or the supply of lapatinib. Furthermore, GlaxoSmithKline would not have informed the clinical community of a potential safety issue with one of its products via a press release. Indeed, a 'Dear Investigator' letter explaining the situation had been approved by the EMEA and sent to all investigators involved in lapatinib clinical trials.

GlaxoSmithKline noted as highlighted by Roche, that the Code stated in the supplementary information to Clause 3.1 that 'the brand name of the product may be included in moderation but it should not be stylized or used to excess'. However, this requirement applied to the provision of advance planning information to health authorities, health boards, trust hospitals and primary care trusts to assist them in estimating the budgetary impact of a new product. A press release on a product's regulatory delay did not constitute advance budgetary notification, and as such, this clause did not apply.

Given the circumstances, GlaxoSmithKline did not consider the use of the Tyverb brand name twelve times in twelve paragraphs of text to be excessive.

The product name was not emboldened and did not appear in logo type and therefore was not in a style such as to make the press release promotional as alleged. In addition, given the nature of the release it was important for the business media and investor community to be entirely clear as to what product the release referred to. The UK operating company had repeatedly advised corporate colleagues that brand names should be used in moderation in press releases, irrespective of their nature or intent. GlaxoSmithKline noted that the latest lapatinib press release (provided) concerning its recent EU marketing authorization reflected this advice.

FINAL COMMENTS FROM ROCHE

Roche had no further comments to add to those previously submitted.

APPEAL BOARD RULING

The Appeal Board noted that the press release had been issued to inform investors/business analysts and the like that the marketing authorization for Tyverb might be delayed due to a review of hepatoxicity data. It was not a good news story. The press release was not directed to clinicians or patients. The Appeal Board noted that there appeared to be a discrepancy between the companies as to how the press release was accessed on www.gsk.com. The intended audience was made clear at the start of the press release. The Appeal Board considered that it was not unacceptable to issue such a press release as long as it complied with the Code. Press releases should be factual and informative and not promote a product.

The Appeal Board considered that although the supplementary information referred to by Roche was specific to the provision of information about the advance notification of products with significant budgetary implication, and thus did not apply to the press release at issue, it nonetheless provided helpful guidance.

The Appeal Board noted that the brand name had appeared in italics in the press release; it was not unusual for brand names to be differentiated in this way from generic names. The brand name was not emboldened, enlarged, or in any other way distinctive from the surrounding text except by the use of italics. The Appeal Board, however, was concerned about the frequency with which the brand name had been used; in its view it would have been preferable if it had been used less often. Companies were obliged to comply with both the spirit and the letter of the Code. Nonetheless, taking all the circumstances into account, the Appeal Board did not consider that the references to Tyverb were excessive or in a style such as to make the press release promotional as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clause 3.1. The appeal was unsuccessful.

Complaint received **15 April 2008**

Case completed **16 July 2008**

GENERAL PRACTITIONER v SANDOZ

Email about Sandoz products

A general practitioner complained about large junk emails sent by Sandoz which crammed up clinical email boxes and slowed the computer. The complainant had tried unsuccessfully to stop receipt, and requested that the Authority find some way to stop them.

The Panel noted that the Code prohibited the sending of promotional emails except with the prior permission of the recipient. The Panel considered that the email was clearly promotional material. Whilst it had not been sent directly by Sandoz 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 since February 2008, when obtaining permission from health professionals to add them to their database, the agency which had sent the email on Sandoz's behalf had been clear that it would, from time to time, send emails which might include, *inter alia*, pharmaceutical promotional materials. The wording used before February 2008 had not been clear on this point. The Panel did not know when the complainant's details had been added to the database. The complainant had not responded to a request for the Authority to be able to reveal his identity to Sandoz. In the circumstances the Panel considered that there was nothing further that could be done. It thus ruled no breach of the Code.

COMPLAINT

A general practitioner complained about large junk emails sent by Sandoz Ltd which crammed up clinical email boxes and slowed the computer. The complainant had tried junk mail rules to stop receipt, but the agency which sent the emails used multiple email addresses which circumvented junk filters. The complainant requested that some way be found to stop them, or just stop them using the internet if the Authority had to.

When writing to the company the Authority asked it to respond in relation to Clause 9.9 of the Code.

RESPONSE

Sandoz stated that the emails in question were part of a marketing activity, which was provided by an agency. This service provider used an email account to send emails only to members of the NHS who consented to receiving information from/via the agency, including doctors, nurses and administrators. The emails contained an embedded link to a special webpage on which an independent article to a special topic (in this case pain therapy), additional information to a related Sandoz product (Fentanyl Mezolar Matrix and Fentalis Reservoir) as well as the summaries of product characteristics (SPCs) for these products could be found.

Sandoz regretted that a health professional might have been inconvenienced in this way. The company relied on the agency to have obtained consent from the health professional.

As a consequence of this complaint Sandoz had informed the agency that it had serious concerns regarding its database and records.

Sandoz provided information from the agency regarding the arrangements. In the first instance the doctor would be contacted by telephone. During this call the agency would outline who it was, what it did and that the doctor's email address was needed in order to allocate an access code to its NHS online directory service.

At that time the doctors was informed that they might, from time to time, receive communications from one of the agency's associated companies which would be relevant to their medical specialisation or administrative responsibilities. The wording was along the lines of: '[the agency] will from time to time send information by email about our affiliates' product and services which may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information.'

As a follow-up to the telephone call the doctor would then receive an email confirming the points raised in the conversation and also confirming the access code for NHS online. This email also invited comment from the recipient and asked them to contact the agency if they had any comments or needed any of their information amended. It also reiterated that they would be sent information about products and services along with other medical and non-medical information. The final paragraph of this email welcomed feedback on any aspect of the service.

The database on health professionals had been built up over approximately 15 years with regular contact between the agency's database research department and NHS organisations. During this time email addresses had been freely given by those who wished to receive information on a variety of topics.

Also, in order to ensure that only those recipients who wished to receive such material did so there was an opt-out facility on emails. The agency sent out thousands of emails each week and received less than 0.5% opt-out request's a year, a figure which spoke for itself. The agency also re-evaluated its opt-in procedures on a regular basis. A copy of Sandoz's policy was provided.

Without knowing the identity of the complainant the agency stated that it was difficult for the database department to provide information on when they were contacted.

In response to a request for further information, Sandoz stated that the wording above, used by the agency to introduce itself and its services, had been used since February 2008. Before then the wording, although similar, had referred to the sending of 'updates on specialist services, conferences and seminars, diagnostic, medical, pharmaceutical and promotional materials as well as official information'. The agency validated/re-checked its database on a six monthly rolling basis and was endeavouring to accelerate that process.

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 was clearly promotional material. Whilst it had not been sent directly by Sandoz 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 since February 2008, when obtaining permission from health professionals to add them to their database, the agency had made it clear to them 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. It was clear that the company intended to send promotional material from pharmaceutical companies. The wording used before February 2008 had not been clear on this point. The Panel did not know when the complainant's details had been added to the database. The complainant had not responded to a request for the Authority to be able to reveal his identity to Sandoz. In the circumstances the Panel considered that there was nothing further that could be done. It thus ruled no breach of Clause 9.9.

Complaint received **24 April 2008**

Case completed **30 July 2008**

CASE AUTH/2125/5/08

GLAXOSMITHKLINE v TAKEDA EUROPE

Actos journal advertisement

GlaxoSmithKline complained about an advertisement for Actos (pioglitazone) placed by Takeda Pharmaceuticals Europe in Diabetologia, April 2008. GlaxoSmithKline supplied Avandia (rosiglitazone). Pioglitazone and rosiglitazone were thiazolidinediones (TZDs).

GlaxoSmithKline noted that a previous Actos advertisement, published in January 2008 by Takeda UK had been reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA) and found in breach of the Medicines (Advertising) Regulations. The MHRA was concerned that claims relating to Actos and cardiovascular (CV) risks did not reflect the balance of risks and benefits for the product as stated in the summary of product characteristics (SPC). It was considered that the advertisement was misleading and would not encourage the rational use of Actos. In March 2008 the MHRA asked Takeda UK to provide a corrective statement and not use the advertisement again.

GlaxoSmithKline considered that the advertisement now at issue, although different to the one reviewed by the MHRA, was similar.

The advertisement in question contained the prominent claim 'There are no long-term cardiovascular concerns regarding the use of Actos (pioglitazone)'. However, there was no mention that Actos was contraindicated in patients with cardiac failure or a history of cardiac failure (NYHA stages I to IV) or might cause fluid retention which might exacerbate or precipitate heart failure and therefore additional monitoring of cardiovascular status might be required in some patients (ref SPC).

Given the limited and inadequate presentation of CV data GlaxoSmithKline alleged that the advertisement was not in accordance with the terms of the marketing authorization and was inconsistent with the particulars listed in the SPC; the information provided and the claims were not accurate and did not reflect the balance of risks and benefits as stated in the Actos SPC or contained in the data in their entirety, and were therefore misleading; by presenting inaccurate and misleading data on the CV profile of Actos the advertisement would not encourage the rational use of the medicine. GlaxoSmithKline was particularly concerned that the advertisement could prejudice patient safety, especially as the appropriate checks, required for some patients, were not specifically mentioned within the item.

GlaxoSmithKline considered the publication of the advertisement at issue shortly after action taken by the MHRA was an amazing disregard for the very serious points raised by itself and the UK regulatory agency and a breach of Takeda's undertaking to the MHRA. GlaxoSmithKline therefore alleged that Takeda had brought discredit upon, and reduced confidence in, the industry in breach of Clause 2.

Diabetologia was published in English in Germany, the editor-in-chief and editorial office was in the UK and it was circulated to UK health professionals as well as to other countries. In the Panel's view promotional material in Diabetologia was subject to the UK Code.

The Panel noted that Takeda Europe had placed the advertisement and was taking responsibility under the Code.

The Panel noted that the claim 'There are no long-term cardiovascular concerns regarding the use of Actos' appeared as a prominent diagonal highlight band across the top right-hand corner of the advertisement. The Panel considered that this claim was the main message of the advertisement and was put forward as a feature of the product which set it apart from rosiglitazone. The Panel noted however that Section 5.1, Pharmacodynamic properties, of the SPC stated 'Although the study [PROactive, a cardiovascular outcome study] failed to reach its primary endpoint, which was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation, the results suggest that there are no long-term cardiovascular concerns regarding the use of pioglitazone. However, the incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.'

Section 4.3, of the SPC stated that pioglitazone was contraindicated in patients with cardiac failure or history of cardiac failure (NYHA stages I to IV). Section 4.4, Special warnings and precautions for use, gave detailed information on fluid retention and cardiac failure stating that pioglitazone could cause fluid retention which might exacerbate or precipitate heart failure.

The Panel noted that the advertisement also included the claims that 'Actos… reduces cardiovascular (CV) risk markers', 'Actos is the only thiazolidinedione (TZD) with clinical and safety evidence from a large cardiovascular outcome study in its prescribing information' and 'Results from the CV outcome study, PROactive, confirm

there are no long-term CV concerns, such as increased risk of MI, regarding use of Actos…'.

The Panel considered that the advertisement sought to minimize prescribers' concerns regarding the CV safety profile of Actos. The claim at issue ('There are no long-term cardiovascular concerns regarding the use of Actos') was not consistent with the SPC which was more qualified regarding the outcome of the study by the use of the phrase 'the results *suggest* [emphasis added] there are no long-term cardiovascular concerns…'. In any event the information in Section 5.1, Pharmacodynamic properties, did not take priority over Sections 4.3, Contraindications, and 4.4, Special warnings and precautions for use. In the Panel's view it was not sufficient to rely on the prescribing information in the advertisement to provide the cautionary note about heart failure. A breach of the Code was ruled.

The Panel considered that the advertisement gave the impression there was no need to worry about long-term cardiovascular concerns and this was not necessarily so given that fluid retention caused by pioglitazone might exacerbate or precipitate heart failure and that pioglitazone should be discontinued if any deterioration in cardiac status occurred. The product was contraindicated in patients with, or with a history of, heart failure. The claim at issue was misleading, did not reflect the entire situation and did not encourage the rational use of Actos. Thus the Panel ruled breaches of the Code.

With regard to the use of the advertisement after the MHRA had ruled that another advertisement, placed by Takeda UK, was in breach of the advertising regulations, the Panel noted that the final date for copy for the May 2008 edition of Diabetologia was 31 March. The agreed action date between the MHRA and Takeda UK was 5 March. Takeda Europe therefore had time to change the advertisement in Diabetologia. The published report on the MHRA website stated that action had been agreed on 19 March.

The Panel noted the MHRA published report that claims relating to pioglitazone did not reflect the balance of risks and benefits as stated in the SPC. The Panel considered that the same point applied to the advertisement in Diabetologia. Given all the circumstances the material should have been amended. In addition the Panel was concerned about the implications for patient safety given its rulings above. Thus the Panel ruled a breach of Clause 2 of the Code.

GlaxoSmithKline UK Ltd complained about an advertisement (ref ACT179) for Actos (pioglitazone) placed by Takeda Pharmaceuticals Europe Limited in Diabetologia, April 2008. Diabetologia was the journal of the European Association for the Study of Diabetes. GlaxoSmithKline supplied Avandia (rosiglitazone). Pioglitazone and rosiglitazone were thiazolidinediones (TZDs). Inter-company dialogue had not resolved the issues.

COMPLAINT

GlaxoSmithKline stated that an Actos advertisement (in the style of an advertorial) published in January 2008 by Takeda UK Ltd, in Pulse and GP, was reviewed as part of the Medicine and Healthcare products Regulatory Agency's (MHRA's) scrutiny of published advertising. The MHRA was concerned that claims relating to pioglitazone and cardiovascular (CV) risks did not reflect the balance of risks and benefits for the product as stated in the summary of product characteristics (SPC). It was considered misleading and did not encourage the rational use of the product. The advertisement was found in breach of the Medicines (Advertising) Regulations. The date of action for this breach was 19 March, and the decision was published by the MHRA, on its website, on 3 April. The MHRA asked that Takeda UK Ltd provide a corrective statement regarding the content of the Actos advertisement and directed Takeda that it would not be used again (location and timeline for corrective statement were not provided in the MHRA announcement).

A similar advertisement for Actos was published in Diabetologia on 4 April 2008 and reprinted in the May edition.

GlaxoSmithKline believed this advertisement fell within the scope of the Code as it had clearly been placed by a UK-based company (Takeda Pharmaceuticals Europe Ltd), the journal content was decided upon in the UK (the editor in chief was in the UK) and the UK formed the second largest single European country in terms of journal circulation (information from publisher). The advertisement also had features suggesting that it had been reviewed under the UK Code (inclusion of black triangle, prescribing information and date of preparation of prescribing information).

GlaxoSmithKline discussed its concerns with Takeda UK Ltd but it referred GlaxoSmithKline to Takeda Europe as the advertisement was developed and placed by that company. GlaxoSmithKline had contacted Takeda Europe separately although continued to believe that Takeda UK needed to take responsibility under the Code for the UK audience that had been exposed to the advertisement.

The advertisement in question contained the prominent claim 'There are no long-term cardiovascular concerns regarding the use of Actos (pioglitazone)'. However, there was no mention that Actos was contraindicated in patients with cardiac failure or a history of cardiac failure (NYHA stages I to IV) or might cause fluid retention which might exacerbate or precipitate heart failure and therefore additional monitoring of cardiovascular status might be required in some patients (ref SPC).

Given the limited and inadequate presentation of CV data within the advertisement GlaxoSmithKline believed that:

- The advertisement was not in accordance with

the terms of the marketing authorisation and was inconsistent with the particulars listed in the SPC.
- The information provided and the claims made for pioglitazone were not accurate and did not reflect the balance of risks and benefits for the product as stated in the SPC or contained in the data in their entirety, and were therefore misleading.
- By presenting inaccurate and misleading data on the CV profile of pioglitazone the advertisement would not encourage the rational use of pioglitazone.

GlaxoSmithKline therefore alleged that Takeda UK was in breach of Clauses 3.2, 7.2, 7.9 and 7.10 of the Code.

Given that the advertisement presented inaccurate, incomplete and misleading information about the CV profile of pioglitazone, GlaxoSmithKline was particularly concerned that it might lead to the irrational use of the medicine and could prejudice patient safety, especially as the appropriate checks, required for some patients, were not specifically mentioned within the item.

Importantly, despite the fact that the MHRA provided its view of the advertorial to Takeda on 19 March and GlaxoSmithKline contacted Takeda with its concerns about this advertisement on 18 April, Takeda nevertheless printed the advertisement in Diabetologia in April and again in May. GlaxoSmithKline found this an amazing disregard for the very serious points raised by itself and the UK regulatory agency and a breach of Takeda's undertaking to the MHRA.

GlaxoSmithKline therefore alleged that Takeda had brought discredit upon, and reduced confidence in, the industry in breach of Clause 2.

RESPONSE

Takeda Europe stated that, contrary to GlaxoSmithKline's view, the Diabetologia advertisement which was the subject of the complaint was very different to the advertorial in Pulse and GP in January 2008. Firstly, the advertorial contained a detailed and discursive presentation of data concerning Actos. In marked contrast, the advertisement now at issue was a short and focussed, up-to-date summary of the Actos SPC, using short bullet points, which closely followed or else exactly reproduced the SPC.

As indicated by the MHRA press release on the previous advertisement, the MHRA considered that the repeated claims about *improved* CV risk were inappropriate in the light of information in the SPC that the product might cause fluid retention, which might exacerbate or precipitate heart failure. The MHRA considered that these positive CV risk claims for improved CV risk for Actos exaggerated the benefits of the product and overshadowed the product's contraindications and the need for ongoing patient monitoring. In its corrective statement Takeda UK accepted that it had got that balance of risks and benefits wrong. Consequently both Takeda UK and Takeda Europe recognised that more prominent statements concerning contraindications and the need for ongoing patient monitoring were appropriate in order to strike the appropriate balance where there was scope for greater discussion of product data.

The focus of the advertisement now at issue was altogether different to that of the advertorial. The advertisement in did not refer to the CV improvement claims like 'protective' or 'improve CV risk', or claim CV risk improvement using the approach developed previously, but rather followed the wording of the SPC. The text was taken from the European SPC, which stated that 'there are no long-term cardiovascular concerns'. This strictly factual approach was altogether different from claiming repeatedly cardio-protection and risk reduction which, the MHRA considered, exaggerated the product's benefits. Takeda Europe considered the information about contraindications and patient monitoring contained in the prescribing information struck an appropriate balance in the advertisement, taking into account its brevity and the low-key, strictly factual approach adopted by virtue of following the SPC. Therefore this advertisement was certainly not 'similar' to the previous advertisement and thus Takeda Europe did not accept that GlaxoSmithKline's references to the MHRA press release were applicable.

Takeda Europe submitted that the copy date for the April edition of Diabetologia was 4 March (before the agreed action date between Takeda UK and the MHRA which was 5 March). The copy date for the May edition was 31 March. Takeda Europe had already informed GlaxoSmithKline that this particular advertising campaign ended with the last advertisement in Diabetologia appearing in the May issue and that there was no intention to re-use the Diabetologia advertisement.

Takeda Europe submitted that Diabetologia was a European publication which had worldwide circulation and was therefore an international journal. Although the journal was published in English, it was not intended solely for the UK market; its largest readership was in Germany where the journal was also produced. Although Takeda Pharmaceuticals Europe had responded to the criticisms by reference to the Code, considering that only 7.4% of its readership was based in the UK, it queried whether the Diabetologia advertisement was in fact subject to the Code.

The claim that 'There are no long-term cardiovascular concerns regarding the use of Actos (pioglitazone)' was taken verbatim from the approved SPC (section 5.1) and therefore could not be stated to be inconsistent with the terms of the marketing authorization or the SPC. In line with Clauses 4.1 and 4.2 of the Code, prescribing information, which included the contraindications

and the additional monitoring requirement referred to by GlaxoSmithKline as well as the other items listed in Clause 4.2 was available on the adjacent page.

The advertisement at issue contained short factual statements about Actos rather than the discursive presentation of the data as in the advertorial in January 2008. This was done with a view to presenting an up-to-date account of the Actos label. However, each bullet point and the diagonal strapline were either taken verbatim from, or else exactly reflected, the SPC. The one exception was the fourth bullet point which referred to the results of the PROactive study – which was of course referenced in the SPC – which simply paraphrased the MHRA's own statement in its 'Drug Safety Update' of December 2007 under the heading 'Myocardial ischaemia' concerning the absence of increased risk of cardiac ischaemia in relation to pioglitazone.

In the absence of any improved CV risk or cardioprotection claims, and taking into account the derivation of each bullet point, Takeda Europe did not accept that the advertisement was not in accordance with the terms of the marketing authorization or that it contained inaccuracies or was misleading or that it failed to encourage the rational use of Actos. After all, it was difficult to see how the company could be more consistent with the SPC than by following it closely and quoting it verbatim.

Since the advertisement promoted Actos within its licence, there was no breach of Clause 3.2.

Since the prescribing information provided clearly stated that Actos could cause fluid retention which might exacerbate or precipitate heart failure and also recommended observation of patients for signs and symptoms of heart failure as well as actions to be taken in case of deterioration of cardiac status (as recommended in the SPC), there was no breach of Clauses 7.2, 7.9 and 7.10. As mentioned above, the company considered that the prescribing information constituted adequate and sufficiently complete information in view of the short format of the advertisement and the factual, closely SPC-oriented approach adopted.

Takeda Pharmaceuticals Europe considered that the advertorial and the advertisement now at issue were both qualitatively and substantively different. Following the concerns raised by the MHRA in relation to the claims made in the advertorial Takeda Europe took care to ensure that no equivalent claims (improved CV risk or cardioprotection) were used in its promotional materials. As the claims in the advertisement closely followed the SPC it believed that the advertisement complied with the Code and was in line with the MHRA's guidance to Takeda UK. Accordingly, Takeda Europe denied a breach of Clause 2.

Takeda Europe was promptly informed by Takeda UK of the MHRA's concerns about the advertorial and took appropriate steps to carefully review all its current promotional materials in the light of the MHRA's comments. As stated above the advertisement did not reproduce the claims which had prompted the MHRA's concerns. Accordingly, Takeda Europe did not accept GlaxoSmithKline's allegations that either company had failed to comply with the requirements for promoting medicines in the UK, whether in a similar fashion to matters raised by the MHRA in connection with the advertorial or otherwise.

PANEL RULING

Firstly the Panel had to decide whether the advertisement was subject to the Code. Diabetologia (Journal of the European Association for the study of Diabetes (EASD)) was published in English in Germany. The editor-in-chief and editorial office was in the UK and it was circulated to the health professionals in the UK as well as to other countries. In the Panel's view the promotional material published in Diabetologia was subject to the UK Code.

Secondly the Panel had to decide which company was responsible under the Code. The usual arrangement was that the UK company was responsible for activities in the UK even if they were carried out by overseas affiliates/head office etc. However in this instance Takeda Europe had placed the advertisement and was taking responsibility under the Code. In these circumstances the Panel considered that this was acceptable in relation to dealing with the complaint. If however Takeda Europe had not been so minded the matter would have been pursued with Takeda UK.

The Panel noted that the claim 'There are no long-term cardiovascular concerns regarding the use of Actos' appeared as a prominent diagonal highlight band across the top right-hand corner of the advertisement. The Panel considered that this claim was the main message of the advertisement and was put forward as a feature of the product which set it apart from rosiglitazone. The Panel noted however that Section 5.1, Pharmacodynamic properties, of the SPC stated 'Although the study [PROactive, a cardiovascular outcome study] failed to reach its primary endpoint, which was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation, the results suggest that there are no long-term cardiovascular concerns regarding the use of pioglitazone. However, the incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.'

Section 4.3, Contraindications, stated that pioglitazone was contraindicated in patients with cardiac failure or history of cardiac failure (NYHA

stages I to IV). Section 4.4, Special warnings and precautions for use, gave detailed information on fluid retention and cardiac failure stating that pioglitazone could cause fluid retention which might exacerbate or precipitate heart failure.

The Panel noted that the advertisement also included the claims that 'Actos… reduces cardiovascular (CV) risk markers', 'Actos is the only thiazolidinedione (TZD) with clinical and safety evidence from a large cardiovascular outcome study in its prescribing information' and 'Results from the CV outcome study, PROactive, confirm there are no long-term CV concerns, such as increased risk of MI, regarding use of Actos…'.

The Panel considered that the advertisement sought to minimize prescribers' concerns regarding the CV safety profile of Actos. The claim at issue ('There are no long-term cardiovascular concerns regarding the use of Actos') was not consistent with the SPC which was more qualified regarding the outcome of the study by the use of the phrase 'the results *suggest* [emphasis added] there are no long-term cardiovascular concerns…'. In any event the information in Section 5.1, Pharmacodynamic properties, did not take priority over Sections 4.3, Contraindications, and 4.4, Special warnings and precautions for use. In the Panel's view it was not sufficient to rely on the prescribing information in the advertisement to provide the cautionary note about heart failure. A breach of Clause 3.2 was ruled.

The Panel considered that the advertisement gave the impression there was no need to worry about long-term cardiovascular concerns and this was not necessarily so given that fluid retention caused by pioglitazone might exacerbate or precipitate heart failure and that pioglitazone should be discontinued if any deterioration in cardiac status occurred. The product was contraindicated in patients with, or with a history of, heart failure.

The claim at issue was misleading, did not reflect the entire situation and did not encourage the rational use of Actos. Thus the Panel ruled breaches of Clauses 7.2, 7.9 and 7.10.

With regard to the use of the advertisement after the MHRA had ruled that another advertisement, placed by Takeda UK, was in breach of the advertising regulations, the Panel noted that the final date for copy for the May 2008 edition of Diabetologia was 31 March. The agreed action date between the MHRA and Takeda UK was 5 March. Takeda Europe therefore had time to change the advertisement in Diabetologia. The published report on the MHRA website stated that action had been agreed on 19 March.

The Panel noted the MHRA published report that claims relating to pioglitazone did not reflect the balance of risks and benefits as stated in the SPC. The Panel considered that the same point applied to the advertisement in Diabetologia. Given all the circumstances the material should have been amended. In addition the Panel was concerned about the implications for patient safety given its rulings above. Thus the Panel ruled a breach of Clause 2 of the Code which was used as a sign of censure and reserved for such use.

Complaint received **7 May 2008**

Case completed **29 July 2008**

CASE AUTH/2126/5/08

PROCTER & GAMBLE v SERVIER LABORATORIES

Misleading and disparaging material about bisphosphonates

Procter & Gamble alleged that in a letter to prescribing advisors, a press release and and at its sponsored symposium at the British Geriatrics Society (BGS) meeting, Servier Laboratories had issued misleading and disparaging information about bisphosphonates, including Procter & Gamble's product Actonel (risedronate sodium). Servier had inferred that the anti-fracture efficacy of bisphosphonates was attenuated when co-prescribed with acid suppressants. In addition Servier was sharing these misleading messages as part of a broad strategy including communications with official bodies such as the National Institute for Health and Clinical Excellence (NICE).

This was a concerted effort by Servier to disparage oral bisphosphonates so as to influence the prescribing market in its own favour. This was achieved by urging caution when co-prescribing acid suppressants and bisphosphonates due to the increased fracture risk associated with acid suppressants; this was not only misleading but also raised inappropriate concerns about the safety of the oral bisphosphonates. Procter & Gamble alleged that by doing so, Servier brought discredit upon and reduced confidence in the pharmaceutical industry in breach of Clause 2. (Servier supplied Protelos (strontium ranelate) an alternative to bisphosphonates in osteoporosis).

There were limited and contradictory data available (two papers and one abstract) to support the first message conveyed by Servier that '…acid suppressant medication, including proton pump inhibitors (PPIs) has been associated with an increased risk of fracture'; the authors concluded that further studies were needed to confirm and explain the results. In some cases, some of the results were not statistically significant. Use of PPIs was not currently considered an established risk factor for an osteoporotic fracture. In a review of the data upon which Servier based its claims, commissioned by NICE, the final report concluded that the quality of the evidence regarding any possible association between acid suppressants and increased risk of fracture was generally poor and their design appeared to be prone to confounding.

The second message was that epidemiological data, such as that recently presented at the National Osteoporosis Conference, suggested that the anti-fracture efficacy of bisphosphonates was potentially attenuated when co-prescribed with acid suppressants (de Vries *et al* 2007). Procter & Gamble noted that this analysis, published only as an abstract, was funded by Servier. It was the first and only analysis to have shown this 'association' and the authors suggested that further studies were needed. The review commissioned by NICE concluded that 'No confidence may be placed in the results of the study by de Vries *et al* because of its failure to demonstrate comparability between exposure groups in terms of key prognostic factors, in particular whether bisphosphonates were prescribed for primary or secondary fracture prevention, and for primary or secondary osteoporosis'. The current summaries of product characteristics (SPCs) for Actonel did not caution against co-prescription of acid suppressants nor was such a potential interaction listed. Data was available for risedronate from a retrospective analysis on a subset of 5,454 patients from three phase-III fracture trials who took either placebo or risedronate (5mg daily) and who were classified as either PPI or H_2 antagonist users, or nonusers. This showed that efficacy of risedronate in reducing the risk of new vertebral fractures was not influenced by concomitant PPI and H_2 antagonist use (Roux *et al* 2008).

In conclusion Procter & Gamble believed that the numerous messages communicated by Servier on this topic were not balanced and were misleading. In addition, the inferences made regarding lack of efficacy of bisphosphonates with concomitant PPI use were disparaging.

Procter & Gamble further alleged that the use of misleading claims in a high level promotional campaign which disparaged bisphosphonates as a drug class, brought discredit upon and reduced confidence in the pharmaceutical industry in breach of Clause 2.

The detailed response from Servier is given below.

The Panel noted that when 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 the data submitted in support of the claims that the use of acid suppressants had been associated with an increased risk of fracture. Yang *et al* (2006) found a significantly increased risk of hip fracture associated with long-term PPI therapy, particularly high dose PPI. The authors, however, stated that further studies were needed to confirm their findings. Yu *et al* (2006) concluded that amongst postmenopausal women, use of acid suppressants *might* (emphasis added) be associated with an increased risk of non-spine fracture. Vestergaard *et al* (2006) concluded that PPIs appeared to be associated with an increased fracture risk in contrast to H_2 antagonists which

seemed to be associated with a decreased fracture risk. The changes in risk estimates were small in all instances and might have limited consequences; further studies were needed. De Vries *et al* concluded that concomitant use of bisphosphonates and acid suppressants was associated with an increased risk of fracture and that possibly acid suppressants attenuated the protective effects of bisphosphonates on fracture risk. The authors stated that given the frequency of co-prescription of bisphosphonates and acid suppressants, the issue required further investigation.

A critique of the evidence suggesting an association between acid suppressants and increased fracture risk stated that the data was generally poor. In its appraisal consultation document on alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women, NICE noted that data indicating that acid suppressants led to a small increase in fracture risk and that co-administration of acid suppressants and bisphosphonates might lead to an increased fracture risk compared with bisphosphonates alone was observational and tentative and different for different fracture sites and different acid suppressants. NICE considered, however, that because various studies showed a trend, caution should be exercised when the co-prescribing of acid suppressants and bisphosphonates was being considered. The committee was not persuaded, however that a change to its recommendations, based on the evidence, was necessary. The Panel noted that the NICE document was an appraisal consultation document and was marked confidential. The document stated that it did not constitute the Institute's formal guidance and its recommendations were preliminary and might change after consultation.

The Panel noted that a template letter to prescribing advisors was headed 'Increased risk of fracture associated with use of acid suppressant medication'. The Panel considered that the quality of the data was such that it could not support such a robust, unqualified claim. Although the reader was told that data *suggested* that the anti-fracture efficacy of bisphosphonates was *potentially* attenuated when co prescribed with acid suppressants (emphasis added) the Panel nonetheless considered that the letter implied that acid suppressants had been unequivocally proven to attenuate the anti-fracture efficacy of biphosphonates. The letter went on to refer to this growing body of evidence and assessment of the implications of the data, in particular the potential effect on health outcomes and healthcare budgets. It appeared that the data had proven clinical implications and this was not so. In that regard the Panel considered the letter was not balanced and did not reflect the data accurately. A breach of the Code was ruled. The implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. Breaches of the Code were ruled and upheld on appeal by Servier.

The press release was headed 'Servier welcomes revised draft NICE guidance'. The third paragraph began 'Servier also welcomes the acknowledgement by NICE in its draft guidance that caution should be exercised when considering the co-prescription of acid suppressants and bisphosphonates'. Readers were also told that NICE had previously failed to address the increased risk of fractures associated with the use of acid suppressants, in particular PPIs, which were commonly co-prescribed with bisphosphonates. The Panel considered that the quality of the data was such that it could not substantiate such robust unqualified claims. The tentative nature of the data acknowledged by NICE, was not referred to in the press release. The Panel considered that the press release was not balanced and did not reflect the data accurately. A breach of the Code was ruled. The Panel also considered that the implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. Breaches of the Code were ruled and upheld on appeal by Servier.

The Panel noted that Servier's sponsored symposium at the BGS meeting had included a presentation entitled 'Acid Suppressant Medication and Fractures'. The speaker's briefing notes stated that the objective was to communicate on the use of PPIs in osteoporotic patients and the associated risks. Then to give a primary care perspective on how to manage patient cases not covered by NICE guidance. Points to include in the presentation were, *inter alia*: acid suppressants and increased risk of fracture; attenuation of bisphosphonate efficacy when acid suppressants were co-prescribed; how to identify patients at risk of PPIs if prescribed an oral bisphosphonate and the conclusion was to consider prescribing an appropriate agent for these patients – eg strontium ranelate [Servier's product Protelos]. The speaker was further advised that the tone of the presentation should cause delegates to think about their current medical practice and then provide them with a simple solution to the problem.

The final slide of the presentation was headed 'Summary: overview of evidence' and detailed the findings of Yang *et al* and Vestergaard *et al*. In the Panel's view the results of the two studies were presented on the slide as if the findings had been unequivocal; the authors' comments as noted above had not been included. There was no transcript of the presentation although the speaker had provided an overview of what he had said. With regard to the last slide the speaker stated that he had said that there might be a reduction in the effect of a bisphosphonate with PPI usage; this needed further study. The Panel considered, however, that the tentative nature of the data was not reflected in the slides and in its view delegates would be left with the impression that acid

suppressants, particularly PPIs, had been unequivocally proven to attenuate the anti-fracture efficacy of bisphosphonates with proven clinical implications. In that regard the Panel considered that the slides were not balanced and did not reflect the data accurately. A breach of the Code was ruled. The implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. A breach of the Code was ruled.

The Panel noted its rulings above but nonetheless did not consider that there had been a breach of Clause 2 of the Code which was reserved for use as a sign of particular censure. This ruling was not appealed

The Appeal Board noted Servier's submission that the slides used at the BGS presentation were not intended to stand alone. The company had emphasised that attendees had not been given copies of the presentation. In the Appeal Board's view, however, a company could not rely on a speaker to qualify or explain otherwise misleading slides and in that regard it was irrelevant as to whether they were given to the attendees.

Servier's sponsored symposium at the BGS was entitled 'Trips, slips and fractured hips'. The title of the speaker's presentation in question was given as 'Global risk management' although the title slide of his presentation read 'Acid Suppressant Medication and Fractures'. The company had specifically briefed the speaker to talk about the potential attenuation of bisphosphonate anti-fracture efficacy when acid suppressants were co-prescribed. The Appeal Board was extremely concerned about the speaker's briefing notes. Although the notes correctly cited the title of the talk ('Global risk management') the objective was much narrower and was to talk about the use of PPIs in osteoporotic patients and the associated risks. Then to give a primary care perspective on how to manage patient cases not covered by NICE guidance. Points Servier briefed the speaker to include in the presentation were, *inter alia*: acid suppressants and increased risk of fracture and attenuation of bisphosphonate efficacy when acid suppressants were co-prescribed. These points echoed Servier's views as expressed in the letter and press release discussed above. The tentative nature of the data was not reflected in the briefing notes. The speaker was further asked to discuss identification of patients at risk of PPIs if prescribed an oral bisphosphonate and the conclusion was to consider prescribing an appropriate agent for these patients – eg strontium ranelate [Servier's product Protelos]. The speaker was further advised that the tone of the presentation should cause delegates to think about their current medical practice and then provide them with a simple solution to the problem. In the Appeal Board's view the briefing notes essentially instructed the speaker to raise concerns amongst the delegates about the co-prescription of bisphosphonates and acid suppressants and to get them to consider prescribing Protelos instead of bisphosphonates in at risk patients. In the Appeal Board's view, to include such a direct and promotional call to action in a brief to an independent speaker was wholly unacceptable and gave a very poor reflection of the company's procedures.

The Appeal Board considered that the presentation at the BGS had exaggerated the clinical importance of the data regarding bisphosphonates and acid suppressants. The presentation was not an accurate or balanced reflection of the data in that regard. The Appeal Board upheld the Panel's ruling of a breach of the Code. The Appeal Board also considered that the implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the existing data. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Procter & Gamble Pharmaceuticals UK, Limited complained about the activities of Servier Laboratories Ltd in relation to alleged misleading and disparaging information about bisphosphonates, including Procter & Gamble's product Actonel (risedronate sodium). Servier supplied Protelos (strontium ranelate).

At issue were a letter to prescribing advisors (ref 07MKA0006), a press release 'Servier welcomes revised NICE Guideline…' (ref 08MC0026) and Servier's sponsored symposium at the British Geriatrics Society (BGS) meeting in Glasgow on 24 April.

Inter-company dialogue between the companies had proved unsuccessful.

COMPLAINT

Procter & Gamble alleged that materials/activities which inferred that the anti-fracture efficacy of bisphosphonates was attenuated when co-prescribed with acid suppressants were in breach of Clauses 7.2 and 8.1 of the Code.

In addition Servier was sharing these misleading messages as part of a strategy that was not limited to promotional activities but extended to communications with official bodies such as the National Institute for Health and Clinical Excellence (NICE). Although such communications did not necessarily fall under the remit of the Code, it illustrated that Servier was sharing these messages as part of a broader strategy.

In summary, this was a concerted effort by Servier to disparage oral bisphosphonates so as to influence the prescribing market in its own favour. This was achieved by portraying messages that caution should be exercised when co-prescribing acid suppressants and bisphosphonates due to the increased fracture risk associated with acid suppressants, which was not only misleading but also raised inappropriate concerns about the safety

of the oral bisphosphonates. Procter & Gamble alleged that by doing so, Servier brought discredit upon and reduced confidence in the pharmaceutical industry in breach of Clause 2.

The messages conveyed by Servier were:

1 **'…acid suppressant medication, including proton pump inhibitors (PPIs) has been associated with an increased risk of fracture.'**

It was important to note that there were limited and contradictory data available (two papers and one abstract) to support this claim and the authors concluded that further studies were needed to confirm and explain the results. In some cases, some of the results were not statistically significant.

- Yang *et al* (2006) '…Thus, further studies are urgently needed to confirm our findings and clarify the underlying mechanism.'
- Vestergaard *et al* (2006), '…In conclusion, PPIs [proton pump inhibitors] appear to be associated with an increased fracture risk, in contrast to histamine H_2 antagonists (H_2 antagonists), which seem to be associated with a decreased fracture risk. The changes in risk estimates were small in all instances and may have limited clinical consequences. However, further studies in the field are needed.'
- Yu *et al* (2006) (abstract), '…There was also a non-significant increase risk of hip fracture among PPI/H_2 antagonists users.' (There was, however, an increased in the risk of non-spine fracture among users of acid suppressants.)

Use of PPIs was not currently considered an established risk factor for an osteoporotic fracture. Established risk factors included a prevalent vertebral fracture, maternal hip fracture, corticosteroid use etc.

NICE had asked the School of Health and Related Research (ScHARR), to view the data upon which Servier made its claims. The ScHARR report stated: 'Servier claim that acid-suppressing medication significantly reduces, if not completely negates, the anti-fracture benefits of bisphosphonate treatment'. The ScHARR report concluded however, that the quality of the evidence regarding any possible association between acid suppressants and increased risk of fracture was generally poor and their design appeared to be prone to confounding.

Procter & Gamble was not asking the Panel to rule on the scientific validity of these data or the clinical interpretation. However it considered that given the uncertain nature of these findings, use in such a high level promotional way by Servier was not consistent with the letter or spirit of the Code and in breach of Clause 7.2.

2 **Epidermiological data, as eg recently presented at the National Osteoporosis Conference, suggested that the anti-fracture efficacy of bisphosphonates was potentially attenuated when co-prescribed with acid suppressants. (de Vries *et al* 2007)**

Procter & Gamble noted the following:

- This analysis, published only as an abstract, was funded by Servier.
- This was the first and only analysis to have shown this 'association' and the authors suggested that further studies were needed.
- ScHARR concluded that 'No confidence may be placed in the results of the study by de Vries *et al* because of its failure to demonstrate comparability between exposure groups in terms of key prognostic factors, in particular whether bisphosphonates were prescribed bisphosphonates for primary or secondary fracture prevention, and for primary or secondary osteoporosis'.

ScHARR also stated, '…. It is possible that the findings are invalidated by imbalances between the groups in the proportions of patients receiving bisphosphonates for primary or secondary fracture prevention, and for primary or secondary osteoporosis'.

- de Vries was also not consistent with the current labelling for risedronate. The current summaries of product characteristics (SPCs) for risedronate did not caution against co-prescription of acid suppressants in Section 4.4 nor was such a potential interaction listed in Section 4.5.
- Data was available for risedronate from a retrospective analysis on a subset of 5,454 patients from three phase-III fracture trials who took either placebo or risedronate (5mg daily) and who were classified as either PPI or H2 antagonist users, or nonusers. This showed that efficacy of risedronate in reducing the risk of new vertebral fractures was not influenced by concomitant PPI and H2 antagonist use (Roux *et al* 2008).
- Procter & Gamble alleged that the claim made by Servier was in breach of Clause 7.2. In addition, the intention was to disparage not only risedronate but all oral bisphosphonates in breach of Clause 8.1.

In conclusion Procter & Gamble believed that the numerous messages communicated by Servier on this topic were not balanced and were misleading and in breach of Clause 7.2. In addition, the inferences made regarding lack of efficacy of bisphosphonates with concomitant PPI use were disparaging, in breach of Clause 8.1.

Procter & Gamble further alleged that the use of misleading claims in a high level promotional campaign which disparaged a drug class, brought

discredit upon and reduced confidence in the pharmaceutical industry in breach of Clause 2.

RESPONSE

Servier vigorously refuted that the activities/materials at issue were misleading or that they disparaged bisphosphonates, including Actonel, as alleged. The company therefore denied breaches of Clauses 7.2 and 8.1. It also did not agree that it had brought discredit upon and reduced confidence in the pharmaceutical industry and so there was no breach of Clause 2.

As the marketing authorization holder for Protelos Servier had participated in the development of the Health Technology Appraisals: 'Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women' and 'Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women'. As part of this process Servier had submitted data to NICE demonstrating an association between use of acid suppressants (PPIs and H_2 antagonists) and increased fracture risk as well as evidence of an attenuation of the bisphosphonate anti-fracture efficacy with use of concomitant acid suppressants. Communication regarding these data had taken place via the formal NICE consultation process and fell outside the scope of the Code.

Acid suppressants (PPIs and H_2 antagonists) were commonly prescribed, particularly in patients with postmenopausal osteoporosis. Therefore, Servier considered that it was important that the demonstrated association between use of acid suppressants and increased fracture risk, as well as evidence that this effect was also apparent in patients taking concomitant acid suppressants and oral bisphosphonates compared with bisphosphonate alone was communicated appropriately to prescribers and bodies such as NICE. Indeed, this was even more important due to differences in acid suppressant use between osteoporotic agents, which could be explained by class differences between these agents in their upper gastro-intestinal (GI) profiles (see below).

Materials/activities related to the complaint

1 Letter to prescribing advisors dated 14 February 2008 (ref 07MKA0006)

This was a mailing sent by Servier's healthcare development managers to tell prescribing advisors about the increased risk of fractures associated with the use of acid suppressants and in particular its possible relevance to the treatment of patients with bisphosphonates. The healthcare development managers reported into the Department of Medical & Corporate Affairs and were responsible for informing budget holders on matters related to healthcare outcomes and healthcare budgets.

2 Press release: 'Servier welcomes revised NICE guidance on postmenopausal osteoporosis but urges NICE to go further …' dated 4 April 2008

Servier issued this press release to the medical press and also placed the document on the UK corporate website in the 'Health Care Professionals' section under Protelos articles. The press release outlined Servier's position regarding the latest NICE draft guidance on the management of osteoporosis. The press release submitted by Procter & Gamble was based on 08MCA0026.

3 Servier's sponsored symposium at the BGS meeting

Servier's sponsored symposium took place at the BGS meeting in Glasgow on 24 April from 7.15am-8.30am. The symposium was entitled 'Trips, slips and fractured hips' and was attended by approximately 100 health professionals. Topics covered at the meeting were: introduction and demonstration of FRAX; the impact of hip fractures; evidence based interventions in the elderly and global risk management.

The speaker for the session 'Global risk management' was asked to speak on the association between acid suppressants and increased risk of fracture, and on the potential attenuation of bisphosphonate anti-fracture efficacy when acid suppressants were co-prescribed. The objective of this session was to appropriately inform geriatricians on this topic relevant to the management of their elderly patients suffering from osteoporosis.

Claim '…acid suppression medication, including proton pump inhibitors (PPIs) has been associated with an increased risk of fracture'

Servier noted that Procter & Gamble had stated that 'there are limited and contradictory data available' to support this claim, however a number of independent studies had now demonstrated a consistent association between acid suppressants, particularly for PPIs, and an increased risk of fracture. These studies employed both retrospective and prospective observational study designs and examined various populations, whilst controlling for a wide range of potential confounding factors. The ScHARR report, undertaken at the request of NICE, summarised the evidence to date and acknowledged that these 'studies are controlled observational studies. This is appropriate: most RCTs are too small to detect adverse events which are either rare or take a long time to develop'.

Procter & Gamble referred to the fact that the authors of two of these papers recommended that further studies were needed in this area. However, it was important to note that three of these studies reported in the same year, and so the various authors were likely to have been unaware of the

growing body of evidence on this topic when their respective studies were published. The evidence base was further supported by additional studies showing similar findings.

The key studies were:

Yang *et al* (2006): This was a retrospective nested case-control study, published in the Journal of the American Medical Association, which used the UK General Practice Research Database (GPRD) to examine the association between PPIs and H_2 antagonist and hip fracture risk. The study cohort comprised patients aged 50 years and older and included 13,556 hip fracture cases and 135,386 controls. One to ten controls per case were drawn from the same cohort as the cases, using incidence density sampling and matching for sex, index date, year of birth, and both calendar period and duration of follow-up before the index date. A comprehensive list of potential confounders that were risk factors for osteoporosis or risk of falling were controlled for in the analysis: body mass index (BMI), smoking history, alcoholism, congestive heart failure, cerebral vascular accident, dementia, impaired mobility, myocardial infarction, chronic obstructive pulmonary disease or asthma, peptic ulcer disease, peripheral vascular disease, rheumatoid arthritis, vision loss, celiac sprue, Paget's disease, osteomalacia, chronic renal failure, Cushings disease, inflammatory bowel disease, seizure disorder and prior history of fracture (> 3 months before the index date). Exposure to various classes of medications were also considered: anxiolytics, antidepressants, antiparkinsonian medicines, thiazide diuretics, statins, corticosteroids, hormone therapy, bisphosphonates, calcitonin, nonsteroidal anti-inflammatory medicines, anticonvulsants, thyroxine and calcium and vitamin D supplements.

This study found an increase in the risk of hip fracture for patients with more than one year of cumulative PPI (Adjusted Odds Ratio (AOR) 1.44; 95% CI 1.30-1.59) or H_2 antagonist use (AOR 1.23, 95% CI 1.14-1.39), compared with acid suppression non-users. The association between hip fracture risk and PPI use was also found to be duration dependent, with risk of hip fracture increasing with duration of PPI use, compared to acid suppression non-users [AOR: 1 year, 1.22 (95% CI 1.15-1.30); 2 years, 1.41 (95% CI, 1.28-1.56); 3 years, 1.54 (95% CI, 1.37-1.73); and 4 years, 1.59 (95% CI 1.39-1.80]. A dose-dependent relationship for PPI and hip fracture risk was also observed, with the risk increasing with higher doses, from AOR 1.40 (95% CI 1.26-1.54) for those receiving ≤1.75 average daily dose of PPI, to AOR 2.65 (95% CI 1.80-3.90) for those receiving more than 1.75 average daily dose, compared to acid suppression non-users.

Vestergaard *et al* (2006): The association between fracture risk and PPIs was also demonstrated in a case-control study using Danish medical records. This study examined the association between the use of PPIs, H_2 antagonist and other acid suppressants and the risk of fracture in 2000 (n = 124,655) and matched controls (n=373,962). Use of a PPI during the year prior to fracture was associated with an increase in overall fracture risk compared with matched controls (AOR 1.18, 95% CI 1.12-1.43), as well as an increase in hip (AOR 1.45, 95% CI 1.28-1.65) and vertebral fracture risk (AOR 1.60, 95% CI 1.25-2.04). There was no increased risk of fracture in patients who had used PPIs in the past, but not in the year before their fracture.

In contrast, H_2 antagonists were associated with a decreased fracture risk. This might be because H2 antagonists had a lower level of acid suppression than PPIs. On average, H_2 antagonists blocked approximately 70% of gastric acid production whilst PPIs suppressed up to 97% (see also below for further discussion on possible mechanism of action). In addition, the decrease in fracture risk was observed regardless of temporal duration of H_2 antagonist exposure, being evident for patients who had not received a H_2 antagonist for more than a year, suggesting that this reduction in fracture risk was not related to drug exposure *per se*.

Grisso *et al* (1997): This was a case-control study designed to identify risk factors for hip fracture in men. It comprised 365 men (aged 45 years and older) admitted to hospital with a radiologically confirmed first hip fracture, and 402 controls matched by age and zip code/telephone exchange, and found that use of the H_2 antagonist cimetidine was associated with an increased risk of hip fracture (OR 2.5, 95% CI 1.4-4.6).

Yu *et al* (2006): The association between PPI and/or H_2 antagonist use and adverse skeletal outcomes in postmenopausal women (n=3,432) was also assessed as part of the Study of Osteoporotic Fractures. After a mean of 4.9 years follow-up and adjustment for potential confounding factors (including age, ethnicity, BMI, calcium intake, health status, exercise, alcohol intake, and use of oestrogens or corticosteroids), an increase in the risk of non-spine fracture was observed among acid suppressant users (Adjusted Relative Hazard (ARH) 1.18, 95% CI 1.01-1.39), and a non-significant increase in the risk of hip fracture (ARH 1.15, 95% CI 0.86-1.52), the latter being potentially under-powered due to the small number of hip fractures observed in this study.

Briot *et al* (2007): Six year data from the prospective multi-centre study, OPUS, (Osteoporosis and Ultrasound Study), examining clinical risk factors for incident vertebral fractures, had also assessed the effects of PPIs. This study included 2,409 postmenopausal women aged between 55-81 years. A variety of baseline clinical risk factors (age, weight, current smoking, personal or familial previous fracture, corticosteroids, medical diseases, physical activity), and bone mineral density (BMD) measurements were included in the analysis. In the age-adjusted multivariate analysis, several clinical factors were significantly associated with incident vertebral fractures (radiologically confirmed),

independently of BMD value, namely age (per 10 years) (sOR=1.7; 95% CI, 1.0-2.7; p<0.04), previous fall (sOR=1.4; 95% CI, 1.0-1.9; p<0.04), previous paternal hip fracture (sOR=3.0; 95% CI, 1.5-5.9; p<0.002), and current intake of PPI therapy (omeprazole) (sOR=1.9; 95% CI, 1.2-2.9; p<0.006). Therefore, this 6-year prospective study provided further evidence of the association between PPI therapy and increased risk of vertebral fracture.

In conclusion, these studies, performed by a variety of research groups utilising different study designs and populations, provided clear evidence for an association between acid suppressants and increased fracture risk.

Servier explained that the potential mechanism underpinning the observed association between acid suppressants and increased fracture risk was that of reduced calcium absorption, secondary to decreased acidity in the stomach and proximal duodenum. Recker (1985) demonstrated that absorption of calcium was impaired in fasting achlorhydric patients. Furthermore, a randomised placebo controlled cross-over trial in healthy postmenopausal women (aged 65–89 years old) found that omeprazole significantly reduced fractional intestinal calcium absorption (O'Connell *et al* 2005). Such a reduction in calcium absorption might consequently lead to an increase in fracture risk.

Servier noted Procter & Gamble's statement that use of PPIs was not currently considered an established risk factor for an osteoporotic fracture. However, as outlined above, there was now a significant body of published evidence demonstrating an association between the use of acid suppressants and fracture risk, and therefore it was entirely appropriate for Servier to refer to this association as it was an important consideration in the management of postmenopausal osteoporosis.

Procter & Gamble also referred to analysis of the data by ScHARR following a request by NICE. Several of the studies discussed above were considered as well as de Vries *et al* (see below) in the development of the latest NICE appraisal consultation documents in osteoporosis (issued 25 March 2008). Based on a consideration of this evidence, NICE concluded that 'caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates' (Section 4.3.33 and 4.3.34 of the primary and secondary prevention appraisal consultation documents respectively).

Therefore, it was clear that there was a significant body of evidence to support the claim that '…acid suppression medication, including proton pump inhibitors (PPIs) has been associated with an increased risk of fracture' and as such, Servier considered this claim to be fair and balanced and not misleading. Consequently, Servier did not agree that this claim was in breach of Clause 7.2.

Epidemiological data, as eg recently presented at the National Osteoporosis Conference, suggested that the anti-fracture efficacy of bisphosphonates was potentially attenuated when co-prescribed with acid suppressants.

The above statement referred to a study conducted using the GPRD, which was funded by Servier, conducted by the GPRD research team, and undertaken in collaboration with leading experts in the fields of epidemiology and osteoporosis (de Vries *et al*). This was a retrospective cohort study assessing the fracture risk of patients taking concomitant bisphosphonate and PPIs or H_2 antagonist vs those taking bisphosphonates alone. Patients were aged 40 years or older starting treatment with PPIs (n = 234,144), H_2 antagonists (n = 166,798) or bisphosphonates (n = 67,309).

The analysis adjusted for an extensive list of potential confounders including age, gender, BMI, smoking status, a history of any fractures, diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, heart failure, cardiovascular disease, chronic obstructive pulmonary disease, hysterectomy/early menopause, and use in the six months before of anticonvulsants, anxiolytics, hypnotics, antidepressants, anti-Parkinson medication, HRT, thiazide diuretics, systemic glucocorticoids, inhaled corticosteroids/ bronchodilators, aluminium/magnesium containing acid suppressants, and calcium/vitamin D supplements. The analyses were also adjusted for the number of non-steroidal anti inflammatories (NSAIDs) in the year before each acid suppressant prescription (none, 1-4, >4).

This study found that concomitant use of bisphosphonates and PPIs was associated with a statistically significant increased risk of any fracture (Adjusted Relative Rate (ARR) 1.08; 95% CI 1.01-1.15) and hip fracture (ARR 1.21; 95% CI 1.05-1.38), but not vertebral fracture (ARR 1.11; 95% CI 0.94-1.31), compared with bisphosphonate use alone. The results suggested that PPIs might attenuate the anti-fracture efficacy of bisphosphonates on fracture risk.

The fact that the study was funded by Servier, as noted by Procter & Gamble, did not invalidate the results. The study was conducted by the respected GPRD Research team (part of the MHRA), which had an extensive heritage in undertaking studies examining medicine-induced fracture risk and were widely published in this area. Furthermore, abstracts from this study had been peer-reviewed and deemed to be of sufficient scientific merit to be worthy of oral presentations at both the 2007 National Osteoporosis Society Conference in Edinburgh and the 2008 European Congress on Clinical and Economical Aspects of Osteoporosis and Osteoarthritis.

Servier noted that Procter & Gamble had specifically referred to comments from ScHARR regarding the potential for confounding in this

study, particular relating to fracture history. However, as described above, the analysis adjusted for an extensive list of potential confounders, including history of fracture, which ensured that this variable was accounted for in the results.

Procter & Gamble also highlighted that this was the first study examining the effect of concomitant acid suppressants and bisphosphonates vs bisphosphonate use alone on fracture risk. The demonstrated attenuation of anti-fracture efficacy as a result of concomitant PPI use was consistent with the results of the multiple studies reviewed above, that demonstrated an association between the use of acid suppressants and increased fracture risk. This study additionally demonstrated that the excess risk of fracture with PPI use remained, despite concomitant bisphosphonate treatment.

Servier noted that Procter & Gamble referred to the analysis by ScHARR of Yang *et al*, Vestergaard *et al*, Yu *et al* and de Vries *et al*. NICE had taken account of the ScHARR analysis in its assessment of data indicating that acid suppressants increased fracture risk and that co-administration with bisphosphonates might lead to an increased fracture risk compared with bisphosphonates alone. Consequently, in the latest osteoporosis Appraisal Consultation Documents, NICE concluded 'caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates' (Section 4.3.33 and 4.3.34 of the primary and secondary prevention appraisal consultation documents respectively).

Servier disagreed with Procter & Gamble's submission that de Vries *et al* was inconsistent with the current labelling of Actonel. The special warnings and precautions sections of the SPCs for oral bisphosphonates, including Actonel, stated that bisphosphonates could cause local irritation of the upper GI mucosa such as oesophagitis. This was consistent with evidence from multiple sources demonstrating that the commonly prescribed oral bisphosphonates were associated with upper GI problems such as dyspepsia. This tolerability profile of oral bisphosphonates was also acknowledged in national and regional guidance documents.

In prescription event-monitoring studies conducted by the Drug Safety Research Unit, dyspeptic symptoms were the most commonly reported side effect for oral bisphosphonates, with the incidence in the first month of treatment being four times more common for risedronate (n=13,164) and five times more common for alendronate (n=11,916), than for comparable patients taking non-gastrointestinal medicines. Therefore, based on the special warnings and precautions section of oral bisphosphonate SPCs and the prescription event monitoring data, it was reasonable to expect that patients taking oral bisphosphonates were more likely to require acid suppressants than osteoporotic agents without such a tolerability profile, eg Protelos.

Indeed, several separate data sources demonstrated an increase in acid suppressant prescriptions with bisphosphonate use. Using the Australian GP Research Network, Roughead *et al* (2004) conducted a case-control study and found that 6 weeks after initiation, 2.9% (95% CI 1.8-3.9, n=1,753) of new bisphosphonate users returned to their GP and were prescribed an acid suppressant, usually a PPI, compared to 0.9 per cent of matched control patients (95 %CI 0.5-1.2, n=3,341), representing a 3-fold increase in use (AOR 3.21, 95% CI 2.02-5.11), while controlling for previous NSAID use. These findings were consistent with the upper GI tolerability profile of the oral bisphosphonates outlined in the relevant SPCs.

Further analysis of de Vries *et al* also provided information on the increased use of acid suppressants in patients initiated on bisphosphonates. The use of acid suppressants in women aged 50 years and older who started treatment with bisphosphonates, and who had not received a prescription for a systemic corticosteroid in the 12 months before or 6 months after starting therapy (n = 36,575) was examined. In the 6 months before initiation of bisphosphonates, 15% of patients were prescribed a PPI and 5.9% had received an H_2 antagonist. Analysis of the proportion of women starting acid suppressants after initiating bisphosphonate therapy over time demonstrated an increased use of acid suppressants following initiation with bisphosphonate, such that a greater proportion of patients were prescribed a PPI or H_2 antagonist in the 6 months following bisphosphonate initiation compared to the 6 month prior to bisphosphonate initiation.

Servier also commissioned an analysis using the primary care database, CSD Patient data, to assess whether PPI usage changed in patients following initiation of treatment for osteoporosis. In this analysis, patients were included if they had been initiated on osteoporotic therapy between August 2005-July 2007. The subset of patients who had subsequently received a second consecutive prescription of treatment for osteoporosis were assessed to see whether they had received PPI therapy in the six months prior to the introduction of osteoporotic treatment and then also in the six months post the second prescription. As expected, these data demonstrated a consistent pattern of increased PPI use following commencement of an oral bisphosphonate, but not with Protelos, an osteoporotic therapy that did not contain a special caution regarding local irritation of the upper gastrointestinal mucosa. Furthermore, *post-hoc* analyses of phase III randomised placebo-controlled trials demonstrating the efficacy of Protelos in the treatment of postmenopausal osteoporosis showed no increase in PPI initiation in the Protelos arm compared with placebo. Therefore, these data demonstrated that PPI usage varied with different anti-osteoporotic agents, with increased use being observed for certain classes, such as the oral bisphosphonates, but not for others, such as Protelos.

The pattern of increased use of acid suppressants in patients started on oral bisphosphonates was consistent with the special warnings and precautions relating to the upper GI tolerability of oral bisphosphonates (see SPCs). Various independent studies had demonstrated an association between acid suppressants and increased risk of fracture, and the data from de Vries *et al* showed that this effect was also apparent in patients receiving bisphosphonate therapy. As stated above, the association between acid suppressants and fracture risk was an important consideration in the management of osteoporotic patients and it was therefore appropriate for Servier to refer this data in it materials/activities.

Servier noted that Procter & Gamble also referred to its own *post-hoc* analysis of three phase III placebo-controlled trials of risedronate (5mg daily; n=5,454) to support the statement that the efficacy of risedronate in reducing the risk of new vertebral fractures was not influenced by concomitant use of PPIs or H_2 antagonists. However, this analysis had many limitations (Roux *et al*), which made interpreting the results difficult. This was a *post-hoc* analysis of phase III clinical trials, which were not designed to investigate the interaction between acid suppressants and fracture risk. There was no assessment of the degree of exposure to PPIs or H_2 antagonists. Subjects were classified as PPI or H_2 antagonist users if they used these agents at any point during the trial and therefore could be classed as a user even if they had only taken an acid suppressant once. This was an important point because studies had shown the risk was dependent on dose and duration. There was also no consideration of the temporal relationship between PPI or H_2 antagonist exposure and fracture incidence; it could not be determined from this study whether fractures occurred either before or after exposure to acid suppressants. Finally, as stated in the abstract, the sub-groups were not balanced in terms of confounding factors, and only the number of prevalent vertebral fractures appeared to have been controlled for in the analysis. Together, these issues made it difficult to draw firm conclusions as to the validity of these data.

In conclusion, Servier considered the claim 'Epidemiological data, as e.g. recently presented at the National Osteoporosis Conference, suggest that the anti-fracture efficacy of bisphosphonates is potentially attenuated when co-prescribed with acid suppressant medication' was fair and balanced and not misleading. Consequently, Servier did not agree that this claim was in breach of Clause 7.2 or that it disparaged risedronate or the oral bisphosphonate class, and therefore it did not consider it to be a breach of Clause 8.1. Consequently, Servier did not agree that there was a breach of Clause 2.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2, emerging clinical or scientific opinion, stated that when 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 the data submitted in support of the claims that the use of acid suppressants had been associated with an increased risk of fracture. Yang *et al* found a significantly increased risk of hip fracture associated with long-term PPI therapy, particularly high dose PPI. The authors, however, stated that further studies were needed to confirm their findings. Yu *et al* concluded that amongst postmenopausal women, use of acid suppressants *might* (emphasis added) be associated with an increased risk of non-spine fracture. Vestergaard *et al* concluded that PPIs appeared to be associated with an increased fracture risk in contrast to H_2 antagonists which seemed to be associated with a decreased fracture risk. The changes in risk estimates were small in all instances and might have limited consequences; further studies were needed. De Vries *et al* concluded that concomitant use of bisphosphonates and acid suppressants was associated with an increased risk of fracture and that possibly acid suppressants attenuated the protective effects of bisphosphonates on fracture risk. The authors stated that given the frequency of co-prescription of bisphosphonates and acid suppressants, the issue required further investigation.

A critique of the evidence suggesting an association between acid suppressants and increased fracture risk stated that the data was generally poor. In its appraisal consultation document on alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women, NICE noted that data indicating that acid suppressants led to a small increase in fracture risk and that co-administration of acid suppressants and bisphosphonates might lead to an increased fracture risk compared with bisphosphonates alone was observational and tentative and different for different fracture sites and different acid suppressants. NICE considered, however, that because various studies showed a trend, caution should be exercised when the co-prescribing of acid suppressants and bisphosphonates was being considered. The committee was not persuaded, however that a change to its recommendations, based on the evidence, was necessary. The Panel noted that the NICE document was an appraisal consultation document and was marked confidential. The document stated that it did not constitute formal guidance and its recommendations were preliminary and might change after consultation.

The Panel noted that a template letter to prescribing advisors was headed 'Increased risk of fracture associated with use of acid suppressant

medication'. The Panel considered that the quality of the data was such that it could not support such a robust, unqualified claim. Although the reader was told that data *suggested* that the anti-fracture efficacy of bisphosphonates was *potentially* attenuated when co prescribed with acid suppressants (emphasis added) the Panel nonetheless considered that the letter implied that acid suppressants had been unequivocally proven to attenuate the anti-fracture efficacy of biphosphonates. The letter went on to refer to this growing body of evidence and assessment of the implications of the data, in particular the potential effect on health outcomes and healthcare budgets. It appeared that the data had proven clinical implications and this was not so. In that regard the Panel considered the letter was not balanced and did not reflect the data accurately. A breach of Clause 7.2 was ruled. The implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. A breach of Clause 8.1 was ruled.

The press release (ref 08MCA0026 April 2008) was headed 'Servier welcomes revised draft NICE guidance'. The third paragraph began 'Servier also welcomes the acknowledgement by NICE in its draft guidance that caution should be exercised when considering the co-prescription of acid suppressants and bisphosphonates'. Readers were also told that NICE had previously failed to address the increased risk of fractures associated with the use of acid suppressants, in particular PPIs, which were commonly co-prescribed with bisphosphonates. The Panel considered that the quality of the data was such that it could not substantiate such robust unqualified claims. The tentative nature of the data acknowledged by NICE, was not referred to in the press release. The Panel considered that the press release was not balanced and did not reflect the data accurately. A breach of Clause 7.2 was ruled. The Panel also considered that the implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. A breach of Clause 8.1 was ruled.

The Panel noted that Servier's sponsored symposium at the BGS meeting had included a presentation entitled 'Acid Suppressant Medication and Fractures'. The speaker's briefing notes stated that the objective was to communicate on the use of PPIs in osteoporotic patients and the associated risks. Then to give a primary care perspective on how to manage patient cases not covered by NICE guidance. Points to include in the presentation were, *inter alia*: acid suppressants and increased risk of fracture; attenuation of bisphosphonate efficacy when acid suppressants were co-prescribed; how to identify patients at risk of PPIs if prescribed an oral bisphosphonate and the conclusion was to consider prescribing an appropriate agent for these patients – eg strontium ranelate [Servier's product Protelos]. The speaker was further advised that the tone of the presentation should cause delegates to think about their current medical practice and then provide them with a simple solution to the problem.

The final slide of the presentation was headed 'Summary: overview of evidence' and detailed the findings of Yang *et al* and Vestergaard *et al*. In the Panel's view the results of the two studies were presented on the slide as if the findings had been unequivocal; the authors' comments as noted above had not been included. There was no transcript of the presentation although the speaker had provided an overview of what he had said. With regard to the last slide the speaker stated that he had said that there might be a reduction in the effect of a bisphosphonate with PPI usage; this needed further study. The Panel considered, however, that the tentative nature of the data was not reflected in the slides and in its view delegates would be left with the impression that acid suppressants, particularly PPIs, had been unequivocally proven to attenuate the anti-fracture efficacy of bisphosphonates with proven clinical implications. In that regard the Panel considered that the slides were not balanced and did not reflect the data accurately. A breach of Clause 7.2 was ruled. The implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the current data. A breach of Clause 8.1 was ruled.

The Panel noted its rulings above but nonetheless did not consider that there had been a breach of Clause 2 of the Code which was reserved for use as a sign of particular censure. This ruling was not appealed.

APPEAL BY SERVIER

Servier appealed all of the Panel's rulings of breaches of Clauses 7.2 (for misleading claims relating to issues of emerging clinical or scientific opinion) and Clause 8.1 (for disparaging references to the medicines of other pharmaceutical companies).

Servier submitted that it was not the Panel's role to evaluate any scientific data. However, Servier appreciated that for the purposes of the complaint the Panel had to consider whether issues of emerging clinical or scientific opinion had been treated in a balanced manner in the promotional material. Further, the Panel had to consider whether references to competitors' products in the promotional material were disparaging. In order to decide whether the issues had been treated in an appropriately balanced way, the Panel had to assess whether Servier's claims were justifiable on the basis of the data on which they were based. Accordingly, the Panel's consideration of the data informed its rulings in relation to the letter, the press release and the symposium.

It was apparent from the ruling that the Panel's view was that the data did not adequately support Servier's claims that the use of acid suppressants had been associated with an increased risk of

fracture. Servier disagreed with this conclusion.

The Panel placed significant weight on the fact that the authors of the published studies submitted by Servier indicated that further investigation of the association between the use of acid suppressants and the increased risk of fractures was necessary. However, Servier noted that Yang *et al* and Vestergaard *et al* were published in the same year, and so they would likely have been unaware of each other's research when writing their respective papers. The Panel also noted that 'A critique of the evidence suggesting an association between acid suppressants and increased fracture risk stated that the data was **generally poor.'** (emphasis added). However, this critique was contradictory to the substance of each individual study.

Servier submitted that Yang *et al* found that the PPI therapy was associated with a significantly increased risk of hip fractures, with the highest risk seen among patients receiving long-term high-dose PPI therapy (adjusted odds ratio 2.65, 95% CI 1.80-3.90). In addition, Yang *et al* also found that long-term H_2 agonist therapy was associated with a significantly increased risk of hip fracture (AOR 1.23, 95% CI 1.14-1.39), compared to acid suppression non-users.

Servier submitted that de Vries *et al* found that concomitant use of bisphosphonates and PPIs was associated with a statistically significant increased risk of any fracture (Adjusted Relative Rate (ARR) 1.08; 95% CI 1.01-1.15) and hip fracture (ARR 1.21; 95% CI 1.05-1.38), but not vertebral fracture (ARR 1.11; 95% CI 0.94-1.31), compared to bisphosphonate use alone. Furthermore, the increased risk of any and hip fracture showed a dose-dependent trend. The results suggested that PPIs might attenuate the anti-fracture efficacy of bisphosphonates on fracture risk.

Servier submitted that Vestergaard *et al* found that recent use of PPI was associated with an increased risk of hip fracture (AOR 1.45, 95% CI 1.28-1.65), whilst distant use was not (AOR 1.08, 95% CI 0.94-1.23). In contrast, H_2 agonist use was not associated with an increase hip fracture risk.

Servier submitted that whilst the findings relating to H_2 agonists had been contradictory, the dose and duration dependent effects of PPI use and increased fracture risk, seen across these three studies, was indicative of an underlying biological mechanism. This had been also noted by Wright *et al* (2008) who commented on Yang *et al* and Vestergaard *et al* that: 'Despite the conflicting conclusion about the risk of fracture with H2RA use, these two very large, long-term, case controlled studies **both report a strong association of PPI use with fracture.'** (emphasis added)

Servier further noted that in its publication IMPACT, which provided information to prescribers, the Scottish NHS-Grampian Medicines Information Centres stated in January 2007 that **'Long-term use of proton-pump inhibitors (PPI) is associated with an increased risk of hip fracture, according to a large epidemiological study using UK data (JAMA 2006).** Risk was further increased with high-dose PPI use, and with longer duration of treatment. Based on their analysis, the authors conclude that long-term use of PPI may be associated with an increased risk of hip fracture, particularly when high doses are used. They note that there may be confounding factors that they could not adjust for, but suggest that doctors should ensure that the lowest effective dose is used if long term PPI use is required' (emphasis added).

Servier submitted that this publication on behalf of the Scottish NHS indicated that the provided piece of evidence was considered of sufficient clinical significance that doctors should be made aware of the risk that long-term PPI use might be associated with an increased risk of hip fracture. It should be noted that no evidence was provided by Procter & Gamble to justify a conclusion that there was no association between the use of PPIs and the increased risk of hip fractures.

Servier therefore submitted that the Panel failed to make a proper assessment of the scientific data. Whilst the authors of the publications submitted by Servier indicated that further studies were necessary in support of the identified association between the use of acid suppressants and the increased risk of fractures, this circumstance should not be used in itself as a justification for dismissing the data. On balance, the studies performed by a variety of research groups utilising different study designs and populations overwhelmingly supported the claim that the use of acid suppressants was associated with an increased risk of fracture. Servier considered the Panel's rulings were made on the basis of a misconceived interpretation of the scientific issues.

Servier disagreed with the comments made by the Panel in relation to the letter to prescribing advisers. The Panel stated that the letter implied that acid suppressants had been unequivocally proven to attenuate the anti-fracture efficacy of bisphosphonates. Servier did not accept that this statement was made or even implied in the letter. As regards the title of the letter, 'Increased risk of fractures associated with the use of acid suppressant medication', the Panel stated that the data could not support 'such a robust, unqualified claim'. However, the claim was not unqualified. The word 'associated' suggested that there was some link between the increased risk of fractures and the use of acid suppressant medication without implying a definite causal relationship between the two. Further, the first sentence stated 'Epidemiological data recently published at the 2007 National Osteoporosis Society Conference, **suggest** that the anti-fracture efficacy of bisphosphonates is **potentially** attenuated when co-prescribed with acid suppressant medication' (emphasis added).

Servier submitted that the choice of the wording (ie

'suggest' and 'potentially') could not lead the prescribing advisers to conclude that this statement was based on unequivocal evidence.

Additionally, Servier opposed the Panel's statement that the content of the data as mentioned in the third paragraph could be interpreted to mean that they had proven clinical implications. The reference to the 'growing body of evidence' was linked to the second paragraph of the letter which contained appropriate statements referenced to the relevant sections of the published data. In addition, all sentences had been appropriately referenced so the reader would be able to check the source of the information. As explained above in relation to the Panel's assessment of the scientific data, all studies concluded that there was an association between the use of PPIs and increased risk of fracture. Rather than suggesting that the data had proven clinical implications, the letter explained that an investigation of the implications of the data was still to come: '**I will be analysing** the implications of the data...' (emphasis added).

Servier submitted that, in an attempt to protect public health, it had sent the letter to prescribing advisers to alert them of the possible risk in prescribing PPIs for long-term use. This was in accordance with Yang *et al* which concluded that: 'At this point, **physicians should be aware of this potential association when considering PPI therapy and should use the lowest effective dose for patients with appropriate indications.** For elderly patients who require long-term and particularly high-dose PPI therapy, it may be prudent to reemphasize increased calcium intake, preferably from a dairy source, and coingestion of a meal' (emphasis added).

Therefore, Servier submitted that all statements in the letter had treated the existing scientific data in a balanced manner. For this reason, the letter was not misleading in relation to issues of emerging clinical/scientific opinion and therefore it was not in breach of Clause 7.2.

Additionally, Servier submitted its discussion of bisphosphonates (ie risedronate and alendronate) was accurate, balanced, fair and capable of substantiation. The information provided relied on the published literature. In addition, Servier also provided the relevant references so the advisers would be able to confirm the validity of the information. Therefore, the references in the letter to bisphosphonates were not disparaging and Servier therefore disagreed with the Panel's ruling of a breach of Clause 8.1.

Servier submitted that it had issued the press release 'Servier welcomes revised NICE guidance on postmenopausal osteoporosis but urges NICE to go further' on 4 April to the medical press; it was also on the Servier UK corporate website in the health professionals' section under articles. Servier also issued a bulletin with the same code number and content. The only differences identified were the title and the conclusion. These outlined Servier's position regarding the latest NICE draft guidance on the management of osteoporosis. The Panel's comments were based on the bulletin.

Servier submitted that the Panel misconstrued the information derived from the appraisal consultation documents as published in March 2008. The Panel in its general comments about the scientific data noted that that these documents were marked as confidential and did not constitute the NICE's formal guidance since the considerations were preliminary and might change after the consultation. However this did not reflect the precise role of the appraisal consultation documents. In particular, the documents were communicated to Servier in confidence in March 2008 and were published on 4 April on NICE's website. The press release had been published on 4 and 8 April 2008. Therefore, the assumption of the Panel that this document was confidential was incorrect.

Furthermore, Servier submitted that the appraisal consultation documents reflected the latest position of the NICE at that time in relation to primary and secondary prevention of post-menopausal osteoporosis. Servier's press release underlined NICE's findings. In particular, it was mentioned that: 'Servier also welcomes the acknowledgement by NICE in its draft guidance that caution should be exercised when considering the co-prescription of acid-suppressive medication and bishphosphonates'. This statement was a quotation from the latest appraisal consultation documents at that time (Section 4.3.33 and 4.3.34 of the primary and secondary prevention documents respectively).

Additionally, the press release also indicated that NICE had previously failed to address the increased risk of fractures associated with the use of acid suppressants, in particular PPIs, which were commonly prescribed with bisphosphonates. This was again a statement of fact since the original version of the final appraisal determinations did not raise that issue.

However, Servier submitted that it had explicitly mentioned in the press release that its comments were derived from the draft guidance and there was no implication that this was the final position of NICE in relation to the co-prescription of bisphosphonates with acid suppressants. After all, Servier had a direct interest to inform the medical community on any progress in the field, it had already appealed the original version of the final appraisal determinations and had also lodged judicial review proceedings on the same issue.

Servier submitted that its press release relied solely on NICE's latest considerations. Therefore, Servier made statements based on the facts and not on assumptions. For this reason Servier was not in breach of Clause 7.2 as it treated the evidence relating to issues of emerging clinical/scientific opinion in a fair and balanced manner in accordance with Clause 7.2.

Further, for the reasons explained above, Servier denied a breach of Clause 8.1 of the Code because references to the oral bisphosphonates were accurate, balanced, fair and capable of substantiation in accordance with Clause 8.1.

The BGS presentation in Glasgow on 24 April 2008 was attended by health professionals with an interest in elderly care medicine. The abstract book was distributed to the attendees on the day of the symposium but they were not given copies of the presentation at issue. Servier submitted that slides generally only formed the basis of a presentation but they were not self-sufficient and not intended to stand alone. The speaker's comments provided important additional information and emphasis. There were no official transcripts from the symposium. However, the speaker had provided a summary of his speech and confirmed that in his last slide he raised the point that there was significant evidence linking the use of PPIs to the increase of fracture risk, especially at the hip. To support this statement the speaker referred to de Vries *et al* which in addition showed the increased risk of hip fracture in patients taking both PPIs and bisphosphonates. However, the speaker explained that there might be an attenuation of the anti-fracture efficacy of the bisphosphonates with PPI use, but that this required further study. Therefore the data had been presented in an appropriately balanced way.

Servier noted that it had not received any comment on behalf of the attendees that they left with the impression that acid suppressants, particularly PPIs, had been unequivocally proven to attenuate the anti-fracture efficacy of bisphosphonates. Therefore, judging that the presentation in its entirety (slides and speaker's comments) covered any potential 'grey' area in relation to the studies, Servier had presented the issues of emerging clinical/scientific opinion in a balanced manner. For this reason, Servier denied a breach of Clause 7.2.

Further, Servier did not breach Clause 8.1 of the Code because references to the oral bisphosphonates were accurate, balanced, fair and capable of substantiation and thus not disparaging.

In conclusion Servier vigorously refuted the Panel's rulings that the letter, press release and the symposium were in breach of Clause 7.2. Further, Servier did not agree that such messages disparaged the oral bisphosphonates and thus denied breaches of Clause 8.1.

COMMENTS FROM PROCTER & GAMBLE

Procter & Gamble alleged that Servier continued to confuse the issue of clinical interpretation and scientific validity with the issue of treating emerging clinical or scientific data in a balanced manner. This debate was based on limited and contradictory data, hence claims should reflect this and must be balanced, not misleading and not disparaging.

Servier justified the dissemination of these messages in an attempt to protect public health. The Medicines and Healthcare products Regulatory Agency (MHRA), however, was responsible for protecting public health in the UK; it was not for pharmaceutical companies to take unilateral action on decisions as to what constituted a public health matter, or to pre-empt the decisions of health authorities.

Procter & Gamble fully supported the Panel's ruling which it considered was appropriate and illustrated the extent to which this was still an emerging debate.

Procter & Gamble had not asked the Panel to rule on the scientific validity of the data or the clinical interpretation. The Panel was asked to rule whether the data used by Servier were presented in a balanced, non-misleading and non-disparaging way. The Panel ruled Servier in breach of Clauses 7.2 and 8.1.

Procter & Gamble submitted that the fact remained that limited and contradictory data were available (two papers, one abstract, Yang *et al*, Vestergaard *et al* and Yu *et al*) to support the claims and inferences made by Servier that acid suppressants, including PPIs had been associated with an increased risk of fracture and anti-fracture efficacy of bisphosphonates was potentially attenuated when co-prescribed with acid suppressants (one abstract de Vries *et al*). The authors rightly called for further investigation to confirm findings and understand potential mechanisms. In no way did these data overwhelmingly support Servier's claims.

Procter & Gamble appreciated that new data emerged that might or might not change scientific thinking. This was, however, the reason why supplementary information to Clause 7.2, 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 the issue was treated in a balanced manner in promotional material. This was not the case with the claims made by Servier, the data as it currently stood did not support robust unqualified claims as ruled by the Panel. This was particularly important in this case since Servier was potentially misleading and disparaging regarding the safety of PPIs, H_2 agonists and bisphosphonates.

Procter & Gamble noted Servier's comment that it had provided no evidence that PPIs did not increase the risk of fracture. This was irrelevant. Procter & Gamble had simply asked that the data that did exist be treated cautiously, consistent with the supplementary information to Clause 7.2 and existing SPCs. Procter & Gamble's overall concern remained that this debate was based on limited and contradictory data, hence claims must be balanced, not misleading and not disparaging.

Procter & Gamble considered that the Panel

correctly interpreted Servier's intent with the prescribing advisor's letter to imply an unequivocal link between acid suppressants and attenuated anti-fracture efficacy of bisphosphonates. In fact, in its appeal Servier again presented data by Yang *et al*, de Vries *et al* and Vestergaard *et al* that Servier concluded overwhelmingly supported its claims. Yet, Servier appeared to consider that adding the words 'suggest' and 'potentially' were necessary in the letter to prescribing advisors and disagreed with the Panel that the letter implied an unequivocal link. Servier could not argue this both ways.

Furthermore, Procter & Gamble alleged that for Servier to state that it would analyse the implications of the data, was intended to acknowledge a tentative link to clinical consequences was also contradictory. The text in the letter was 'potential effect on health outcomes and healthcare budgets'. If Servier acknowledged that the clinical implications were not so concrete, why would one assess budgetary impact?

Servier's response to the Panel illustrated the second major concern of Procter & Gamble. As justification for the dissemination of its messages, Servier stated that, in an attempt to protect public health, it had sent this letter to prescribing advisors to alert them of the possible risk in prescribing PPIs for long-term use. Procter & Gamble considered this justification illustrated a lack of appreciation for the UK regulatory infrastructure and the roles and responsibilities of health authorities, in particular the MHRA.

Procter & Gamble reiterated that the MHRA was responsible for protecting public health. The MHRA executed this responsibility via a number of well established mechanisms such as robust license procedures, structure and content of a product's SPC, the establishment of Pharmacovigilance Advisory Groups to assess data on behalf of the agency and direct communication to health professionals on safety matters.

Procter & Gamble stated that all of its safety data were regularly reviewed by health authorities as part of the licence renewal and, to date, the potential signal of attenuation of risedronate efficacy by acid suppressants has not been raised by any European agency, including the MHRA. The current SPCs for risedronate did not caution against co-prescription of acid suppressants in Section 4.4, nor was such a potential interaction listed in Section 4.5. The MHRA Pharmacovigilance Expert Advisory group (MHRA PEA) met on 12 September 2007 to discuss PPIs and risk of fracture. The conclusion stated: 'on the basis of current evidence and the limitations of these recent studies regulatory action was not warranted at this time'. On 23 July 2008 that statement continued to reflect the current position of the MHRA on the issue of PPIs and risk of bone fracture.

Procter & Gamble stated the MHRA Pharmacovigilance Expert Advisory group regularly reviewed all potential signals on behalf the MHRA, formed part of the UK Commission on Human Medicines and advised the European Committee for Medicinal Products for Human use. The published objectives of this body were to advise the Commission of the public health importance of potential new signals, the confirmation and quantification of risks identified and the appropriate risk minimisation measures including communication. No direct communication to health professionals had been sanctioned by MHRA, for example via 'Dear Doctor' letters, and no direct communication to health professionals had been endorsed by the MHRA Pharmacovigilance Expert Advisory Group.

It was not for pharmaceutical companies to take unilateral action on decisions as to what constituted a public health matter, or to pre-empt the decisions of health authorities; pharmaceutical companies had a duty to support UK regulatory systems not undermine them. Procter & Gamble considered that Servier's justification of its actions as an attempt to protect public health demonstrated a concerning lack of understanding of, and support for, these systems.

Procter and Gamble mentioned Servier's communications with NICE to illustrate that the misleading messages were part of a concerted broad strategy that was not limited to promotional activities. As shown by the Panel's ruling, the messages were misleading and disparaging and thus, the communications by Servier that affected the appraisal consultation documents were an attempt to inappropriately influence subsequent guidance for its own commercial ends. Sections 4.3.37 (primary prevention of osteoporosis) and 4.3.38 (secondary prevention of osteoporosis) of the latest final appraisal determinations by NICE (published online on 8 of July 2008), now stated: 'The Committee was made aware of data indicating that acid-suppressive medication leads to a small increase in fracture risk and that co-administration of acid-suppressive medication and bisphosphonates may lead to an increased fracture risk compared with bisphosphonate administration alone. **The Committee was not persuaded by this evidence**; [emphasis added] it noted that the data are observational and have not been reported in full, and are different for different fracture sites and for different acid suppressors. Furthermore, the Committee was informed, during consultation, of analyses showing that acid-suppressive medication given in addition to risedronate did not increase fracture risk. However, the Committee concluded that **caution should be exercised when considering the evidence about co-prescription of acid-suppressive medication and bisphosphonates.'** (emphasis added).

Procter & Gamble alleged that the above text supported the Panel's initial ruling of breaches of Clauses 7.2 and 8.1 of the Code. Servier, however, appeared to not only disagree with the Panel but also with NICE, as it had appealed the original

version of the final appraisal determinations and had lodged judicial review proceedings on the same issue.

Procter and Gamble noted that Servier stated that slides presented at Servier's symposium held in Glasgow on 24 April 2008, were not self-sufficient and not intended to stand alone. Whilst Procter & Gamble agreed that some clarification could be given verbally, the slides should be sufficiently stand-alone as not to create a misleading impression when presented to the audience. To present bold statements on acid suppressants and fracture risk on slides to be (or not) clarified verbally as requiring further study was not acceptable. Whilst Procter & Gamble disagreed in this instance with the speaker's opinion, it had not challenged his right to share his own perspective. Procter & Gamble expected, however, that Servier briefed its speakers to present in a fair, balanced and non misleading way and ensured that each material presented in promotional activities complied with the Code.

Procter & Gamble therefore considered that the Panel was correct to rule breaches of Clauses 7.2 and 8.1.

APPEAL BOARD RULING

The Appeal Board noted the data upon which the claims implying that the anti-fracture efficacy of bisphosphonates was attenuated when co-prescribed with acid suppressants were based. In particular the Appeal Board noted the conclusions of Vestergaard *et al* ie that 'The changes in risk estimates were small in all instances and may have limited clinical consequences. However, further studies in the field are needed'. In the Appeal Board's view the data provided were not robust enough to support claims such as 'Increased risk of fracture associated with the use of acid suppressant medication' which appeared as the heading on the letter to prescribing advisors and the reference to '… the increased risk of fractures associated with the use of acid suppressive medication …' which appeared in the press release. The Appeal Board further noted the submission by Procter & Gamble at the appeal hearing that the original efficacy trials on bisphosphonates had not excluded patients also taking PPIs and the like. Thus it was very likely that the reported efficacy of bisphosphonates already took some account of patients co-prescribed acid suppressants.

The Appeal Board considered that the letter to prescribing advisors and the press release had exaggerated the clinical importance of the data regarding the consequences of co-prescribing bisphosphonates and acid suppressants. The documents were not balanced and did not accurately reflect the data. The Appeal Board upheld the Panel's rulings of breaches of Clause 7.2. The Appeal Board also considered that the implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the existing data. The Appeal Board upheld the Panel's rulings of breaches of Clause 8.1. The appeal on these points was unsuccessful.

The Appeal Board noted Servier's submission that the slides used at the BGS presentation were not intended to stand alone. The company had emphasised that attendees had not been given copies of the presentation. In the Appeal Board's view, however, a company could not rely on a speaker to qualify or explain otherwise misleading slides and in that regard it was irrelevant as to whether they were given to the attendees.

Servier's sponsored symposium at the BGS was entitled 'Trips, slips and fractured hips'. The title of the speaker's presentation in question was given as 'Global risk management' although the title slide of his presentation read 'Acid Suppressant Medication and Fractures'. The company had specifically briefed the speaker to talk about the potential attenuation of bisphosphonate anti-fracture efficacy when acid suppressants were co-prescribed. The Appeal Board was extremely concerned about the speaker's briefing notes. Although the notes correctly cited the title of the talk ('Global risk management') the objective was much narrower and was to talk about the use of PPIs in osteoporotic patients and the associated risks. Then to give a primary care perspective on how to manage patient cases not covered by NICE guidance. Points Servier briefed the speaker to include in the presentation were, *inter alia*: acid suppressants and increased risk of fracture and attenuation of bisphosphonate efficacy when acid suppressants were co-prescribed. These points echoed Servier's views as expressed in the letter and press release discussed above. The tentative nature of the data was not reflected in the briefing notes. The speaker was further asked to discuss identification of patients at risk of PPIs if prescribed an oral bisphosphonate and the conclusion was to consider prescribing an appropriate agent for these patients – eg strontium ranelate [Servier's product Protelos]. The speaker was further advised that the tone of the presentation should cause delegates to think about their current medical practice and then provide them with a simple solution to the problem. In the Appeal Board's view the briefing notes essentially instructed the speaker to raise concerns amongst the delegates about the co-prescription of bisphosphonates and acid suppressants and to get them to consider prescribing Protelos instead of bisphosphonates in at risk patients. In the Appeal Board's view, to include such a direct and promotional call to action in a brief to an independent speaker was wholly unacceptable and gave a very poor reflection of the company's procedures.

The Appeal Board considered that the presentation at the BGS had exaggerated the clinical importance of the data regarding bisphosphonates and acid suppressants. The presentation was not an accurate

or balanced reflection of the data in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The Appeal Board also considered that the implication that bisphosphonates were less effective if co-prescribed with acid suppressants was disparaging given the existing data. The Appeal Board upheld the Panel's ruling of a breach of Clause 8.1. The appeal on these points was unsuccessful.

Complaint received **9 May 2008**

Case completed **23 September 2008**

CASE AUTH/2130/6/08

GENERAL PRACTITIONER v PFIZER

Toviaz journal advertisement

A general practitioner complained about an advertisement for Toviaz (fesoterodine fumarate) placed by Pfizer in GP, 6 June. Pfizer also marketed Detrusitol (tolterodine). Both products were for the symptomatic treatment of patients with overactive bladder syndrome (OAB).

The complainant noted that the advertisement for Toviaz also promoted tolterodine for the same indication. The complainant was concerned that the standards pertaining to ensuring prescriber confidence, and therefore patient safety, had been seriously compromised by the omission of the tolterodine prescribing information as required by the Code.

The absence of the tolterodine prescribing information in this advertisement was misleading and potentially harmful to patients because the prescriber could not assess the relationship of the prescribing information to the promotional claims and indications for tolterodine. Consequently prescribers were unlikely to be able to make an entirely rational/informed prescribing decision with respect to tolterodine.

Given the very serious and obvious breach of the Code, and the likelihood that it impacted other Toviaz promotional materials and activities, the Authority should require Pfizer to immediately withdraw all affected materials. This would ensure continued confidence amongst prescribers that the lengthy timelines often associated with the complaints procedure did not provide the opportunity for Pfizer to obfuscate from its responsibilities and continue disseminating incomplete, misleading and potentially harmful promotional materials.

The Panel considered that, although only referred to by its non-proprietary name, the advertisement nonetheless promoted Detrusitol; prescribing information should have been provided. Given that the prescribing information had not been provided the Panel ruled a breach of the Code as acknowledged by Pfizer.

The Panel did not consider that the lack of prescribing information for Detrusitol rendered the advertisement misleading. The Panel further did not consider that the absence of the prescribing information meant that the advertisement had not encouraged the rational use of Detrusitol. No breach of the Code was ruled.

A general practitioner complained about an advertisement (ref TOV097b) for Toviaz (fesoterodine fumarate) placed by Pfizer Limited in GP, 6 June. Pfizer also marketed Detrusitol (tolterodine). Both products were for the symptomatic treatment of patients with overactive bladder syndrome (OAB).

COMPLAINT

The complainant stated that in support of its promotion of Toviaz, Pfizer relied on the following statements: 'From Pfizer, the maker of tolterodine, Toviaz is a new step in the treatment of OverActive Bladder.' and 'Toviaz 8mg demonstrated improvements with statistical significance vs. tolterodine ER in important treatment outcomes. Tolterodine is the market leading therapy in OAB'.

It therefore appeared that alongside promoting Toviaz for the treatment of OAB, Pfizer had also promoted tolterodine for the same indication.

The complainant was concerned that the standards pertaining to ensuring prescriber confidence, and therefore patient safety, had been seriously compromised in this advertisement by the omission of the tolterodine prescribing information as was required by the Code.

The extent and gravity of this omission invited the question whether Pfizer really understood its responsibilities to prescribers and patients and why it was that the Authority described the provision of prescribing information as 'obligatory information'.

The absence of the tolterodine prescribing information in this advertisement was misleading and potentially harmful to patients because the prescriber could not assess the relationship of the information that one would normally have expected to be specified in the prescribing information to the promotional claims and indications being made for tolterodine. Consequently, based on the advertisement, prescribers were unlikely to be able to make an entirely rational/informed prescribing decision with respect to tolterodine.

Given the very serious and obvious breach of the Code, and the likelihood that it impacted other promotional materials and activities supporting Toviaz, the Authority should require that Pfizer urgently remedy this matter by withdrawing immediately all affected materials. This would ensure continued confidence amongst prescribers that the lengthy timelines often associated with the complaints procedure did not provide the opportunity and platform for Pfizer to obfuscate from its responsibilities and continue disseminating incomplete, misleading and potentially harmful

promotional materials.

When writing to Pfizer, the Authority asked it to respond in relation to Clauses 4.1, 7.2 and 7.10 of the Code.

RESPONSE

Pfizer accepted that the statement 'Tolterodine is the market leading therapy in OAB' could be considered as a promotional claim for tolterodine which therefore required prescribing information to be provided as part of the advertisement. Since this had not been provided Pfizer acknowledged a breach of Clause 4.1.

Pfizer stated that as it aimed to uphold the highest standards of professional practice and compliance with the Code it would immediately cease any further publication of this advertisement and ensure that all similar promotional material was reviewed to ensure all relevant prescribing information was provided. Pfizer noted that due to publication processes, it was not possible to immediately amend or withdraw the advertisement from two publications. Pfizer provided a list of journals containing the advertisement which had either been published or where it had been unable to immediately amend or withdraw the advertisement.

Pfizer denied a breach of Clause 7.2 of the Code. The claim 'Toviaz 8mg demonstrated improvements with statistical significance vs. tolterodine ER in important treatment outcomes' could be substantiated with Chapple *et al*, accepted for publication by the British Journal of Urology International. The claim 'Tolterodine is the market leading therapy in OAB' was substantiated by market research data.

Pfizer did not consider that Clause 7.10 had been breached as there was no element of exaggeration or lack of objectivity.

PANEL RULING

The Panel considered that, although only referred to by its non-proprietary name, the advertisement nonetheless promoted Detrusitol; prescribing information should have been provided. Given that the prescribing information had not been provided the Panel ruled a breach of Clause 4.1 as acknowledged by Pfizer.

The Panel did not consider that the lack of prescribing information for Detrusitol rendered the advertisement misleading. No breach of Clause 7.2 was ruled. The Panel further did not consider that the absence of the prescribing information meant that the advertisement had not encouraged the rational use of Detrusitol. No breach of Clause 7.10 was ruled.

Complaint received **9 June 2008**

Case completed **10 July 2008**

CASE AUTH/2131/6/08

COMMUNITY PHARMACIST v GRÜNENTHAL

Promotion of Versatis

A community pharmacist complained that a representative from Grünenthal had told her that a study showed that Versatis (lidocaine medicated plaster) had roughly equivalent efficacy to gabapentin, with a much lower incidence of interactions and side-effects. The complainant asked for further information and was told it was still being worked on, and was not due out until September. The representative did not offer to supply information in September. The complainant did not make notes at the time, and it was possible that the representative had referred to a study against pregabalin.

The detailed responses from Grünenthal are set out below.

The Panel noted that the complainant referred to a comparison with gabapentin although she observed that it was possible she was referring to a study against pregabalin. Grünenthal's responses related to both products. Further comments from the complainant referred to pregabalin.

It appeared that the complaint referred to the use of interim data in the detail aid to support a claim 'Versatis is comparable to pregabalin in patient response at four weeks'. It appeared that the complainant had asked for the substantiating data and was told it would not be available until September. Grünenthal submitted that the complainant had asked to see the data when the study was completed, not the interim data.

On the basis of the parties' submissions, the Panel did not consider that there was sufficient evidence to show that on the balance of probabilities the complainant had asked for the interim data. With regard to the failure to supply the interim data the Panel ruled no breach of the Code.

The Panel then considered the use of interim data to support the claim made by the representative that Versatis had approximately equal efficacy to pregabalin and similar claims in the detail aid. Page 4 of the detail aid was headed 'First comparative study in PHN' [post herpetic neuralgia] and featured the claim 'Versatis is comparable to pregabalin in patient response at 4 weeks' referenced to data on file. Beneath the heading the claim 'Statistically shown to be at least comparable in efficacy to pregabalin (interim analysis p=0.0083)' appeared. The page included a bar chart of response rate after 4 weeks and other details.

Page 5 was referenced to the same interim analysis. It had the headline claim 'Versatis is comparable to pregabalin in reducing pain intensity at 4 weeks'. This was followed by the claim 'Interim efficacy parameters reported how many patients had 30% and 50% reductions in pain intensity'. The data was shown in a bar chart.

The Panel noted the data for pregabalin in Hempenstall *et al* (2005). The meta-analysis of published studies compared current therapies and calculated NNT to reach a 50% pain reduction. This was neither shown nor referenced on pages 4 and 5 of the detail aid. Hempenstall *et al* was not a direct clinical comparison of Versatis and pregabalin and nor was the data limited to the response with either medicine at 4 weeks.

The interim data provided by Grünenthal to substantiate the 4 week claims for Versatis (n=27) vs pregabalin (n=24) consisted of one page; page 53 of 418. No details of the inclusion criteria, study design and its intended length etc were provided. The page provided stated that the study was a non-inferiority study. The Panel considered there was a difference between showing non-inferiority to showing comparability. The Panel considered that on the basis of the interim data provided the claims for comparable efficacy for Versatis and pregabalin had not been substantiated and were misleading in that regard. Breaches of the Code were ruled.

Page 8 of the detail aid featured a comparison between Versatis and pregabalin for adverse events. The claims referred to fewer patients in the Versatis group having drug-related adverse events at week 4 compared with the pregabalin group. The associated bar chart was adapted from data on file. No information from the data on file with regard adverse events had been supplied by Grünenthal. The company had made a brief submission in relation to the content of the summary of product characteristics (SPC). The Panel considered, however, that the SPC provided general data regarding adverse events and as such could not be used to substantiate the very specific four week claims in the detail aid. The Panel considered that its comments above regarding the use of interim data for efficacy also applied to the use of interim data for the adverse events. Breaches of the Code were ruled.

A community pharmacist complained about the promotion of Versatis (lidocaine medicated plaster) by a representative from Grünenthal Ltd.

COMPLAINT

The complainant stated that in June a

representative from Grünenthal called at her pharmacy to discuss Versatis.

During the discussion the representative told the complainant that a study showed that Versatis had roughly equivalent efficacy to gabapentin, with a much lower incidence of interactions and side-effects. The complainant asked for further information and was told it was still being worked on, and was not due out until September. The representative did not offer to supply information in September. The complainant did not make notes at the time, and it was possible that the representative had referred to a study against pregabalin.

When writing to Grünenthal, the Authority asked it to respond in relation to Clauses 7.2, 7.4 and 7.5 of the Code.

RESPONSE

Grünenthal explained that with a high level of local prescribing of Versatis, the representative in question made a courtesy call on this pharmacist; the pharmacist was very busy and there was no more than a three minute discussion. The pharmacist was interested in the Versatis vs pregabalin interim data and stated that she would like to see the data when the study was completed. In response to the pharmacist's question, the representative said that she could not give the complete trial data now as it was not finished, but would call back with it when it was available – probably in September. The representative left her card and asked if there was anything else she could help with to which the pharmacist answered 'no'.

Where the pharmacist cited 'further information' in her complaint, it therefore referred to the full trial data that she said she would like to see. The representative was correct in that the final results of the whole trial would be available later, once fully analysed. The representative's electronic call notes, made just after the call, corroborated the discussion; a copy was provided. The representative specifically noted that the pharmacist wanted the data when complete and that this was the 'Next Objective' with this customer. The intention was, therefore, to comply with the pharmacist's request for the further data as available in September. The call entry recorded the fact that the pharmacist raised no further questions. Hence, there was no breach of Clause 7.5.

The detail aid the representative used with the pharmacist compared the efficacy of gabapentin and pregabalin in post herpetic neuralgia (PHN) – as adapted from Hempenstall *et al* (2005) – and supported the representative's comment about efficacy. Therefore, there was no breach of Clause 7.2.

The representative's comments about efficacy and side-effects were also supported from the interim data in the detail aid and were not in breach of Clause 7.2.

In terms of the representative's comments about drug interactions, the Versatis summary of product characteristics (SPC) stated: 'No interaction studies have been performed. No clinically relevant interactions have been observed in clinical studies with the plaster. Since the maximum lidocaine plasma concentrations observed in clinical trials with the plaster were low (see section 5.2), a clinically relevant pharmacokinetic interaction is unlikely'.

Hence, on balance, the representative's comments about drug interactions were reasonable, could be substantiated and, therefore, did not breach Clauses 7.2 or 7.4.

It seemed, therefore, that a simple misunderstanding had arisen with regard to what the pharmacist had asked for. When retail pharmacists were busy, it was possible that time constraints here had created inadvertent misunderstandings. Grünenthal would never intend to mislead customers.

COMMENTS FROM THE COMPLAINANT

Having given preliminary consideration to the matter, the Panel decided that it would be helpful to have the complainant's comments on Grünenthal's response with regard to exactly what information she had asked the representative for.

The complainant submitted that the representative did not initially state that the data to which she referred was interim only. She talked about how the study showed that Versatis had approximately equal efficacy to pregabalin, with a lower incidence of side-effects. It was only when the complainant asked if she could see a copy of the data that she learned it was incomplete, and might be available in September.

It was correct that she wished to see the data from the full trial, when complete, and the complainant emphasized that she had not disputed any findings from that trial, when complete. It was quite feasible that the representative's comments would be supported by the full results, but the complainant felt strongly that interim results should not be referred to as if they were finalised.

The complainant stated that she had raised no further questions at the time because she was so taken aback at what appeared to be a breach of the Code – the first apparent breach she had ever encountered. Grünenthal referred to misunderstandings three times in its letter.

FURTHER COMMENTS FROM THE RESPONDENT

In response to the complainant's comments Grünenthal referred to Hempenstall *et al* – the only published meta-analysis to date, investigating the comparative efficacy of current therapies available

for the treatment of PHN. This was a robust, peer reviewed journal publication produced by world experts in the field of pain management. It used the validated technique of number needed to treat (NNT) to define the treatment-specific effect of an intervention. This in turn ensured a fair and effective comparison of efficacy across different therapies. It was also important to note that Hempenstall *et al* used the strictest inclusion criteria to ensure that papers included were of the highest scientific standard.

Hempenstall *et al* reported that, the NNT to reach a pre-ordained 50% pain reduction for gabapentin was 4.39 (3.34 - 6.07), compared with 2 (1.43 - 3.31) for Versatis. In clinically meaningful terms, 2 patients needed to be treated with Versatis for one to find a clinical effect (in this case a 50% reduction in pain) and 4 with gabapentin for one to reach a similar clinical effect.

In terms of drug interactions, the Versatis SPC stated:

> 'No interaction studies have been performed. No clinically relevant interactions have been observed in clinical studies with the plaster. Since the maximum lidocaine plasma concentrations observed in clinical trials with the plaster were low (see section 5.2), a clinically relevant pharmacokinetic interaction is unlikely. Although normally the absorption of lidocaine from the skin is low, the plaster must be used with caution in patients receiving Class 1 antiarrhythmic drugs (eg tocainide, mexiletine) and other local anaesthetics since the risk of additive systemic effects cannot be excluded.'

With reference to <u>likely</u> interactions, part of the equivalent SPC data for gabapentin [Pfizer's product Neurontin, to be taken orally] stated that:

> 'In a study involving healthy volunteers (N=12), when 60mg controlled-release morphine capsule was administered 2 hours prior to a 600mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.
>
> Coadministration of gabapentin with antacids containing aluminium and magnesium reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.
>
> A slight decrease in renal excretion of gabapentin that is observed when it is coadministered with cimetidine is not expected to be of clinical importance.'

The fact that topically applied Versatis had been shown to generate limited systemic levels of lidocaine supported the claim that there were fewer interactions to be expected in this type of application.

In conclusion, it was clear from the SPC that there was a reduced potential for interactions for Versatis when compared with gabapentin.

In relation to adverse events Grünenthal referred to the latest SPCs for gabapentin and Versatis. It was evident that the adverse events reported for Versatis were mild to moderate in nature and mainly related to application site reactions. However, it was clear from the gabapentin SPC that there were a significant number of serious adverse events reported, many of which were very common (≥1/100, <1/10).

Grünenthal noted that section 4.8 of the Versatis SPC stated: 'Approximately 16% of patients can be expected to experience adverse reactions. These are localised reactions due to the nature of the medicinal product. The most commonly reported adverse reactions were administration site reactions including erythema, rash, application site pruritus, application site burning, application site dermatitis, application site erythema, application site vesicles, dermatitis, skin irritation, and pruritus.'

The SPC stated that adverse reactions reported in PHN studies were predominantly of mild and moderate intensity and less than 5% led to treatment discontinuation. Systemic adverse reactions following the appropriate use of the plaster were unlikely since the systemic concentration of lidocaine was very low. Systemic adverse reactions to lidocaine were similar in nature to those observed with other amide local anaesthetics.

The gabapentin adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain were provided in a single list in the SPC by class and frequency. Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported. Within each frequency grouping, undesirable effects were presented in order of decreasing seriousness.

Grünenthal submitted that it was clear from SPC comparisons that significantly more frequent adverse events had been reported for gabapentin compared with Versatis. This would be expected given the nature of comparing a systemic anti-convulsant with a peripherally acting analgesic plaster that generated low levels of systemic lidocaine.

Grünenthal submitted that these data and evidence substantiated the claim that 'Versatis has roughly equivalent efficacy to gabapentin with a much lower incidence of interactions and side- effects'.

FURTHER INFORMATION FROM THE RESPONDENT

The Panel considered that it needed further

information from the respondent in relation to a comparison with pregabalin.

Grünenthal submitted that the interim data was never referred to as finalised. The detail aid clearly marked the results as 'interim analysis' next to the p value. Grünenthal had confirmed this with the representative involved, who made it clear these data were interim.

The complainant did not question the validity of data presented at the time. Also, an opportunity was given at the end of the meeting where the representative specifically checked if she could do anything else to help before the complainant ended the discussion.

The relevant page of the detail aid was based on the planned statistical interim analysis of the data, of which the complainant requested the full data set when available in September. In an internal report from the statistician, 'A test of non-inferiority in the PHN strata results in a p-value of 0.0083, strongly suggesting that lidocaine 5% medicated plaster is non-inferior to pregabalin in PHN subjects alone'. This was not something Grünenthal had claimed. However, it was statistically correct to view the efficacy of Versatis as comparable to pregabalin at this interim stage.

Further substantiation of the comparison of Versatis with pregabalin was given in Hempenstall *et al*. It was the only published meta-analysis to have investigated the comparative efficacy of current therapies available for the treatment of post herpetic neuralgia (PHN). To reiterate, this paper was a robust, peer reviewed journal publication produced by world experts in the field of pain management. It used the validated technique of number needed to treat (NNT) to define the treatment-specific effect of an intervention. This in turn enabled an effective comparison of efficacy across different therapies. It was also important to note that Hempenstall *et al* used the strictest inclusion criteria to ensure that papers included were of the highest scientific standard.

As could be seen from this review, the NNT to reach a pre-ordained 50% pain reduction for pregabalin was 4.93 (3.66 - 7.58), compared with an NNT for Versatis of 2 (1.43 - 3.31).

In clinically meaningful terms, two patients needed to be treated with Versatis for one patient to receive a clinical effect (in this case a 50% reduction in pain) compared with five patients with pregabalin for one to receive a clinical effect. Hence, from this comprehensive analysis of the data comparing these two products, one could conclude that Versatis had a comparable efficacy to that of pregabalin.

PANEL RULING

The Panel noted that the complainant referred to a comparison with gabapentin in her complaint although she noted that it was possible she was referring to a study against pregabalin. Grünenthal's response related to both products. The further comments from the complainant referred to pregabalin. The further comments from Grünenthal referred to both products.

The Panel noted that the representative had used the detail aid with the complainant. It appeared from the complainant's comments that the complaint referred to the use of interim data to support claims. The detail aid used interim data to support a claim 'Versatis is comparable to pregabalin in patient response at four weeks'. It appeared that the complainant had asked for data to substantiate this claim and was told it would not be available until September. Grünenthal submitted that the complainant had asked to see the data when the study was completed not the interim data.

The Panel noted the parties' accounts of the request differed. It was difficult in such cases to know what had transpired. A judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually necessary on the part of the individual before he or she was moved to actually submit a complaint.

On the basis of the parties' submissions, the Panel did not consider that there was sufficient evidence to show that on the balance of probabilities the complainant had asked for the interim data. With regard to the failure to supply the interim data the Panel ruled no breach of Clause 7.5.

The Panel then went on to consider the acceptability of using interim data to support the claim made by the representative that Versatis had approximately equal efficacy to pregabalin and similar claims in the detail aid. Page 4 of the detail aid was headed 'First comparative study in PHN' and featured the headline claim 'Versatis is comparable to pregabalin in patient response at 4 weeks' referenced to data on file. Beneath the heading the claim 'Statistically shown to be at least comparable in efficacy to pregabalin (interim analysis p=0.0083)' appeared. The page included a bar chart of response rate after 4 weeks and other details.

Page 5 was referenced to data from the same interim analysis. It had the headline claim 'Versatis is comparable to pregabalin in reducing pain intensity at 4 weeks'. This was followed by the claim 'Interim efficacy parameters reported how many patients had 30% and 50% reductions in pain intensity'. The data was shown in a bar chart.

The Panel noted the data for pregabalin in Hempenstall *et al*. The meta-analysis of published studies compared current therapies and calculated NNT to reach a 50% pain reduction. This was neither shown nor referenced on pages 4 and 5 of the detail aid. Hempenstall *et al* was not a direct clinical comparison of Versatis and pregabalin and nor was the data limited to the response with either medicine at 4 weeks.

The interim data provided by Grünenthal to substantiate the 4 week claims for Versatis (n=27) vs pregabalin (n=24) consisted of one page; page 53 of 418. No details of the inclusion criteria, study design and its intended length etc were provided. The page provided stated that the study was a non-inferiority study. The Panel considered there was a difference between showing non-inferiority to showing comparability. The Panel considered that on the basis of the interim data provided the claims for comparable efficacy for Versatis and pregabalin had not been substantiated and were misleading in that regard. Breaches of Clauses 7.2 and 7.4 were ruled.

Page 8 of the detail aid featured a comparison between Versatis and pregabalin for adverse events. The claims referred to fewer patients in the Versatis group having drug-related adverse events at week 4 compared with the pregabalin group. The associated bar chart was adapted from data on file. No information from the data on file with regard adverse events had been supplied by Grünenthal. The company had made a brief submission in relation to the content of the SPC. The Panel considered, however, that the SPC provided general data regarding adverse events and as such could not be used to substantiate the very specific four week claims in the detail aid. The Panel considered that its comments above regarding the use of interim data for efficacy also applied to the use of interim data for the adverse events. Breaches of Clauses 7.2 and 7.4 were ruled.

During its consideration of this case the Panel had some concerns as to whether the meta-analysis by Hempenstall *et al* was sufficient to substantiate the comparative claims for Versatis and other therapies including pregabalin and gabapentin. The study concluded that the evidence base supported the use of gabapentin and pregabalin for PHN and also supported lidocaine patches. The discussion stated that data extracted from small and/or single unreplicated studies needed to be viewed with a particular degree of caution. This applied to lidocaine patches (1 study, 64 patients). The data for gabapentin was from 3 studies, (n=559) and three studies had also been used for pregabalin (n=411). The difference in size of the three data sets was not reported in the detail aid. Hempenstall *et al* stated that the dichotomous data for adverse events needed to be viewed with caution for a number of reasons. The Panel requested its concerns regarding the use of the meta-analysis be drawn to Grünenthal's attention.

Complaint received **10 June 2008**

Case completed **29 August 2008**

CASE AUTH/2135/6/08

ANAESTHETIST v BAYER SCHERING PHARMA

Advertisement in The Economist

An anaesthetist alleged that an advertisement placed in The Economist by Bayer Schering Pharma promoted a medicine to the public, in breach of the Code.

The advertisement was headed 'Fighting Multiple Sclerosis' followed by the Bayer corporate logo which included the phrase 'Science For A Better Life', followed by 'Providing Hope'. The advertisement stated that in the fight against multiple sclerosis Bayer had brought to market the first therapy with long-term efficacy in significantly reducing the frequency of periods of exacerbation. It also stated that the company was continuing to investigate new therapies to give patients the most precious gift possible: a life full of hope for the future.

Bayer Schering's product Betaferon (interferon beta-lb) was indicated for treatment of certain types of multiple sclerosis (MS).

The complainant stated that the advertisement referred to a medicine marketed by Bayer to treat symptoms of MS. Although the name of the medicine was not given, there was enough information provided to allow a reader to request this medicine from a doctor.

The Panel noted Bayer Schering's submission that the advertisement was to show Bayer as an ethical company committed to scientific research and the provision of high quality healthcare. The advertisement, however, was clearly about MS and text referred to Bayer Schering's treatment for MS and included clinical claims for the product. Further the advertisement also hinted that something else would become available and this would give patients 'a life full of hope for the future'. It was not simply corporate promotion of the company as submitted. The Panel considered that the advertisement contained statements which would encourage patients to ask their doctor to prescribe the Bayer product which was a prescription only medicine. The mention of giving patients 'a life full of hope' raised unfounded hopes of successful treatment given that MS was an incurable disease. The Panel ruled a breach of the Code.

High standards had not been maintained and hence a further breach of the Code was ruled. Taking all the circumstances into account the Panel did not consider that the advertisement brought discredit on, or reduced confidence in, the pharmaceutical industry. This clause was used as a sign of particular censure and reserved for such use. Thus no breach of Clause 2 was ruled.

An anaesthetist complained about an advertisement placed in The Economist (week of 23 June) by Bayer Schering Pharma.

The advertisement was headed 'Fighting Multiple Sclerosis' followed by the Bayer corporate logo which included the phrase 'Science For A Better Life', followed by 'Providing Hope'. Text at the bottom of the advertisement stated that in the fight against multiple sclerosis Bayer had brought to market the first therapy with long-term efficacy in significantly reducing the frequency of periods of exacerbation. It also stated that the company was continuing to investigate new therapies to give patients the most precious gift possible: a life full of hope for the future.

Bayer Schering's product Betaferon (interferon beta-lb) was indicated for treatment of certain types of multiple sclerosis (MS).

COMPLAINT

The complainant stated that the advertisement referred to a medicine marketed by Bayer to treat symptoms of MS. Although the name of the medicine was not given, there was enough information provided to allow a reader to request this medicine from a doctor.

The complainant alleged that this was an example of promotion of a medicine to the public and therefore in breach of the Code.

When writing to Bayer Schering, the Authority asked it to respond in relation to Clauses 2, 9.1, 20.1 and 20.2.

RESPONSE

Bayer Schering stated that it did not consider it appropriate to encourage members of the public to ask their doctor to prescribe a specific medicine in any circumstances. It did not accept that the advertisement did this.

Bayer Schering had an internal local and global certification procedure for ensuring compliance of corporate activities with the Code.

The Economist was targeted at individuals with an interest in finance and politics, not the general public *per se*. The purpose of the advertisement was to show Bayer as an ethical company committed to science research and the provision of high quality healthcare. It was not intended to

highlight a specific medicine. The advertisement did not refer to any named medicine.

MS patients were an especially well-informed group. The MS Society stated that 'patients are entitled to participate in the decision making process'. MS decisions, an independent aid for patients funded by the Department of Health, provided information to 'crystallise your thinking and make a careful decision in the collaboration with your specialist'. Bayer Schering supported this view but it was inconceivable that the prescription of a disease modifying drug (DMD) would be made on the basis of a patient request. Furthermore the fact that one DMD was developed first did not mean it was superior to newer DMDs.

Treatment could only be initiated by a specialist and the Association of British Neurologists had agreed criteria for which patients were eligible. The supply of DMDs on the NHS was tightly regulated. It was administrated under a special scheme between the NHS, Bayer Schering Pharma and the other manufacturers. This was the Department of Health Risk Sharing Scheme. It was in no-one's interest to encourage patients to ask for a medicine which was inappropriate.

Bayer Schering did not accept that the advertisement was an example of promotion of a medicine to the public, it was a promotion of the company to the financial and political sectors.

PANEL RULING

The Panel noted that the advertisement did not mention any product by name, either brand or generic. However it was possible to promote a product without mentioning it by name.

The Panel considered that The Economist was a publication aimed at the public, albeit a readership that would have an interest in finance and politics. It was not a publication aimed at a health professional audience *per se*, such as the BMJ. The advertisement needed to comply with Clause 20.

The Panel noted Bayer Schering's submission that the advertisement was to show Bayer as an ethical company committed to scientific research and the provision of high quality healthcare. The advertisement, however, was clearly about MS and text referred to Bayer Schering's treatment for MS and included clinical claims for the product. Further the advertisement also hinted that something else would become available and this would give patients 'a life full of hope for the future'. It was not simply corporate promotion of the company as submitted. The Panel considered that the advertisement failed to meet the requirements of Clause 20.2. It contained statements which would encourage patients to ask their doctor to prescribe the Bayer product which was a prescription only medicine. Whether that product was subsequently prescribed or not was not relevant in this regard. The mention of giving patients 'a life full of hope' raised unfounded hopes of successful treatment given that MS was an incurable disease. The Panel ruled a breach of Clause 20.2.

The Panel noted Bayer Schering's submission that the supply of beta-interferon, like all prescription only medicines, was tightly regulated and that treatment could only be initiated by a specialist. It failed to see the relevance of this submission in relation to whether the advertisement constituted promotion of a prescription only medicine to the public. On balance the Panel considered that the advertisement in effect constituted an advertisement for Betaferon to the public. A breach of Clause 20.1 was ruled.

High standards had not been maintained and hence a breach of Clause 9.1 was ruled. Taking all the circumstances into account the Panel did not consider that the advertisement brought discredit on or reduced confidence in the pharmaceutical industry. This clause was used as a sign of particular censure and reserved for such use. Thus no breach of Clause 2 was ruled.

Complaint received **23 June 2008**

Case completed **4 August 2008**

CONSULTANT DERMATOLOGIST v RANBAXY

Co-Cyprindiol 'Dear Sir or Madam' letter

A consultant dermatologist complained that a 'Dear Sir or Madam' letter about Co-Cyprindiol (cyproterone acetate and ethinyloestradiol), sent by Ranbaxy, stated that Co-Cyprindiol was a combination of isotretinoin 20mg with erythromycin 250mg. Bearing in mind that Co-Cyprindiol was specifically named in the National Institute for Health and Clinical Excellence (NICE) guidelines for the treatment of acne in women prior to referral to a consultant dermatologist, the complainant was worried if it really did contain isotretinoin and erythromycin.

The Panel noted that the letter stated that Co-Cyprindiol was an addition to Ranbaxy's dermatology portfolio which consisted of isotretinoin 20mg capsules (30 pack) and erythromycin 250mg tablets (28 pack). It did not state that Co-Cyprindiol contained isotretinoin and erythromycin. Although the Panel ruled that there had been no breach of the Code it nonetheless considered that the letter could have been clearer.

A consultant dermatologist complained about a 'Dear Sir or Madam' letter about Co-Cyprindiol (cyproterone acetate and ethinyloestradiol) which she had received from Ranbaxy Europe Ltd.

COMPLAINT

The complainant stated that the letter said that Co-Cyprindiol was a combination of isotretinoin 20mg with erythromycin 250mg. Bearing in mind that Co-Cyprindiol was specifically named in the National Institute for Health and Clinical Excellence (NICE) guidelines for the treatment of acne in women prior to referral to a consultant dermatologist, the complainant thought it was very worrying if it really did contain isotretinoin and erythromycin.

Perhaps this was a typographical error but the complainant found Ranbaxy's attitude, which she contacted first, very worrying in that it was not in the least bit concerned that there might be some gross misinformation in the letter, which the complainant presumed had been sent to all practising doctors.

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

RESPONSE

Ranbaxy stated that the letter, which had been sent to consultant dermatologists, stated that 'Co-Cyprindiol will be a new addition to our dermatology *portfolio*, which consists of Isotretinoin 20mg capsules (30 pack) and Erythromycin 250mg tablets (28 pack)'. Ranbaxy currently had these two products on the market for treatment of dermatological conditions, and was simply notifying physicians about the additional availability of Co-Cyprindiol. The letter did not state that Co-Cyprindiol was a combination of isotretinoin and erythromycin, as it clearly was not. The letter had prescribing information on the back of it.

Ranbaxy believed that the information was correct and not misleading, and did not breach Clause 7.2.

PANEL RULING

The Panel noted that the letter stated that Co-Cyprindiol was an addition to Ranbaxy's dermatology portfolio which consisted of isotretinoin 20mg capsules (30 pack) and erythromycin 250mg tablets (28 pack). It did not state that Co-Cyprindiol contained isotretinoin and erythromycin.

The Panel accordingly ruled that there had been no breach of Clause 7.2.

Nonetheless, the complainant had been misled and the Panel considered that the drafting of the letter could have been clearer. The letter did not state the active ingredients of Co-Cyprindiol – the only reference to cyproterone acetate and ethinyloestradiol was in the prescribing information on the reverse. In that regard the Panel noted that Clause 4.3 of the Code required the non-proprietary name of a medicine to appear immediately adjacent to the most prominent display of the brand name. The supplementary information stated that in a promotional letter the most prominent display of the brand name would usually be that in the letter itself, rather than in the prescribing information on the reverse of the letter. The Panel considered that the failure to comply with Clause 4.3 had been the root cause of the confusion caused by the letter. No allegation had been made in this regard and thus the Panel could make no ruling. The Panel further considered that prescribing information should have been provided for both isotretinoin and erythromycin. The Panel asked that Ranbaxy be advised of its views on these points.

Complaint received **30 June 2008**

Case completed **30 July 2008**

CASE AUTH/2138/7/08

PUBLIC HEALTH PHYSICIAN v RECKITT BENCKISER HEALTHCARE

Gaviscon Advance journal advertisements

A public health physician complained about two advertisements for Gaviscon Advance (sodium alginate and potassium bicarbonate) issued by Reckitt Benckiser Healthcare and published in the BMJ.

The complainant stated that the advertisements presented data from *in-vitro* studies but made claims about expected *in-vivo* effects. The conclusions presented misled the reader because they made unsubstantiated claims about clinical situations that could not be reasonably extrapolated from the *in-vitro* data presented.

The detailed response from Reckitt Benckiser is given below.

Both abstracts, and therefore both advertisements, detailed *in-vitro* studies. The Panel noted that supplementary information to the Code stated that care must be taken with, *inter alia*, the use of data derived from *in-vitro* studies so as to not mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The Panel noted that it was a principle under the Code that claims related to the clinical situation unless clearly stated otherwise.

The advertisement entitled 'The Role for Liquid Alginate Suspension (Gaviscon Advance) in the Protection of the Oesophagus Against Damage by Bile in the Refluxate' featured a schematic diagram of a cell model used to assess diffusion of bile acids. Under the heading 'Conclusion' the first bullet point clearly referred to an *in-vitro* model. The third bullet point, however, stated '*In-vivo*, the mode of action of Gaviscon Advance is expected to give oesophageal protection from the damaging potential of bile acids'. The Panel noted Reckitt Benckiser's submission that it was not unreasonable to consider that Gaviscon Advance *might* [emphasis added] produce the same results *in-vivo* as *in-vitro*. The company had not produced any data to support this statement. In the Panel's view, the claim was based on assumption and together with the title of the advertisement suggested that Gaviscon Advance *would* [emphasis added] protect the oesophagus from damage by bile in the refluxate; the use of the wording 'expected to give' in the claim did not negate this otherwise misleading impression. Further the Panel noted that the final bullet point referred to '… a wider clinical benefit…' for Gaviscon Advance. The Panel considered that the third and fourth bullet points appeared to relate directly to the clinical situation. The data presented in support of the conclusions was from an *in-vitro* study; the Panel noted its comments above regarding the applicability of the *in-vitro* data to the clinical situation. The Panel considered the advertisement was misleading and a breach of the Code was ruled.

The advertisement entitled 'The Role for Liquid Alginate Suspension (Gaviscon Advance) in the Protection of the Oesophagus Against Damage by Pepsin in the Refluxate' referred only twice to the study at issue being *in-vitro*; the 'Methods' section described a simulated gastric refluxate and the fact that reflux events were mimicked. The 'Conclusion' section, however, did not refer to an *in-vitro* study, it appeared that all of the bullet points related directly to the clinical situation. The data presented in support of the conclusions was from an *in-vitro* study; the Panel noted its comments above regarding the applicability of the *in-vitro* data to the clinical situation. The Panel considered that the advertisement was misleading and a breach of the Code was ruled.

A public health physician complained about two advertisements (ref G-NHS-UK-51-07) for Gaviscon Advance (sodium alginate and potassium bicarbonate) issued by Reckitt Benckiser Healthcare (UK) Limited. The advertisements were titled 'The Role for Liquid Alginate Suspension (Gaviscon Advance) in the Protection of the Oesophagus Against Damage by Bile in the Refluxate' and 'The Role for Liquid Alginate Suspension (Gaviscon Advance) in the Protection of the Oesophagus Against Damage by Pepsin in the Refluxate' and were published in the BMJ of 22 March and 12 April respectively.

This case was considered under the 2008 Constitution and Procedure. Reckitt Benckiser was asked to bear in mind the requirements of Clause 7.2 which was the same in the 2008 Code as in the 2006 Code.

COMPLAINT

The complainant stated that the advertisements presented data from *in-vitro* studies but made claims about expected *in-vivo* effects. The complainant believed that the conclusions presented in both advertisements misled the reader because they made unsubstantiated claims about clinical situations that could not be reasonably extrapolated from the *in-vitro* data presented in breach of the Code.

RESPONSE

Reckitt Benckiser stated that it could see no justifiable

reason for a genuine grievance against either advertisement with respect to Clause 7.2.

The complainant suggested that *in-vivo* conclusions had been based upon the *in-vitro* studies described. In the advertisements, however, the conclusions did not make claims to suggest that either *in-vivo* studies had been conducted or that Gaviscon Advance had been proven to have *in-vivo* activity relating to bile and pepsin. All conclusions clearly related to the studies described immediately preceding and these were very obviously conducted *in-vitro* as was clearly stated on numerous occasions throughout the articles. In fact Reckitt Benckiser did not expect Gaviscon Advance to behave differently in these two instances, which was reasonable considering that Gaviscon Advance was a non-systemic product which worked by physical means but the claims made did not state an *in-vivo* action, merely that it was not unreasonable to consider this might be the case.

The advertisements concerned abstracts of two posters that had been accepted and presented at eminent scientific meetings worldwide including Digestive Disease Week, United European Gastroenterology World and the British Society of Gastroenterology Annual Meeting. The abstracts had thus been peer reviewed and were presented in full in each advertisement. No additional claims or conclusions were included with either abstract, thus those that were included were deemed accurate by experts in this field.

Furthermore the abstracts were included in the BMJ which was aimed solely at health professionals. Therefore, the target audience was scientific and the advertisements were presented in a fashion that befitted the BMJ. The abstracts were scientifically structured and included a brief background, a clear aim, sufficient details of the methods for the reader to be able to repeat the experiment if they wished, a succinct outline of the results and the authors' interpretation of the findings. It was this content that would have been considered by BMJ reviewers and then deemed to be accurate and appropriate to its readers.

PANEL RULING

The Panel noted that each advertisement was headed 'Advertisement Feature' below which appeared the relevant abstract. The Panel understood that the abstracts appeared in the advertisements essentially in the same way as they had been originally presented at the scientific meetings. Reckitt Benckiser had submitted that they were presented in full with no additional claims or conclusions. The Panel was thus concerned to note that the abstracts, although written for a scientific purpose, were now being used unchanged for a promotional purpose. The Gaviscon Advance prescribing information appeared at the bottom of the right hand page of each double page spread.

Both abstracts, and therefore both advertisements, detailed *in-vitro* studies. In that regard the Panel noted that the supplementary information to Clause 7.2 stated that care must be taken with, *inter alia*, the use of data derived from *in-vitro* studies so as to not mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The Panel noted that it was a principle under the Code that claims related to the clinical situation unless clearly stated otherwise.

The advertisement published on 22 March, entitled 'The Role for Liquid Alginate Suspension (Gaviscon Advance) in the Protection of the Oesophagus Against Damage by Bile in the Refluxate', featured a schematic diagram of a cell model used to assess diffusion of bile acids. Under a heading of 'Conclusion' the first bullet point clearly referred to an *in-vitro* model. The third bullet point, however, stated '*In-vivo*, the mode of action of Gaviscon Advance is expected to give oesophageal protection from the damaging potential of bile acids'. The Panel noted Reckitt Benckiser's submission that it was not unreasonable to consider that Gaviscon Advance *might* [emphasis added] produce the same results *in-vivo* as it did *in-vitro*. The company had not produced any data to support this statement. In the Panel's view, the claim was based on assumption and together with the title of the advertisement suggested that Gaviscon Advance *would* [emphasis added] protect the oesophagus from damage by bile in the refluxate; the use of the wording 'expected to give' in the claim did not negate this otherwise misleading impression. Further the Panel noted that the final bullet point referred to '… a wider clinical benefit…' for Gaviscon Advance. The Panel considered that the third and fourth bullet points appeared to relate directly to the clinical situation. The data presented in support of the conclusions was from an *in-vitro* study; the Panel noted its comments above regarding the applicability of the *in-vitro* data to the clinical situation. The Panel considered the advertisement was misleading. A breach of Clause 7.2 was ruled.

The advertisement published on 12 April, entitled 'The Role for Liquid Alginate Suspension (Gaviscon Advance) in the Protection of the Oesophagus Against Damage by Pepsin in the Refluxate', referred only twice to the study at issue being *in-vitro*; the 'Methods' section described a simulated gastric refluxate and the fact that reflux events were mimicked. The 'Conclusion' section, however, did not refer to an *in-vitro* study, it appeared that all of the bullet points related directly to the clinical situation. The data presented in support of the conclusions was from an *in-vitro* study; the Panel noted its comments above regarding the applicability of the *in-vitro* data to the clinical situation. The Panel considered that the advertisement was misleading. A breach of Clause 7.2 was ruled.

Complaint received **7 July 2008**

Case completed **26 August 2008**

CONSULTANT RHEUMATOLOGIST v ROCHE

Meeting at the Royal College of Physicians

A consultant rheumatologist complained about a meeting broadcast on the Internet from the Royal College of Physicians (RCP) on 19 June, which had been sponsored by Roche.

The complainant had not had a satisfactory reply from the RCP to her enquiries about Roche's role in sponsoring the meeting which in essence was about what to do with patients with inflammatory arthritis who had failed anti-TNF therapy. The options presented were switching to abatacept or to rituximab (Roche's product MabThera). Since abatacept had not been approved by the National Institute of Health and Clinical Excellence (NICE), it was effectively unavailable in the UK, hence the speakers were only promoting the use of rituximab. The complainant submitted that the speakers were paid by the RCP but she had not had an answer to emails about payment to the RCP by Roche. The complainant did not know whether the company's involvement was appropriate; it was declared, but the complainant did not think that the RCP should be effectively promote a medicine in which it had a financial interest when there were other clinical options, not mentioned at the meeting, such as changing or switching medicines for these patients.

The detailed response from Roche is given below.

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

The Panel noted that Roche's representatives had promoted the webcast by the use of flyers which incorporated the logos of the RCP and Roche on the front cover together with the statement 'Sponsored by an educational grant from Roche Products Limited'. A briefing note instructed representatives to encourage as many customers as possible to log on 'live' or to view the archived event over the next 12 months. In the Panel's view, the use of representatives to distribute flyers brought the webcast within the scope of the Code.

The Panel noted that Roche's sponsorship of the webcast was obvious at the outset on both the flyer and the webcast. It appeared that the complainant was more concerned about the role of the RCP. The agreement regarding the live webcast stated that Roche could suggest topics and speakers but final approval of the programme rested with the RCP. The agreement required that Roche must not contact the speakers or discuss the programme with them prior to or during the event. The speakers were responsible for exercising full control over the lectures and discussions and any content therein. Roche could have no involvement in that process.

The Panel had some concerns about the webcast. Clearly the topic 'Identifying and Managing Anti-TNF Inadequate Responders in RA' was relevant to MabThera as that was a possible alternative treatment choice for such inadequate responders. The speakers would presumably know which company had sponsored the webcast. The presentation on 'Managing anti-TNF inadequate responders' had included favourable statements about rituximab. Other medicines such as infliximab, etenercept and abatacept were also referred to. In theory products could be used irrespective of approval by NICE. In summing up the Chairman had specifically referred to rituximab. Nonetheless the Panel did not consider that the sponsorship arrangements were unreasonable; the RCP had the final approval of the programme and speakers. The Panel did not consider that Roche's involvement was inappropriate as alleged. The webcast was clearly sponsored by Roche and so was not misleading in that regard. No breach of the Code was ruled.

A consultant rheumatologist complained about a meeting broadcast on the Internet from the Royal College of Physicians (RCP) on 19 June, which had been sponsored by Roche Products Limited.

COMPLAINT

The complainant stated that she had not had a satisfactory reply to her enquiries from the RCP about Roche's role in sponsoring the meeting which in essence was about what to do with patients with inflammatory arthritis who had failed anti-TNF therapy. The options presented were switching to abatacept or to rituximab [Roche's product MabThera]. Since abatacept had not been approved by the National Institute of Health and Clinical Excellence (NICE), it was effectively unavailable in the UK, hence the speakers were only promoting the use of rituximab. The complainant

submitted that the speakers were paid to speak by the RCP directly but she had not had an answer to two emails about payment to the RCP by Roche. The complainant did not know if the company's involvement was appropriate or not, certainly it was declared, but the complainant did not think that the RCP should be effectively promoting the use of a particular medicine in which it had a financial interest when there were other clinical options such as changing or switching medicines for these patients which were not mentioned at the meeting.

When writing to Roche, the Authority asked it to respond in relation to Clauses 2, 7.2, 9.1 and 19 of the 2006 Code. The case would be considered under the 2008 Constitution and Procedure.

RESPONSE

Roche stated that the complaint concerned the 'RCPLive' Internet lecture 'Identifying and Managing Anti-TNF Inadequate Responders in RA [rheumatoid arthritis]' which had been launched recently on the RCPLive website.

Roche noted that the complainant was dissatisfied about a lack of response to her enquiries from the RCP, the involvement of the RCP in holding meetings that focussed on a specific treatment, or class of treatments and the receipt of sponsorship by the RCP from Roche for this meeting.

Roche believed that the first two matters of complaint were aimed at the RCP and as such fell outside of the scope of the Code. Regarding the third, Roche believed the arrangements for the sponsorship were appropriate.

Roche explained that it was approached by a third party acting on behalf of the RCP to sponsor the RCPLive lecture on rheumatology. The sponsorship was subject to the terms and conditions of the contract, which was provided. These terms and conditions were in line with Roche's obligation to be clear and transparent as to its involvement in the sponsorship of this lecture. It clearly established the roles and responsibilities of both Roche and the third party in the implementation of the project.

Roche did not select the speakers at the meeting. Although the company was able to suggest topics and speakers, the final selection and approval of the programme rested with the RCP.

Roche did not see the presentations. The contract stated that 'The sponsor must not make contact with speakers or discuss the programme content with them prior to or during the event'. There was no transcript of the meeting available. The lecture could be viewed directly from the RCPLive website.

The approval and payment of sponsorship to the RCP followed the appropriate internal operating procedure for medical and education goods and services for which the paperwork was provided.

In summary Roche believed that the sponsorship of the RCPLive Internet lecture in rheumatology was appropriate and followed the procedures set out in both internal process and the Code.

Roche believed that the issues the complainant raised were directed at the RCP and her perception of the activities with which the RCP should involve itself.

FURTHER RESPONSE FROM ROCHE

In response to a request from the Panel for further information, Roche stated that its representatives had advertised the webcast via a flyer, as allowed by the RCPLive initiative, which gave guidance on flyer production. The use of this RCP-approved flyer was briefed to the representatives via email.

Roche reiterated that it had no influence on either the speakers or the content of their presentations. Roche did not see the presentations prior to them being broadcast. The company had made no use, nor did it intend to, of any materials from the webcast lecture in any format.

PANEL RULING

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

The Panel noted that Roche's representatives had promoted the webcast by the use of flyers. The RCP guidance on flyer production referred to the need for them to be approved by the RCP prior to use as well as setting out requirements for content and layout. The flyers incorporated the logos of the RCP and Roche on the front cover together with the statement 'Sponsored by an educational grant from Roche Products Limited'. Inside the flyer readers were given the programme for the webcast and instructions as to how to participate. Representatives were instructed to encourage as many customers as possible to log on 'live' or to view the archived event over the next 12 months. The one page briefing was sent by the MabThera brand manager and incorporated the brand logo in the top right-hand corner. In the Panel's view, the use of representatives to distribute flyers brought the webcast within the scope of the Code.

The Panel noted that Roche's sponsorship of the webcast was obvious at the outset on both the flyer and the webcast. It appeared that the complainant was more concerned about the role of the RCP. The agreement between Roche and the third party referred to a live webcast on rheumatoid arthritis. Roche could suggest topics and speakers but final approval of the programme rested with the RCP. The agreement required that Roche must not contact the speakers or discuss the programme with them prior to or during the event. The speakers were responsible for exercising full control over the lectures and discussions and any content therein. Roche could have no involvement in that process.

The Panel had some concerns about the webcast. Clearly the topic 'Identifying and Managing Anti-TNF Inadequate Responders in RA' was relevant to MabThera as that was a possible alternative treatment choice for such inadequate responders. The speakers would presumably know which company had sponsored the webcast. The presentation on 'Managing anti-TNF inadequate responders' had included favourable statements about rituximab. Other medicines such as infliximab, etenercept and abatacept were also referred to. In theory products could be used irrespective of whether or not they had been approved by NICE. In summing up the Chairman had specifically referred to rituximab. Nonetheless the Panel did not consider that the sponsorship arrangements were unreasonable; the RCP had the final approval of the programme and speakers. The Panel did not consider that Roche's involvement was inappropriate as alleged and ruled no breach of Clauses 9.1 and 19. The webcast was clearly sponsored by Roche and so was not misleading in that regard. No breach of Clause 7.2 was ruled. The Panel also ruled no breach of Clause 2; as that clause was used as a sign of particular censure and reserved for such.

Complaint received **8 July 2008**

Case completed **25 September 2008**

CASE AUTH/2141/7/08

NOVO NORDISK v SANOFI-AVENTIS

Promotion of Lantus

Novo Nordisk complained about the promotion of Lantus (insulin glargine) by Sanofi-Aventis. The materials at issue were: four leavepieces and a mailer. Novo Nordisk marketed Levemir (insulin determir).

A '24 hour efficacy' claim appeared as part of the Lantus product logo in one of the leavepieces and as a discreet claim 'Once daily – provides 24-hour efficacy' in all of the other materials.

Novo Nordisk was concerned about the substantiation of this claim and noted the Appeal Board ruling in Case AUTH/2028/7/07 which stated that results from a clamp study (Lepore *et al* 2000) could not substantiate the efficacy of insulin in terms of glycaemic control. This was also true for other comparable clamp trials (Porcellati *et al* 2007a and Porcellati *et al* 2007b) provided by Sanofi-Aventis to substantiate this claim. Novo Nordisk agreed with Sanofi-Aventis that the efficacy of a medicine was its capacity to produce a desired effect. However, it strongly disagreed with the argument that the lack of qualification of this term (ie efficacy) made it capable of substantiation by results from clamp trials. In fact the desired effect of an insulin was to provide proper glycaemic control by reducing blood glucose levels in patients. The undertaking in Case AUTH/2028/7/07 clearly prohibited the use of the claim '24-hour control' or similar. Thus Novo Nordisk believed that the claim of '24-hour efficacy' was in breach of the Code.

In relation to the same claim used alongside a graph from Porcellati *et al* (2007b), Novo Nordisk was concerned that Sanofi-Aventis had cherry-picked the only clamp trial which revealed a significant difference in terms of duration of action between Lantus and Levemir. Other data, of which details were given, had been overlooked. Novo Nordisk alleged that the claim, based on a comparison from a single trial which provided contradictory results, whilst disregarding all other published evidence, misled health professionals and disparaged Levemir.

The detailed response from Sanofi-Aventis is given below.

The Panel noted that in Case AUTH/2028/7/07 claims for '24-hour control' or '24-hour glycaemic control' for Lantus had been considered to not be capable of substantiation and exaggerated and misleading in that regard by the Appeal Board. Breaches of the Code had been ruled.

In Case AUTH/2028/7/07 the data submitted in support of the claims had demonstrated the 24-hour duration of action of Lantus, not its efficacy in terms of glycaemic control. In the Appeal Board's view, control, in the context of diabetes, referred to glycaemic control ie the maintenance of blood glucose between set parameters. The Appeal Board noted that Lantus was a basal insulin designed to provide a background, constant suppression of blood glucose. Sanofi-Aventis had submitted that no type 1 diabetic would be controlled solely on Lantus and only about half of type 2 diabetics would be controlled on a combination of Lantus and oral agents. Most diabetics would thus not be 'controlled' with Lantus and would require short-acting insulin to cope with post prandial glucose peaks.

The Panel noted that the claim now at issue was '24-hour efficacy'. In the Panel's view the claim would be read by prescribers in the context of a basal insulin. Prescribers would take it to mean that Lantus provided a constant suppression of blood glucose over 24-hours ie that it had a 24-hour duration of action.

The Panel noted that the claim 'once daily – provides 24-hour efficacy' appeared in two leavepieces immediately under the prominent headline 'Lantus – control without compromise for your diabetes patients'. In that context the Panel considered that '24-hour efficacy' implied '24-hour control' and was thus in breach of the undertaking given in Case AUTH/2028/7/07. A breach of the Code was ruled. This ruling was appealed by Sanofi-Aventis.

The Panel considered that an undertaking was an important document. It included an assurance that that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings. In breaching its undertaking the Panel considered that Sanofi-Aventis had not maintained high standards and had brought discredit upon, and reduced confidence in the industry. Breaches of the Code were ruled including Clause 2. These rulings were appealed by Sanofi-Aventis.

The Appeal Board noted that the intended audience for the two leavepieces were diabetes nurse specialists, diabetologists and GPs with an interest in diabetes. The Appeal Board considered that although the claim 'Once-daily – provides 24-hour efficacy' appeared below the claims 'Lantus-control without compromise for your diabetes patients', given the audience it would not be taken to imply '24-hour-control' but a claim for duration of action.

The Appeal Board had some concerns about the claim and its context but on balance decided that Sanofi-Aventis had not breached its undertaking given in Case AUTH/2028/7/07. The Appeal Board ruled no breaches of the Code including Clause 2.

In one leavepiece, the claim '24-hour efficacy' was used as part of the Lantus product logo. Although page 2 of the leavepiece included the claim 'Lantus can enable people to improve their glycaemic control', the Panel did not consider that in the context in which it appeared, '24-hour efficacy' implied '24-hour control' as in the leavepieces considered above. In another leavepiece the claim 'once daily – provides 24-hour efficacy' appeared beneath the claim 'Lantus – established efficacy ….' and in the mailer the claim '24-hour efficacy' appeared as a headline claim above data relating to duration of action. The Panel noted its comments above regarding a prescriber's expectation of Lantus and the view that would be taken of the claim '24-hour efficacy' in the context of a basal insulin. The Panel considered that there was data to show that Lantus had a 24-hour duration of action; section 5.1 of the SPC included a graph which showed that the activity profile of Lantus was smooth, peakless and almost constant between 9 and 24-hours in type 1 diabetics. The Panel considered that in the context in which it appeared in two of the leavepieces and the mailing, the claim '24-hour efficacy' could be substantiated and no breach of the Code was ruled.

The Panel noted that the leavepiece and the mailing both featured a graph depicting plasma glucose levels over time with Lantus and Levemir (Porcellati 2007b). The graph of results generated after two weeks of treatment and showed that in type 1 diabetics Lantus suppressed plasma glucose for 24-hour post injection whereas blood glucose levels started to rise in the Levemir group 15 hours post dose.

The Panel noted that Heise and Pieber (2007) had reported that in the clinically relevant range of 0.35-0.8U/kg the duration of action for Lantus and Levemir was close to 24 hours in type 1 diabetes. Heise and Pieber had further commented that the data from Porcelatti was an outlier. Given data from Plank *et al* (2005), and the comments from Heise and Pieber, the Panel considered that the graph at issue did not represent the balance of evidence with regard to the duration of action of Levemir in type 1 diabetes. Furthermore, the graph implied a duration of action of only 15 hours ie when plasma glucose levels began to rise whereas the authors themselves reported the duration of action to be 17.5 hours. The graph did not include a threshold blood glucose level beyond which the insulin could be regarded as no longer acting. The Panel considered that the graph was misleading and a breach of the Code was ruled. The Panel further considered that the graph disparaged Levemir and a breach of the Code was ruled. These rulings were appealed by Sanofi-Aventis. Although noting its rulings above the Panel did not consider that high standards had not been maintained. No breach of the Code was ruled.

The Appeal Board considered that the results depicted in the graph at issue were not inconsistent with the products' SPCs. Lantus should be administered once daily. The recommended initiation of Levemir in combination with oral antidiabetic agents was once daily. When Levemir was used as part of a basal-bolus regimen it should be administered once or twice daily based on individual patient needs. The Appeal Board noted that the balance of evidence showed that Lantus suppressed plasma glucose for a longer period of time than Levemir.

The Appeal Board did not consider that the graph was either misleading or that it disparaged Levemir. No breach of the Code was ruled.

Novo Nordisk noted that the claim 'In clinical practice, after switching from other treatments, Lantus is associated with a lower risk of hypoglycaemia compared to insulin detemir' appeared in one of the leavepieces and in the mailer.

Novo Nordisk noted that the claim was substantiated by findings from a retrospective GP database analysis (Currie *et al* 2007). The authors compared the reported hypoglycaemic event rate prior to and following initiation of basal Lantus and Levemir (a secondary endpoint of the analysis) and concluded that the risk reduction in hypoglycaemia was significantly greater with Lantus. However, there were some limitations of this analysis which needed to be considered to decide whether the claim, substantiated by this paper, was misleading or not. The authors compared the clinical outcomes of 5,683 patients using Lantus with outcomes of only 694 patients using Levemir. The huge difference in patient numbers obviously reflected the more established clinical experience of using Lantus at that time, ie prescribers were more familiar with its use. Therefore the analysis was biased in favour of Lantus.

Although Currie *et al* analysed the primary endpoint of HbA1c change, and the secondary endpoint of weight change separately in type 1 and type 2 diabetes patients, they failed to follow this fair and highly relevant approach with regard to hypoglycaemia. Further, they failed to differentiate between major and minor hypoglycaemic episodes or episodes that occurred during the day or at night. This lack of clarification raised the question of whether this analysis provided clinicians with any useful findings regarding hypoglycaemia. Defining the types of hypoglycaemic events would be crucial in order to make clinically relevant conclusions from this analysis.

It was well know that hypoglycaemic risk was markedly different in type 1 and type 2 diabetes. Major and minor hypoglycaemic events were more common in type 1 diabetes than in type 2. There

was also agreement in the literature that there was a higher incidence of hypoglycaemic episodes in patients with a more advanced stage of type 2 diabetes ie those requiring more intensive antihyperglycaemic therapy (Cryer *et al* and Zammitt and Frier).

These differences in hypoglycaemic risk could be partially explained by the use of different insulin regimens. Whilst type 1 diabetics almost exclusively used a basal-bolus regimen, in type 2 diabetes basal insulins could be used as part of basal-oral or basal-bolus regimens. Since basal-bolus therapy was a much more aggressive approach to control blood glucose levels, and was usually applied at a considerably more severe stage of type 2 diabetes, it was connected with a significantly higher hypoglycaemic event rate than a basal-oral regimen.

One might reasonably assume that in the case of type 1 diabetes, the only flaw in Currie *et al* was the above mentioned 'familiarity' effect in terms of Lantus, since both preparations were used as part of a basal-bolus regimen. However in type 2 diabetes it had to be presumed that apart from this effect there was at least one more bias in favour of Lantus. Whilst it was not clear from the published paper, it was reasonable to assume that many more patients in the Lantus group would have been treated with basal-oral treatment. In the Levemir group the vast majority of the patients would have been treated with a basal-bolus regimen. This was because Lantus had a licence for both basal-oral and basal-bolus use, whilst Levemir only had a licence for basal-bolus use during the analysed period.

Therefore to compare the hypoglycaemic rate reduction without taking into account the type of diabetes and the insulin regimen for those with type 2 diabetes was misleading. In addition, the fact that information on the use of bolus insulin, readily available from the THIN database, had been clearly overlooked and not taken into account in this analysis was disappointing. The authors simply chose to compare the hypoglycaemic risk reduction in the combined cohort of type 1 and type 2 patients and failed to make any distinction between basal-oral users and basal-bolus users in the type 2 cohort.

The claim at issue was purely based on the results from this flawed analysis. Relevant data from published randomized clinical trials detailed by Novo Nordisk had been overlooked.

Novo Nordisk believed that Sanofi-Aventis had again cherry-picked the results from a retrospective database analysis, which was severely flawed in terms of hypoglycaemic risk analysis, to substantiate the claim. The company had clearly disregarded all the other published evidence which had revealed completely different results. Therefore the claim was inaccurate, unbalanced, unfair, and ambiguous, it was not based on an up-to-date evaluation of all available evidence and disparaged Levemir.

The Panel noted that one leavepiece was specifically about the use of Lantus in type 2 diabetics. The final page featured the claim at issue referenced to Currie *et al* a study which had demonstrated that in a pooled cohort of type 1 and type 2 diabetics, patients switched to Lantus had a lower relative risk of hypoglycaemia than those switched to Levemir. Given the specificity of the leavepiece, however, the Panel considered that a claim based on pooled data from type 1 and type 2 diabetics was misleading. A breach of the Code was ruled. The Panel did not consider that the claim disparaged Levemir and so no breach of the Code was ruled. The Panel noted that use of Currie *et al* and the need to ensure that readers understood that the hypoglycaemia data was from a pooled cohort of patients had been at issue in Case AUTH/2038/8/07. The Panel considered that to again use the pooled data in a way that was misleading meant that high standards had not been maintained. A breach of the Code was ruled. This ruling was upheld by the Appeal Board on appeal by Sanofi-Aventis.

The mailing, 'Why choose Lantus' was not specific as to the type of diabetic patients at issue – the mailing referred to both type 1 and type 2 patients. As in the leavepiece above the claim at issue had been derived from Currie *et al*. The Panel noted that the data was generated when the licence for Levemir did not include management of type 2 diabetes except as part of a basal-bolus regimen. Levemir could now be used as part of a basal-oral regimen and so patients who were less prone to hypoglycaemic attacks could be treated. The pooled cohort of type 1 and type 2 diabetics included in Currie *et al* was thus likely to be different to the mixed group of diabetics that a prescriber might now treat with either Lantus or Levemir and so on that basis the Panel considered that the claim at issue was misleading. A breach of the Code was ruled. This ruling was appealed by Sanofi-Aventis. Although noting this ruling the Panel did not consider that high standards had not been maintained nor that the claim disparaged Levemir. No breach of the Code was ruled.

The Appeal Board noted the mailing, referred to both type 1 and type 2 diabetes patients. As in the leavepiece above the claim at issue had been derived from Currie *et al*. In this instance, however, the Appeal Board considered that as the mailing had referred to both type 1 and type 2 diabetes, the claim based on pooled data from type 1 and 2 patients was not misleading. The Appeal Board ruled no breach of the Code.

Novo Nordisk complained about the promotion of Lantus (insulin glargine) by Sanofi-Aventis. The materials at issue were: four leavepieces (refs LAN07/1333; LAN08/1037; LAN08/1038 and LAN08/1039) and a mailer (ref LAN08/1041).

Novo Nordisk marketed Levemir (insulin determir).

This case was considered under the 2008 Constitution and Procedure. The clauses cited, 2, 7.2, 7.4, 9.1 and 22, were the same in the 2006 Code as the 2008 save for Clause 22 which had been renumbered as Clause 25. Thus the 2008 Code was used.

1 Claim '24-hour efficacy'

This claim appeared as part of the Lantus product logo in one of the leavepieces (ref LAN07/1333) and as a discreet claim 'Once daily – provides 24-hour efficacy' in all of the other materials.

COMPLAINT

Novo Nordisk was concerned about the substantiation of this claim and noted the Appeal Board ruling in Case AUTH/2028/7/07 which stated that results from a clamp study (Lepore *et al* 2000) could not substantiate the efficacy of insulin in terms of glycaemic control. This was also true for other comparable clamp trials (Porcellati *et al* 2007a and Porcellati *et al* 2007b) which were provided by Sanofi-Aventis to substantiate this claim. Novo Nordisk agreed with Sanofi-Aventis that the efficacy of a medicine was its capacity to produce a desired effect. However, it strongly disagreed with the argument that the lack of qualification of this term (ie efficacy) made it capable of substantiation by results from clamp trials. In fact the desired effect of an insulin was to provide proper glycaemic control by reducing blood glucose levels in patients. The undertaking in Case AUTH/2028/7/07 clearly prohibited the future use of the claim '24-hour control' and any similar claim. Thus Novo Nordisk believed that the claim of '24-hour efficacy' was not only in breach of Clause 7.4 of the Code but also of Clauses 2, 9.1 and 22.1.

In relation to the same claim used alongside a graph from Porcellati *et al* (2007b) (LAN/08/1039 and LAN08/1041), Novo Nordisk was concerned that Sanofi-Aventis had cherry-picked the only clamp trial which revealed a significant difference in terms of duration of action between Lantus and Levemir. Sanofi-Aventis had clearly overlooked published results from other clamp trials and a comprehensive review paper which supported a similar duration of action for both. Klein *et al* (2007) demonstrated that duration of action in type 2 diabetes was similar for Lantus and Levemir. Plank *et al* (2005) (duration of action was 19.9 hours at a dose of 0.4U/kg) confirmed that also in type 1 diabetes Levemir had a similar duration of action as Lantus (defined by Lepore *et al*: duration of action was 20.5 hours at a dose of 0.3U/kg). Furthermore Porcellati *et al* (2007b) reported relevant clinical data from the 2-week long treatment period prior to the clamp procedures. During the treatment period, patients used a once daily dose of either Lantus or Levemir as the basal part of their basal-bolus regimen. The blood glucose findings from this treatment period contradicted the findings from the clamp phase of this trial. It would be very difficult to explain how once-daily Levemir, as part of a basal-bolus regimen, provided exactly the same metabolic control as the basal-bolus regimen using once-daily Lantus (in combination with rapid-acting insulin analogues), despite having a substantially shorter duration of action as was suggested by the clamp part of the same trial. Novo Nordisk alleged that the claim, based on a comparison from a single trial which provided contradictory results, whilst disregarding all other published evidence, misled health professionals and disparaged Levemir, in breach of Clauses 7.2, 8.1 and 9.1 of the Code.

RESPONSE

Sanofi-Aventis submitted that this complaint followed Case AUTH/2028/7/07, in which Novo Nordisk complained that claims for, '24-hour control' and 24- hour glycaemic control' in relation to Lantus were not capable of substantiation.

In its original defence of these claims, Sanofi-Aventis provided information from three isoglycaemic clamp studies which demonstrated that Lantus had a duration of action of at least 24-hours:

- Firstly, that a euglycaemic clamp was the appropriate methodology to assess the pharmacokinetics and pharmacodynamics of insulin performed by Lepore *et al*. In a real life setting, a basal insulin was used to maintain a steady background (or fasting) level of blood glucose. The most relevant clinical measure in clamp studies such as Lepore *et al* was the ability of each insulin to keep blood glucose levels below a clinically relevant threshold – typically 150mg/dl (8.3mmol/L). Lepore *et al* demonstrated that at the end of the 24-hour study period the mean blood glucose level for Lantus patients was 141mg/dl, ie below the 150mg/dl threshold that would have indicated that Lantus was no longer effective. As the primary end-point of the study, this result in particular strongly supported the claim that Lantus could be expected to confer 24-hour efficacy, even with the limitation of this study representing only a single dose of Lantus (ie not at steady state as would be the case in clinical practice).

- Secondly, Porcellati *et al* (2007a) assessed the pharmacokinetics and pharmacodynamics of Lantus in the same manner, this time after the first dose and also after seven days of treatment ie at steady state conditions. The clamp assessment on the seventh day was continued for 32 hours as opposed to 24 to better assess the duration of action of Lantus. Even at a low dose of 0.3U/kg, the median duration of action at seven days was again 24 hours.

- Finally, Porcellati *et al* (2007b) assessed the pharmacokinetics and pharmacodynamics of

Lantus in 24 patients with type-1 diabetes using a euglycaemic clamp technique, this time after two weeks of treatment. This study was performed at a dose of 0.35U/kg (approximately 24.5 units for a 70kg man), and again at this relatively low dose all subjects had satisfactory maintenance of glycaemic control at the end of a 24-hour study period performed at steady state conditions.

In Case AUTH/2028/7/07 the Panel and Appeal Board had both agreed that the data supported the claim that Lantus had a 24-hour duration of action. However, the Appeal Board 'considered that a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control', as a proportion of patients would require additional mealtime insulin to fully control their diabetes. The inability of Lantus alone to provide 'glycaemic control' in all patients with diabetes rendered the statement incapable of substantiation, despite its 24-hour duration of action as a background basal insulin.

In view of this ruling, Sanofi-Aventis withdrew the claim '24-hour control' and replaced it with '24 hour efficacy', now the subject of this complaint (Case AUTH/2141/7/08). The '24-hour efficacy' claim took into account the Appeal Board's ruling together with the agreed robust evidence previously provided to substantiate the 24-hour duration.

Sanofi-Aventis could understand that Novo Nordisk wanted to challenge the change from 'control' to 'efficacy', and responded accordingly in inter-company dialogue. It was disappointing that a large part of the argument made to support this complaint appeared to be an attempt to reopen concerns dismissed in Case AUTH/2028/7/07, as outlined above.

In response to Novo Nordisk's concern that the term 'efficacy' still implied 'control', Sanofi-Aventis made this change and took full note of the Appeal Board's ruling that Lantus was a 'basal insulin designed to provide a background, constant suppression of blood glucose and that it considered that a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control', with the implication that basal insulin action and glycaemic control could not therefore be considered the same.

The claim '24-hour efficacy' was therefore made in relation to the fact that Lantus demonstrated a 24-hour course of action as a basal insulin - in that it provided the continuous level of insulin required to regulate hepatic glucose production, which occurred at a relatively constant rate. 'Efficacy' referred to this continuous basal insulin effect - the claim '24-hour efficacy' meant '24-hour duration of pharmacodynamic action' (as a basal insulin), and this had already been readily demonstrated in the three clamp studies referred to above. Sanofi-Aventis considered that this claim did not allude to the fact that Lantus would provide full glycaemic control - clinicians who treated diabetes would know that Lantus was a basal insulin intended to provide background insulin cover only, and that mealtime insulin would be required in all patients with type 1 diabetes and a proportion of those with type 2 diabetes.

Sanofi-Aventis noted that Novo Nordisk objected to the fact that the graph reproduced from Porcellati *et al* (2007b) cherry-picked the available data, with a suggestion that Sanofi-Aventis had overlooked Klein *et al* and Plank *et al*. Again, this was disappointing since similar points were made and considered in Case AUTH/2028/7/07.

- Although Novo Nordisk stated that Klein *et al* (key to its original argument) was relevant, the point was made in the paper itself that the methodology was flawed - glucose infusion rate was not an effective measure of an insulin's duration of action (a point considered significant in the original case). This position was again repeated in a review of clamp studies with basal insulin analogues (Heise and Pieber 2007). In both cases the suggestion was that blood glucose concentration over 24-hours was the most appropriate measure to demonstrate duration of action, again a point agreed when this matter was first considered.

- Klein *et al* also suffered from the disadvantage that the methodology was that of a single dose, as opposed to the steady state dosing that was usual in clinical practice. In total, Sanofi-Aventis did not consider therefore that the methodology or conclusions of Klein *et al* were comparable to those of Porcellati *et al* (2007b), and as this presented a like-with-like comparison the allegation of omission was not warranted.

That said, the graph reproduced in the leavepiece (LAN08/1039) and the mailer (LAN08/1041) from Porcellati *et al* (2007b) demonstrated that blood glucose concentrations remained below a threshold level for 24-hours after treatment with Lantus – the most appropriate measure of insulin activity considered by Klein *et al* and Heise and Pieber – whereas blood glucose levels increased after approximately 16 hours with Levemir.

Taking the same measure from Klein *et al*, it appeared that the findings in Klein *et al* were similar to those of Porcellati *et al* (2007b) ie that Lantus demonstrated maintenance of normal blood glucose levels for 24-hours whereas the effects of Levemir appeared to decline after approximately 16 hours, evidenced by the increase in blood glucose levels.

It was difficult to accept that cherry-picking had occurred in reference to Porcellati *et al* (2007b) when Klein *et al* demonstrated such a similar result, at this dose level at least.

- In response to the suggestion that Plank *et al* should also have been quoted, Sanofi-Aventis noted that this study did not compare Lantus and

Levemir. As the promotional item sought to directly compare the two products this did not appear to be relevant to the argument – it was indirect evidence only and not appropriate when a direct comparison of the two products was made.

- Finally, Novo Nordisk submitted that in Porcellati *et al* (2007b) there was a similar level of glycaemic control after two weeks of treatment with both Levemir and Lantus, each once daily, and suggested that this was proof that Levemir had a 24-hour duration of action. Novo Nordisk failed to note, however, that in the 2 week run-in period subjects in the study also received mealtime insulin as required, and that the glycaemic control exhibited could not be attributed to once daily Levemir alone.

In summary, Sanofi-Aventis believed that the claim, '24-hour efficacy' fairly reflected the 24-hour duration of action that the Panel and the Appeal Board had already considered appropriate and that the word 'efficacy', made in respect to the action of Lantus as a basal insulin, was now a fair and appropriate reflection that Lantus did what it was intended to do (provide basal insulin cover) for 24-hours. Sanofi-Aventis considered that the claim could be substantiated, was not misleading and had been amended according to the previous Appeal Board ruling.

Sanofi-Aventis also considered that using Porcellati *et al* (2007b) to demonstrate the 24-hour duration of action of Lantus, and the shorter duration of action of Levemir, was justified as it was the most relevant and only study conducted in the steady state condition, which reflected clinical practice, and whose conclusions were not limited by the methodological concerns identified in Klein *et al*. In view of these facts, Sanofi-Aventis did not believe reference to this study was misleading or misrepresentative of clinical data.

Sanofi-Aventis considered that high standards had been maintained throughout and that no breach of the Code had occurred.

PANEL RULING

The Panel noted that in Case AUTH/2028/7/07 claims for '24-hour control' or '24-hour glycaemic control' for Lantus had been considered to not be capable of substantiation and exaggerated and misleading in that regard by the Appeal Board. Breaches of the Code were ruled.

In Case AUTH/2028/7/07 the data submitted in support of the claims had demonstrated the 24-hour duration of action of Lantus, not its efficacy in terms of glycaemic control. In the Appeal Board's view, control, in the context of diabetes, referred to glycaemic control ie the maintenance of blood glucose between set parameters. The Appeal Board noted that Lantus was a basal insulin designed to provide a background, constant suppression of blood glucose. In response to a question, Sanofi-Aventis had submitted that no type 1 diabetic would be controlled solely on Lantus and only about half of type 2 diabetics would be controlled on a combination of Lantus and oral agents. Most diabetics would thus not be 'controlled' with Lantus and would require short-acting insulin to cope with post prandial glucose peaks.

The Panel noted that the claim now at issue was '24-hour efficacy'. In the Panel's view the claim would be read by prescribers in the context of a basal insulin. Prescribers would take it to mean that Lantus provided a constant suppression of blood glucose over 24-hours ie that it had a 24-hour duration of action.

The Panel noted that the claim 'once daily – provides 24-hour efficacy' appeared in two leavepieces (LAN08/1037 and LAN08/1038) immediately under the prominent headline 'Lantus – control without compromise for your diabetes patients'. In that context the Panel considered that '24-hour efficacy' implied '24-hour control' and was thus in breach of the undertaking given in Case AUTH/2028/7/07. A breach of Clause 25 was ruled which was appealed.

The Panel considered that an undertaking was an important document. It included an assurance that that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings. In breaching its undertaking the Panel considered that Sanofi-Aventis had not maintained high standards and had brought discredit upon, and reduced confidence in the industry. Breaches of Clauses 9.1 and 2 of the Code were ruled which were appealed.

In the leavepiece LAN07/1333, '24-hour efficacy' was used as part of the Lantus product logo. Although page 2 of the leavepiece included the claim 'Lantus can enable people to improve their glycaemic control', the Panel did not consider that in the context in which it appeared, '24-hour efficacy' implied '24-hour control' as in the leavepieces considered above. In leavepiece LAN08/1039 the claim 'once daily – provides 24-hour efficacy' appeared beneath the claim 'Lantus – established efficacy ….' and in the mailer the claim '24-hour efficacy' appeared as a headline claim above data relating to duration of action. The Panel noted its comments above regarding a prescriber's expectation of Lantus and the view that would be taken of the claim '24-hour efficacy' in the context of a basal insulin. The Panel considered that there was data to show that Lantus had a 24-hour duration of action; section 5.1 of the SPC included a graph which showed that the activity profile of Lantus was smooth, peakless and almost constant between 9 and 24-hours in type 1 diabetics. The Panel considered that in the context in which it appeared in LAN07/1333, LAN08/1039

and LAN08/1041, the claim '24-hour efficacy' could be substantiated and no breach of Clause 7.4 was ruled. This ruling was not appealed.

The Panel noted that the leavepiece LAN08/1039 and the mailing LAN08/1041 both featured a graph depicting plasma glucose levels over time with Lantus and Levemir (Porcellati 2007b). The graph was drawn using results generated after two weeks of treatment and showed that in type 1 diabetics Lantus suppressed plasma glucose for 24-hour post injection whereas blood glucose levels started to rise in the Levemir group 15 hours post dose.

The Panel noted that Klein *et al* had measured the duration of action of Lantus and Levemir in type 2 diabetes and thus these results were not relevant to the graph at issue which detailed results in type 1 diabetes. Plank *et al* investigated the duration of action for five doses of Levemir (0.1, 0.2, 0.4 0.8 and 1.6U/kg) in type 1 diabetes. The results showed that the duration of action was dose dependent with doses of 0.8 and 1.6U/kg sufficient to maintain glucose levels for most subjects throughout a 24-hour period. The 0.4U/kg dose had a duration of action of 19.9 (± 3.2) hours). Heise and Pieber reviewed the pharmacodynamic data for Lantus and Levemir as derived from the glucose clamp technique. A common definition for duration of action (time from injection to plasma glucose >8.3mmol/l) was applied and study data were recalculated as necessary. The authors reported that the mean duration of action with both analogues was dose dependent, but in the clinically relevant range of 0.35-0.8U/kg it was close to 24-hours for both in type 1 diabetes. Heise and Pieber considered an abstract by Porcellati *et al* (2006) to be an outlier as it reported a shorter duration of action for Levemir (17.5 hours) than other authors. The Panel assumed that the abstract referred to was the forerunner of the full paper (Porcellati *et al* 2007b) from which the graph at issue was taken.

The Panel noted the comments of Heise and Pieber and considered that the graph at issue did not represent the balance of evidence with regard to the duration of action of Levemir in type 1 diabetes. Furthermore, the graph implied a duration of action of only 15 hours ie when plasma glucose levels began to rise whereas the authors themselves reported the duration of action to be 17.5 hours. The graph did not include a threshold blood glucose level beyond which the insulin could be regarded as no longer acting. The Panel considered that the graph was misleading and a breach of Clause 7.2 was ruled. The Panel further considered that the graph disparaged Levemir and a breach of Clause 8.1 was ruled. These rulings were appealed.

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. This ruling was not appealed.

APPEAL BY SANOFI-AVENTIS

Sanofi-Aventis submitted that this complaint followed Case AUTH/2028/7/07, in which Novo Nordisk complained that the claims '24-hour control' and '24-hour glycaemic control' relating to Lantus were not capable of substantiation, arguing that a 24-hour duration of action had not been demonstrated. In its defence of these claims, Sanofi-Aventis provided information from three isoglycaemic clamp studies which demonstrated that Lantus exerted a duration of action of at least 24 hours (Lepore *et al*, Porcellati *et al*, 2007a and Porcellati *et al* 2007b). The Panel and the Appeal Board both agreed that the data provided supported the claim that Lantus had a 24-hour duration of action.

Although Lantus demonstrated a 24-hour duration of action, the Appeal Board recognised that its efficacy as a basal insulin was primarily the control of background or basal blood glucose levels (ie in the fasted intervals between meals), and that a proportion of patients required additional mealtime insulin doses to fully control their diabetes. All parties agreed that this observation was important and that as Lantus alone was unable to provide full 'glycaemic control' in all patients, the claims '24-hour control' and '24-hour glycaemic control' were therefore incapable of substantiation, despite the 24-hour duration of action as a background, basal insulin.

In response to this ruling, that 'a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control', Sanofi-Aventis immediately withdrew the claim '24-hour control' from all materials and this wording had not been repeated in any subsequent item. This demonstrated the maintenance of high standards and fulfilment of all undertakings required as a consequence of this case.

In relation to the present complaint, Case AUTH 2141/7/08, Sanofi-Aventis submitted that having withdrawn '24-hour control', it sought to develop a claim to convey the 24-hour duration of action of Lantus that the Panel and Appeal Board recognised to exist, whilst avoiding the suggestion that Lantus alone was sufficient treatment for all patients with diabetes. The phrase '24-hour efficacy' was considered acceptable in this respect, given that efficacy was defined as 'the ability to produce a desired effect', and that the desired effect of a basal insulin such as Lantus was to provide constant suppression of background (non-meal-related) blood glucose levels. This wording was decided upon, taking directly into account the Appeal Board's observations.

Sanofi-Aventis was pleased that the Panel had decided it was clear that the claim '24-hour efficacy' would be read by prescribers in the context of a basal insulin, and that prescribers would take it to mean that Lantus provided a constant suppression of blood glucose over 24 hours, ie that it had a 24-

hour duration of action. This was exactly the intent of Sanofi-Aventis in making this claim, and it was pleased that the Panel considered the claim in itself met these requirements, and was not in breach of the Code (as demonstrated by the ruling of 'no breach' made in respect of every use of the claim bar two).

In relation to items LAN 08/1037 and LAN 08/1038 Sanofi-Aventis appealed the Panel's rulings of breaches of Clauses 2, 9.1 and 25. Sanofi-Aventis disagreed that the use of the claim '24-hour efficacy' in these two items implied glycaemic control. In considering its understanding of this claim in general, the Panel was clear in how this statement would be perceived: 'the claim would be read by prescribers in the context of a basal insulin. Prescribers would take it to mean that Lantus provided a constant suppression of blood glucose over 24 hours, ie that it had a 24-hour duration of action'.

Sanofi-Aventis submitted that this was a firm conclusion that indicated that the intended audience would be clear that the claim referred to the duration of efficacy of the product and not the ability of Lantus to achieve glycaemic control in all patients – the finding in Case AUTH/2028/7/08. Furthermore, this conclusion was matched by the Appeal Board's conclusion in Case AUTH/2028/7/08, which implied that 24-hour effect and glycaemic control could not be considered the same: 'a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control'.

Sanofi-Aventis therefore submitted that the statement '24-hour efficacy', as used in these two items, still had the primary meaning that Lantus had a 24-hour period of efficacy as a basal insulin, and did not suggest that it could of itself achieve full glycaemic control in all diabetics.

The Panel stated that it was the context in which this statement was made that had resulted in the finding of a breach of Clause 25. The concern of the Panel was that in the item, the claim (although made as a stand-alone statement with the primary intent above) would be interpreted as implying 24-hour control, as it appeared below the headline 'Lantus – control without compromise for your diabetes patients'.

Whilst agreeing that it was appropriate to look at the statement 'in context', Sanofi-Aventis submitted that the context should not be limited to this headline alone, but that the item must be viewed in its entirety. The breach ruled in Case AUTH/2028/7/07 was that '24-hour control' implied that Lantus alone could achieve glycaemic control for all patients with diabetes. In both of these pieces, for which a breach had been ruled, it was made clear that once Lantus had been titrated to an effective dose, it was then appropriate to consider the addition of rapid acting insulin. Therefore, when viewed in the context of the entire item, Sanofi-Aventis disagreed that these promotional items sought to promote Lantus as an agent that, when used in isolation, could provide effective glycaemic control in all patients – the need for additional insulin was clearly recognised and overtly stated in both. In conclusion, Sanofi-Aventis considered that these two items had been developed taking fully into account the findings from Case AUTH/2028/7/07:

- The claim '24-hour efficacy' was agreed to reflect the duration of action of Lantus.
- It was not claimed that Lantus could provide glycaemic control in isolation – the need for additional rapid acting insulin was overtly stated.

Sanofi-Aventis therefore considered that the undertaking in Case AUTH/2028/7/07 had been met, that items LAN 08/1037 and LAN 08/1038 complied with the Code and that high standards had been maintained throughout.

In relation to items LAN 08/1039 and LAN 08/1041 in which the Panel ruled a breach of Clauses 7.2 and 8.1 Sanofi-Aventis noted that both contained a graph, reproduced without amendment (other than extending the suppressed scales back to zero) from Porcellati *et al* 2007b.

The Panel considered that the graph, although accurately representing the 24-hour duration of action of Lantus in patients with type 2 diabetes, misled as to the duration of action of Levemir. The Panel appeared to have formed an opinion that a duration of action of close to 24 hours existed for Levemir in patients with type 1 diabetes, and that this study, being substantially shorter, misled through being inconsistent with the wider body of evidence. Sanofi-Aventis submitted that this position was not an accurate assessment of the existing body of evidence, and therefore it appealed both breaches of the Code in respect to these two items.

Firstly, the Panel had disregarded Klein *et al* on the basis that it was in patients with type 2 diabetes, irrelevant to the graph at issue. Sanofi-Aventis agreed with the Panel in this respect.

The Panel next considered Plank *et al*, which examined the duration of action of Levemir at a range of doses from 0.1 to 1.6U/kg. The Panel noted that doses of 0.8 and 1.6U/kg were sufficient to maintain glucose levels for most subjects throughout 24 hours. These doses were considerably greater however than the dose used by Porcellati *et al* (2007b) (0.35U/kg). The Panel had also not taken into account how these doses (tested in a phase 1 dose proportionality study) related to the dose usually found in clinical practice. Plank *et al* made no comment on how these doses related to clinical practice; however, the EPAR for Levemir indicated that in all studies of patients with type 1 diabetes the dose of Levemir ('basal') had a range of only 0.27 to 0.49U/kg:

Taking this into consideration, Sanofi-Aventis

submitted that it was clear that although in this pharmacokinetic study Levemir might have a duration of action of close to 24 hours at supra-therapeutic levels of 0.8 and 1.6U/kg, at the range encountered in usual care (0.27 to 0.49U/kg) the duration of action was less (12.1 hours for 0.2U/kg; 19.9 hours at 0.4U/kg). These findings were consistent with Porcellati *et al* (2007b), especially when it was considered that the latter used a normal clinical dose of 0.35U/kg of Levemir. Sanofi-Aventis therefore considered that the data in Porcellati *et al* (2007b) was consistent with that demonstrated by Plank *et al*.

Next, the Panel considered the review by Heise and Pieber, and focused on the statement that 'the mean duration of action of both analogues was dose dependent, but in the clinically relevant range of 0.35 - 0.8 units/kg it was close to 24 hours'. Sanofi-Aventis was again concerned about the Panel's interpretation of this statement. Firstly, this review only contained three studies of Levemir in type 1 diabetes in which a duration of action was given:

- Plank *et al*, in which the duration of action of Levemir at clinical doses of 0.2 - 0.4U/kg was approximately 12.1 - 19.9 hours.
- Heise *et al* (2004) demonstrated a duration of action of action of 23 hours at a clinical dose of 0.4U/kg.
- Porcellati *et al* (2007b) demonstrated a duration of action of 17.5 hours at a dose of 0.35U/kg.

The Panel highlighted the authors' statement that the last study, by Porcellati, should be disregarded as an outlier simply because the values were lower than those in the other studies. In stating this, the authors had, however, failed to provide any quality assessment of the study or rational, evidence-based reason for disregarding the statement.

Taking into account the similar results from Plank *et al* (dose for dose), Porcellati *et al* (2007b) should be considered as replicating the findings, not falling as an outlier, and the authors' statements appeared to have misled the Panel. Far from failing to represent the body of evidence for the duration of action of Levemir in type 1 diabetes, Porcellati *et al* (2007b) and Plank *et al* demonstrated similar durations of action for Levemir and between them represented the bulk of the evidence (two out of three clamp studies in this review for which a duration of action of Levemir was stated).

In addition to this, the Levemir SPC quoted further durations of actions of Levemir in patients with type 1 diabetes ie 12, 17 and 20 hours at doses of 0.2, 0.3 and 0.4 U/kg respectively (presumably derived from Plank *et al*), representing the doses expected in clinical practice, not the supra-therapeutic 0.8 - 1.6U/kg doses focussed on by Heise and Pieber which appeared to have dominated the Panel's conclusions.

In summary, Sanofi-Aventis disagreed with the Panel's conclusion that Porcellati *et al* (2007b) did not represent the balance of evidence with regard to Levemir's duration of action; when similar doses were considered – doses that would be used in clinical practice – the Porcellati data were entirely consistent with, and formed a substantial component of, this body of evidence. As such, Sanofi-Aventis considered use of this data was not misleading nor disparaging, the latter particularly in view of the fact that the Porcellati data were also consistent with the 12-20 hour duration of action of Levemir in type 1 diabetes quoted in the Levemir SPC. Sanofi-Aventis considered that high standards had been maintained throughout and that no breach of the Code had occurred.

COMMENTS FROM NOVO NORDISK

Novo Nordisk upheld all its arguments detailed in its complaint and agreed with the Panel that the claim '24 hour efficacy' tried to communicate the same product message (namely '24-hour control') which had been ruled to be misleading by the Appeal Board (Case AUTH/2028/7/07). Thus it had breached Clauses 25, 9.1 and 2 of the Code.

Furthermore Novo Nordisk noted that if Sanofi-Aventis' definition of 'efficacy' ('the ability to produce a desired effect') was accepted then Lantus would be expected to provide normoglycaemic or near normoglycaemic blood glucose values in terms of fasting and pre-meal blood glucose levels. However, as it was discussed and agreed in Case AUTH/2028/7/07, Lantus itself could not provide these values (especially in the case of pre-lunch and pre-dinner blood glucose levels), in all cases of type 1 and in a significant proportion of type 2 diabetes, without combining it with a soluble insulin preparation in a clinical setting.

Although Novo Nordisk agreed with Sanofi-Aventis that the item must be viewed in its entirety, it strongly disagreed that the bullet-point about adding rapid acting insulin would eliminate the implication of the claim that Lantus could provide glycaemic control in isolation. In fact the bullet-point in question actually recommended adding rapid acting insulin to avoid weight gain, with a higher basal insulin dose (in case of further titration), and *did* not highlight the limitation of Lantus therapy in achieving appropriate blood glucose control without post prandial cover. Therefore Novo Nordisk still alleged that Sanofi-Aventis was trying to imply the same message with the claim of '24-hour efficacy' in context with the claim of 'Once daily' (as it appeared on the back page of each item), as it had implied with the claim of '24-hour control'.

With regard to using the graph from the Porcellati *et al* (2007b), Novo Nordisk agreed with the Panel's ruling. With regard to the appeal Novo Nordisk did not agree with Sanofi-Aventis (or with the Panel) that Klein *et al* would be irrelevant to the graph at issue. Since promotional materials should be balanced, fair and consider all the available medical

evidence, Klein *et al* could not be omitted in materials dealing with both types of diabetes (LAN 08/1039). It should be considered as an even more important source of scientific information in the case of the other promotional item (LAN 08/1041) which focused solely on type 2 diabetes. In fact from this perspective, the result from Porcellati *et al* (2007b), conducted solely in type 1 diabetic patients, could be regarded as irrelevant.

Novo Nordisk noted that Sanofi-Aventis consistently suggested that Plank *et al* confirmed the results of Porcellati *et al* (2007b). In fact the closest comparable dose in Plank *et al* to that used in the clamp study by Porcellati *et al*, (2007b) (0.35U/kg) was 0.4U/kg. At this dose the duration of action for Levemir was revealed as 19.9±3.2 hours which was considerably longer than that suggested by the graph from Porcellati *et al* (2007b).

Sanofi-Aventis criticised the Panel's interpretation of a conclusion from the comprehensive clamp review paper published by Heise and Pieber. The Panel noted the limitation of the review that only three clamp studies with Levemir in type 1 diabetes were analyzed. However there were four trials with Lantus which the authors considered on the basis of pre-defined criteria. Novo Nordisk submitted that this kind of difference would not make the conclusions from the Levemir studies irrelevant. Furthermore a recent clamp trial comparing Lantus and Levemir in type 1 diabetes (Bock *et al* 2008) revealed completely different results to Porcellati *et al*, (2007b). In fact Bock *et al* confirmed the conclusion of Heise and Pieber, in that the durations of action of Levemir and Lantus were comparable over a 24-hour period which made them suitable for once-daily dosing in most subjects (23.3±4.9 hrs and 27.1±7.7 hrs respectively at steady state). Novo Nordisk alleged that the evidence from these clamp studies which suggested similar durations of action for Lantus and Levemir were reassuring and further confirmed the conclusion by Heise and Pieber that Porcellati *et al*, (2007b) should be considered as an outlier. Novo Nordisk also noted again the contradiction between the results from the clinical part and the clamp part of Porcellati *et al* (2007b). Sanofi-Aventis had only referred to the results from the clamp part of this study in its promotional materials, and had hidden the inconsistent results from the clinical part.

APPEAL BOARD RULING

The Appeal Board noted that in Case AUTH/2028/7/07 claims for '24-hour control' or '24-hour glycaemic control' for Lantus had been considered to not be capable of substantiation and exaggerated and misleading. Breaches of the Code were ruled.

Turning to the case now before it the Appeal Board noted that the intended audience for the two leavepieces (LAN08/1037 and LAN08/1038) were diabetes nurse specialists, diabetologists and GPs with an interest in diabetes. The Appeal Board considered that although the claim 'Once-daily – provides 24-hour efficacy' appeared below the claims 'Lantus-control without compromise for your diabetes patients', given the audience it would not be taken to imply '24-hour-control' but a claim for duration of action. The Appeal Board had some concerns about the claim and its context but on balance decided that Sanofi-Aventis had not breached its undertaking given in Case AUTH/2028/7/07. The Appeal Board ruled no breach of Clause 25 and consequently no breach of Clauses 9.1 and 2. The appeal on this point was thus successful.

The Appeal Board noted that the leavepiece LAN08/1039 and the mailer LAN08/1041 both featured a graph depicting plasma glucose levels over time with Lantus and Levemir (Porcellati 2007b). The graph was drawn using results generated after two weeks of treatment and showed that in type 1 diabetics Lantus constantly suppressed plasma glucose over a 24-hour period post dose whereas blood glucose levels started to rise in the Levemir group after 15 hours.

The Appeal Board considered that the results were not inconsistent with the products' SPCs. Lantus should be administered once daily. The recommended initiation of Levemir in combination with oral antidiabetic agents was once daily. When Levemir was used as part of a basal-bolus regimen it should be administered once or twice daily based on individual patient needs. The Appeal Board noted that the balance of evidence showed that Lantus suppressed plasma glucose for a longer period of time than Levemir.

The Appeal Board did not consider that the graph was either misleading or that it disparaged Levemir. No breach of Clauses 7.2 and 8.1 were ruled. The appeal on these points was successful.

2 Claim 'In clinical practice, after switching from other treatments, Lantus is associated with a lower risk of hypoglycaemia compared to insulin detemir'

Novo Nordisk noted that this claim appeared in one of the leavepieces (LAN08/1038) and in the mailer (LAN08/1041).

COMPLAINT

Novo Nordisk noted that the claim was substantiated by findings from a retrospective GP database analysis (Currie *et al* 2007). The authors compared the reported hypoglycaemic event rate prior to and following initiation of basal Lantus and Levemir (a secondary endpoint of the analysis) and concluded that the risk reduction in hypoglycaemia was significantly greater with Lantus. However, there were some limitations of this analysis which needed to be considered to decide whether the

claim, substantiated by this paper, was misleading or not. The authors compared the clinical outcomes of 5,683 Lantus patients with outcomes of only 694 patients using Levemir. The huge difference in patient numbers obviously reflected the more established clinical experience of using Lantus at that time, ie prescribers were more familiar with its use. Therefore the analysis was biased in favour of Lantus.

Although Currie *et al* analysed the primary endpoint of HbA1c change, and the secondary endpoint of weight change separately in type 1 and type 2 diabetes patients, they failed to follow this fair and highly relevant approach with regard to hypoglycaemia. Further, they failed to differentiate between major and minor hypoglycaemic episodes or episodes that occurred during the day or at night. This lack of clarification raised the question of whether this analysis provided clinicians with any useful findings regarding hypoglycaemia. Defining the types of hypoglycaemic events would be crucial in order to make clinically relevant conclusions from this analysis.

It was well know that hypoglycaemic risk was markedly different in type 1 and type 2 diabetes. The literature clearly differentiated between major and minor hypoglycaemic episodes. Whilst the major hypoglycaemic event rate was approximately 1 event/patient-year in type 1 diabetes (Cryer *et al*, 2007 and Zammitt and Frier 2005), in type 2 diabetes treated by insulin it was at least a third of that: 0.28 (Henderson *et al* 2003) to 0.35 (Donnelly *et al* 2005) events/patient-year. In case of minor events the typical event rate in type 1 diabetes was 104 events/patient-year (Cryer *et al* and Zammitt and Frier) whilst in type 2 diabetes it was approximately 16.5 events/patient-year (Abraira *et al* 1995 and Donnelly *et al*). There seemed to be agreement in the literature that there was a higher incidence of hypoglycaemic episodes in patients with a more advanced stage of type 2 diabetes ie those requiring more intensive antihyperglycaemic therapy (Cryer *et al* and Zammitt and Frier).

These differences in hypoglycaemic risk could be partially explained by the use of different insulin regimens. Whilst type 1 diabetics almost exclusively used a basal-bolus regimen, in type 2 diabetes basal insulins could be used as part of basal-oral or basal-bolus regimens. Since basal-bolus therapy was a much more aggressive approach to control blood glucose levels, and was usually applied at a considerably later (more severe) stage of type 2 diabetes, it was connected with a significantly higher hypoglycaemic event rate than a basal-oral regimen.

One might reasonably assume that in the case of type 1 diabetes, the only flaw in Currie *et al* was the above mentioned 'familiarity' effect in terms of Lantus, since both preparations were used as part of a basal-bolus regimen. However in type 2 diabetes it had to be presumed that apart from this effect there was at least one more bias in favour of Lantus. Whilst it was not clear from the published paper, it was reasonable to assume that many more patients in the Lantus group would have been treated with basal-oral treatment. In the Levemir group the vast majority of the patients would have been treated with a basal-bolus regimen. This was because Lantus had a licence for both basal-oral and basal-bolus use, whilst Levemir only had a licence for basal-bolus use during the analysed period.

Therefore to compare the hypoglycaemic rate reduction without taking into account the type of diabetes and the insulin regimen for those with type 2 diabetes was misleading. Further, it was disappointing that information on the use of bolus insulin, readily available from the THIN database, had been clearly overlooked. The authors simply chose to compare the hypoglycaemic risk reduction in the combined cohort of type 1 and type 2 patients and failed to make any distinction between basal-oral users and basal-bolus users in the type 2 cohort.

The claim at issue was purely based on the results from this flawed analysis. However relevant data from published randomized clinical trials (RCTs) provided a much higher level of evidence. These trials provided detailed results in terms of different types of hypoglycaemic events, relating to Levemir and Lantus when used as part of the same regimen. There were at least two direct, randomized comparisons of Lantus and Levemir (Pieber *et al* 2007 and Rosenstock *et al* 2008). The results from Pieber *et al*, which compared the two as part of basal-bolus therapy in type 1 diabetes, contradicted those of Currie *et al*. In Pieber *et al* Levemir was associated with a significantly lower risk of all nocturnal minor (RR=0.68 [0.46-0.99], p=0.045) and 24-hour major (RR=0.28 [0.08-0.98], p=0.047) hypoglycaemic events despite providing the same overall metabolic control (final HbA1c of 8.16% and 8.19% for Levemir and Lantus respectively, p=ns). Rosenstock *et al* compared Lantus and Levemir as part of basal-oral therapy in type 2 diabetes and was unable to detect any difference between the two in terms of any type of hypoglycaemic risk.

Novo Nordisk believed that Sanofi-Aventis had again cherry-picked the results from a retrospective database analysis, which was severely flawed in terms of hypoglycaemic risk analysis, to substantiate the claim. The company had clearly disregarded all the other published evidence which had revealed completely different results. Therefore the claim was inaccurate, unbalanced, unfair, and ambiguous, it was not based on an up-to-date evaluation of all available evidence and disparaged Levemir in breach of Clauses 7.2, 8.1 and 9.1 of the Code.

RESPONSE

Sanofi-Aventis noted that this complaint followed Case AUTH/2038/7/07 in which Novo Nordisk had alleged that the claim 'Lantus significantly reduced

hypoglycaemia over Levemir in both type 1 and type 2 diabetes', based on the retrospective observational study by Currie *et al*, was not capable of substantiation.

The argument presented by Novo Nordisk was that Currie *et al* was conducted in a pooled population of type 1 and type 2 diabetics, and that differing evidence from RCTs had been overlooked. Novo Nordisk cited Pieber *et al* and Rosenstock *et al* to illustrate the different findings between observational studies and RCTs.

This original statement was ruled in breach of the Code because the heading implied that both type 1 and type 2 patients would expect this benefit, and this could not be substantiated from the pooled analysis. To address the Panel's comments and rulings Sanofi-Aventis removed the final wording from the claim ('… in both type 1 and type 2 diabetes').

With respect to the assertion that the study was of a retrospective database analysis, and did not take into account different findings observed in RCTs, the Panel ruled that there were important differences between observational studies and RCTs, and that it was appropriate to report the data of observational studies. The Panel also considered that the origin of the data was clear to readers. No breach was ruled in this respect.

In the complaint now at issue, Novo Nordisk had once again alleged that use of Currie *et al* to support the claim 'In clinical practice, after switching from other treatments, Lantus is associated with a lower risk of hypoglycaemia compared with insulin detemir' was inappropriate because:

- Firstly, that the authors' analysis was flawed – having been performed on a pooled cohort as opposed to separate cohorts for patients with type 1 and type 2 diabetes.

Whilst Sanofi-Aventis agreed that although this might have been desirable, the analysis performed would have been limited by the nature of information recorded in GP systems. In almost all cases differentiation between severe/mild, nocturnal/daytime hypoglycaemia would not be possible as there was only a single Read code for hypoglycaemia, preventing such sub-classification.

Nonetheless, although the published paper might be open to some critique, it had been published and peer reviewed and was a robust analysis of the rates of hypoglycaemia associated with the use of the two insulins as observed in everyday clinical practice. The hypoglycaemia claim in question was a straightforward representation of this published data. Challenge of the content of the article should be addressed to the journal, not through the Authority.

In conclusion, Novo Nordisk considered that different use of the two insulins might have been responsible for a difference in the observed hypoglycaemia rates. This point had already been considered and dismissed in the initial case; the Panel concluded that the Levemir SPC referred to use with oral hypoglycaemic agents at the time the analysis was performed, and that therefore the difference in usage suggested by Novo Nordisk could not simply be assumed to have occurred.

- Secondly, Novo Nordisk was again concerned that the use of Currie *et al* to support this claim overlooked RCT data, Pieber *et al* and Rosenstock *et al* as put forward in Case AUTH/2038/7/07 and ruled not to be in breach of the Code.

With respect to this assertion, Sanofi-Aventis' response was the same as that provided in the original case. To summarise, this was that: whilst RCT data was fundamental to the evaluation of any new product, a range of data sources were collectively crucial in determining the impact of any given therapy in real life, including observational data; RCTs had their own limitations, in particular being performed on a highly selected cohort of patients which reduced the ability to generalise results to real life practice and a large observational study such as Currie *et al* was much more generalisable to the population than a small RCT, and a good quality observational study was rated level 2b in standard evidence based medicine hierarchies, the same level as a poor quality RCT.

In considering Case AUTH/2038/8/07 the Panel recognised that there were important differences between observational studies and RCTs, and that it was appropriate to report the data of observational studies. In recognition of this, Sanofi-Aventis continued use Currie *et al* to support the claim now in question.

With respect to the current allegation made by Novo Nordisk, Sanofi-Aventis disagreed with the assertion that the claim continued to be made contrary to it being an up-to-date evaluation of all the evidence available. Currie *et al* remained a robust report of a large scale observational study of the effectiveness of the two insulins when used in normal clinical practice, and it was important for physicians to know about it. Novo Nordisk did not appear to have advanced its argument beyond that considered in Case AUTH/2038/8/07, and Sanofi-Aventis was disappointed to have to restate the same response to the same allegations made a year ago. As opposed to cherry-picking, this appeared to be a second bite at the cherry, the opportunity for Novo Nordisk to appeal the original finding was declined.

- Finally, Sanofi-Aventis re-iterated that the claim had already been voluntarily withdrawn as a result of inter-company dialogue (on 18 June 2008).

Although Sanofi-Aventis steadfastly defended the right to publicise the comparative rates of

hypoglycaemia seen in Currie *et al*, it recognised that the phrase 'In clinical practice', although intended to convey that this data was from an observational study, might not be perceived as such by all readers. This claim had therefore been discontinued in this form and all materials in which it was contained had been withdrawn.

In summary, Sanofi-Aventis was confident that the items quoted by Novo Nordisk had been produced taking into account the requirements of the Code and the findings in Cases AUTH/2028/7/07 and AUTH/2038/8/07. All breaches ruled in these two cases had been acted upon and the items amended accordingly.

Sanofi-Aventis denied that it had breached its undertaking and also with Novo Nordisk's other assertions, most of which appeared to be a restatement of complaints which the Panel found to be unproven when first considered. Sanofi-Aventis considered that all actions had been in accordance with the requirements of the Code, and that high standards had been maintained throughout.

Finally, Sanofi-Aventis was disappointed that concerns regarding a claim which it considered had been resolved through inter-company dialogue had regardless been referred for consideration by the Authority.

PANEL RULING

The Director noted Sanofi-Aventis' submission that in its view inter-company dialogue regarding the claim at issue had been successful. Sanofi-Aventis had agreed to withdraw all materials which featured the claim 'In clinical practice, after switching from other treatments, Lantus is associated with a significantly lower risk of hypoglycaemia compared with insulin detemir ($p<0.05$)' only in as much as the phrase 'In clinical practice' did not convey the fact that the data was from a retrospective database analysis. It appeared that in all other respects Sanofi-Aventis intended to continue using the claim. The Director thus considered that inter-company dialogue had not been successful and so the matter was referred to the Panel for it to consider the claim minus the phase 'In clinical practice'.

The Panel noted that the leavepiece (LAN08/1038) was specifically about the use of Lantus in type 2 diabetics. The final page featured the claim at issue referenced to Currie *et al* a study which had demonstrated that in a pooled cohort of type 1 and type 2 diabetics, patients switched to Lantus had a lower relative risk of hypoglycaemia than those switched to Levemir. Given the specificity of the leavepiece, however, the Panel considered that a claim based on pooled data from type 1 and type 2 diabetics was misleading. A breach of Clause 7.2 was ruled which was appealed. The Panel did not consider that the claim disparaged Levemir and so no breach of Clause 8.1 was ruled. The Panel noted that use of Currie *et al* and the need to ensure that readers understood that the hypoglycaemia data was from a pooled cohort of patients had been at issue in Case AUTH/2038/8/07. The Panel considered that to again use the pooled data in a way that was misleading meant that high standards had not been maintained. A breach of Clause 9.1 was ruled which was appealed.

The mailing (LAN08/1041), 'Why choose Lantus' was not specific as to the type of diabetic patients at issue – the mailing referred to both type 1 and type 2 patients. As in the leavepiece above the claim at issue had been derived from Currie *et al*. The Panel noted that the data was generated when the licence for Levemir did not include management of type 2 diabetes except as part of a basal-bolus regimen. Levemir could now be used as part of a basal-oral regimen and so patients who were less prone to hypoglycaemic attacks could be treated. The pooled cohort of type 1 and type 2 diabetics included in Currie *et al* was thus likely to be different to the mixed group of diabetics that a prescriber might now treat with either Lantus or Levemir and so on that basis the Panel considered that the claim at issue was misleading. A breach of Clause 7.2 was ruled which was appealed. Although noting this ruling the Panel did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled. The Panel did not consider that the claim disparaged Levemir. No breach of Clause 8.1 was ruled.

APPEAL BY SANOFI-AVENTIS

Sanofi-Aventis noted that this complaint followed Case AUTH/2038/7/07, in which Novo Nordisk complained that the statement 'Lantus significantly reduced hypoglycaemia over Levemir in both type 1 and type 2 diabetes', based on a retrospective observational study by Currie *et al*, was not capable of substantiation. Novo Nordisk had argued that Currie *et al* was conducted in a pooled population of type 1 and type 2 diabetics, and that the claim overlooked differing evidence from RCTs. Pieber *et al* 2007 and Rosenstock *et al* were cited by Novo Nordisk to illustrate the different findings between observational studies and RCTs.

With respect to the assertion that Currie *et al* was of retrospective database analysis and did not take into account different findings observed in RCTs, the Panel ruled (in Case AUTH/2038/7/07) that there were important differences between observational studies and RCTs, and that it was appropriate to report the data of observational studies. The Panel also considered that the origin of the data was clear to the reader. No breach was ruled in this respect, and Sanofi-Aventis therefore considered it appropriate to continue to utilise this data, provided that it was made clear that the study was observational (reflecting clinical practice) rather than from an RCT.

The breach of the Code that was found with respect to this claim arose from the heading implying that

both type 1 and type 2 patients would expect this benefit, whereas this could not be substantiated from the pooled analysis (despite the author's conclusion that 'Treatment with insulin glargine in both type 1 and type 2 diabetes resulted in … a reduction in hypoglycaemia when compared to treatment with insulin detemir').

In response to this ruling Sanofi-Aventis removed '… in both type 1 and type 2 diabetes' from the claim. The Panel's finding was that benefits had been claimed separately in patients with type 1 and type 2 diabetes, and this could not be supported by the pooled analysis in which no such differentiation had been made – only an overall benefit in the total cohort of patients had been demonstrated. Sanofi-Aventis considered that removing the specific references to individual patient types had made the claim consistent with the pooled analysis from the supporting reference.

Sanofi-Aventis noted that in the present complaint, Case AUTH/2141/7/08, Novo Nordisk had once again alleged that use of Currie *et al* to support this claim was inappropriate because the analysis performed by the authors was methodologically flawed as the use of the products might have been different in clinical practice than in RCTs. Specifically, that a difference in the SPCs of the two insulins might have been responsible for a difference in the observed hypoglycaemia rates. Further, that using Currie *et al* to support the claim again overlooked RCT data (quoting only the same studies Pieber *et al* and Rosenstock *et al* as quoted in Case AUTH/2038/7/07 – ruled then not to be in breach of the Code).

Sanofi-Aventis was disappointed that Novo Nordisk had ignored the voluntary undertaking and withdrawal of these items, as agreed through inter-company dialogue – this seemed contrary at least to the spirit of the Code. Sanofi-Aventis was also disappointed that despite the ruling in Case AUTH/2038/7/07 (in which the Panel recognised that there were important differences between observational studies and RCTs, and that it was appropriate to report the data of observational studies), Novo Nordisk had raised the same objection using the same argument as in this case (which resulted in a finding of no breach). Sanofi-Aventis was similarly disappointed that, as a result of this unwarranted complaint, the Panel had reversed its earlier decision without any additional evidence presented by Novo Nordisk to advance its argument other than that proposed in support of its initial case. Sanofi-Aventis was also concerned that the Panel had been directed to consider how Sanofi-Aventis might use a claim in the future, rather than making a judgement on the use that had occurred. Sanofi-Aventis therefore appealed the Panel's rulings of breaches of the Code.

Sanofi-Aventis noted the Panel's rulings of a breach of Clauses 7.2 and 9.1 in relation to LAN08/1038 and submitted that the Panel had considered that this leavepiece was specifically about type 2 diabetes, and had ruled that to include information on hypoglycaemia in a pooled group of patients with both types of diabetes was therefore misleading. However, the leavepiece did not specifically discuss type 2 diabetes, but discussed use of Lantus in combination with oral hypoglycaemic agents. There was no 'Type 2 Diabetes' title to the document (as opposed to that found in LAN 07/1333 for example), and although the majority of oral hypoglycaemic agents were used in type 2 diabetes, there was still some use, low but significant nonetheless, in type 1 diabetics who were obese and had an element of insulin resistance in addition to their insulin deficiency (so called 'double diabetes') (Moon *et al* 2007).

Sanofi-Aventis therefore submitted that this 'Oral Hypoglycaemic Agent' (not 'Type 2 Diabetes') leavepiece could be considered relevant to both type 1 and type 2 diabetes, and that the Panel's decision that it was limited to type 2 diabetes had resulted in the ruling that the use of data from type 1 and type 2 patients was misleading and not in keeping with high standards. As the leavepiece was not restricted solely to type 2 diabetes, Sanofi-Aventis considered that it was appropriate to include data on patients with diabetes as a whole, and that the leavepiece was not misleading, and that high standards had been maintained.

Sanofi-Aventis noted the Panel's rulings of a breach of Clause 7.2 in relation to item LAN08/1041 and submitted that it was concerned that the Panel, in making this ruling, had reversed its findings in Case AUTH/2038/7/07, without any additional substantive evidence having been demonstrated by Novo Nordisk.

Having defended exactly the same allegation in Case AUTH/2038/7/07, Sanofi-Aventis had continued to use this information regarding rates of hypoglycaemia in clinical practice in the belief that it continued to meet the requirements of the Code. If Novo Nordisk considered that this was not so then it should have appealed the initial ruling – to simply repeat the argument in a new complaint in the hope of a different ruling appeared unjust and set a dangerous precedent. Sanofi-Aventis therefore appealed this finding.

The Panel had reached the opinion that that different patterns of use of the two insulins might have been responsible for a difference in the observed hypoglycaemia rates demonstrated in Currie *et al*, in particular that in type 2 diabetes use in the absence of oral hypoglycaemic agents might have been favoured. This point was considered in Case AUTH/2038/7/07 and dismissed, the Panel concluded that the absence of a specific indication for use with oral hypoglycaemic agents would not prevent this occurring in clinical practice, given that this was the usual pattern of care in type 2 diabetes and especially as the Levemir SPC referred to use with oral hypoglycaemic agents when the analysis was performed. The difference in usage suggested

by Novo Nordisk could not simply be assumed to have occurred.

In reiterating this same argument, again no evidence had been put forward that demonstrated in patients with type 2 diabetes a different pattern of use when the study was performed compared with current practice; Novo Nordisk had only suggested that this might have been the case. In fact, Novo Nordisk highlighted that the overall rate of hypoglycaemia was approximately three times higher in type 1 diabetics than type 2 diabetics – as there were equal numbers of each in the study any impact from different use in patients with type 2 diabetes might therefore be considered small with respect to the overall results demonstrated, and unlikely to significantly alter the conclusion. Not withstanding this point, although the published paper might be open to some critique, it had been published and peer reviewed and it represented a robust demonstration of the effects of using each of the two insulins in clinical practice rather than in RCTs.

In summary, Sanofi-Aventis submitted that in the absence of any new evidence to suggest otherwise, this claim remained robust and its use did not mislead, rather it provided valuable information on the outcomes seen when Levemir and Lantus were used in clinical practice as opposed to within clinical trials, and that the item met the requirements of the Code. The claims in question were capable of substantiation.

COMMENTS FROM NOVO NORDISK

Novo Nordisk noted Sanofi-Aventis' disappointment that it had ignored the voluntary undertaking and withdrawal of all items that included the claim 'In clinical practice, after switching from other treatments, Lantus is associated with a lower risk of hypoglycaemia compared to insulin detemir'. However the undertaking Sanofi-Aventis agreed in the inter-company dialogue related to the current format of the claim. As Sanofi-Aventis had emphasised the part of the claim 'In clinical practice' was not sufficiently clear in communicating that the results came from a retrospective database analysis (Currie *et al*), Sanofi-Aventis also noted that the claim was used in a 'one-off' mailer. However, this was not the only 'one-off' mailer in which Sanofi-Aventis had used this claim. This was the second 'one-off' mailer to use the same claim with minor changes. Sanofi-Aventis' clear message was that Lantus was associated with significantly fewer hypoglycaemic events than Levemir which Novo Nordisk considered to be seriously misleading, particularly given the results coming from head-to-head comparisons in RCTs between the two compounds and the flaws in the substantiating analysis. Given that Sanofi-Aventis slightly modified the wording of the claim without actually changing its essence and meaning, Novo Nordisk was seriously worried about further future promotional materials that portrayed the same claim (ie that Lantus was better than Levemir with regard to hypoglycaemic risk). For these reasons Novo Nordisk considered that Sanofi-Aventis' undertaking offered in the inter-company dialogue was wholly inadequate.

Sanofi-Aventis' appeal suggested that the promotional item LAN 08/1038 did not specifically discuss type 2 diabetes. Since it focused on the use of Lantus in combination with oral antidiabetics it could be relevant to both type 1 and type 2 diabetes. However, no oral antidiabetic medicine was licensed for use in combination with insulin therapy in type 1 diabetes. In fact all the currently available oral agents indicated in Section of 4.1 of their respective SPCs that they could be used in type 2 diabetes not type 1 diabetes. Any use of these medicines in type 1 diabetes would be outside the licence. Sanofi-Aventis' argument was therefore completely irrelevant. Although a limited number of scientific papers had investigated the use of oral antidiabetic medicines in type 1 diabetes, the evidence was so limited that there was no guideline recommending such use (NICE Type 1 diabetes in adults: national clinical guideline for diagnosis and management, 2004). It was inevitable that readers would consider this material was only relevant to type 2 diabetes.

Lastly Novo Nordisk turned to the argument relating to the difference in the product licences and potential impact on the hypoglycaemic results. Sanofi-Aventis noted that when the analysis was conducted by Currie *et al*, there was no difference between the licences and suggested that it could not be considered as a flaw of the study; this was incorrect. The period analysed and not the time of the analysis, covered the years 2004-2006. Levemir was not approved for use in combination with oral antidiabetics until March 2007 – Currie *et al* was published in February 2007! This meant that the difference in their licences would have significant impact on the hypoglycaemia results, as discussed in detail above.

On the basis of the above Novo Nordisk agreed with the Panel's decisions and upheld its complaints regarding the materials which were the subject of the appeal by Sanofi-Aventis.

APPEAL BOARD RULING

The Appeal Board did not accept Sanofi-Aventis' submission that Novo Nordisk's allegations were the same in Case AUTH/2038/7/07 as in the case currently under consideration. The Panel had considered that in Case AUTH/2038/7/07 it was sufficiently clear that the data was from an observational study (Currie *et al*). Further the Panel did not consider that, on the basis of the two studies cited by Novo Nordisk (Pieber *et al* and Rosenstock *et al*), that the data presented by Currie *et al* was *per se* misleading as alleged. The Appeal Board then turned to the materials now at issue in Case AUTH/2141/7/08

The Appeal Board noted that the leavepiece (LAN08/1038) was specifically about the use of Lantus in type 2 diabetics. The final page featured the claim 'In clinical practice, after switching from other treatments, Lantus is associated with a lower risk of hypoglycaemia compared with insulin determir' referenced to pooled data on type 1 and type 2 diabetes from Currie *et al*. Given the specificity of the leavepiece to type 2 diabetes the Appeal Board considered that a claim based on pooled data was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The Appeal Board noted that use of Currie *et al* and the need to ensure that readers understood that the data was from a mixed group of patients had been at issue in Case AUTH/2038/8/07 where a breach had been ruled. The Appeal Board considered that to again use the data in a way that misled meant that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

The mailing (LAN08/1041), 'Why choose Lantus' referred to both type 1 and type 2 diabetes patients. As in the leavepiece above the claim at issue had been derived from Currie *et al*. In this instance, however, the Appeal Board considered that as the mailing had referred to both type 1 and type 2 diabetes, the claim based on pooled data from type 1 and 2 patients was not misleading. The Appeal Board ruled no breach of Clause 7.2. The appeal on this point was successful.

Complaint received **14 July 2008**

Case completed **28 October 2008**

GLAXOSMITHKLINE CONSUMER HEALTHCARE v PFIZER

Champix detail aid

GlaxoSmithKline Consumer Healthcare complained about a Champix (varenicline) detail aid issued by Pfizer. GlaxoSmithKline marketed NiQuitin Clear Patch (nicotine), a nicotine replacement therapy (NRT). Both Champix and NiQuitin were indicated for smoking cessation.

The claims 'Champix at 12 weeks – significantly higher quit success vs NRT' and 'Champix at 12 weeks enables significantly more smokers to quit than NRT' appeared on page 6 of the detail aid. They were referenced to Aubin *et al* (2008) which was the first direct comparison of varenicline with a specific type of NRT.

GlaxoSmithKline was concerned that although Aubin *et al* showed significantly higher end of treatment (12 week) quit rates for Champix compared with NiQuitin, there was no significant difference in long term (52 week) quit rates between the two. This new evidence needed to be incorporated in any comparison of Champix and NRT to ensure that the promotional material was up-to-date and reflected all available evidence clearly.

GlaxoSmithKline did not dispute that the primary endpoint of the study showed a significantly greater quit success at the end of treatment with Champix than with NiQuitin Clear Patch. This difference was no longer significant at six and twelve months. However, the impression created was that Champix was more effective overall than NiQuitin Clear Patch which was not true.

GlaxoSmithKline considered that the longer term results must be given equal (if not greater) prominence to the short term results in an effort to balance the material.

The six and twelve month results were highly clinically relevant, with long term quit being the goal of all smoking cessation interventions. The fact that the short term results were the primary endpoint of Aubin *et al* did not negate this, and were likely to have been chosen simply for regulatory expediency. The real health benefits of smoking cessation required continued long term cessation. The European Medicines Evaluation Agency's (EMEA's) draft guidelines on smoking cessation products were clear that it should be persistent abstinence rates one year post treatment that were the primary endpoint, with end of treatment abstinence rates a secondary endpoint. The Cochrane collaboration, the National Institute for Health and Clinical Excellence (NICE) and the Thorax smoking cessation guidelines for health professionals all used trials with a minimum of six months' follow up on which to base their recommendations, and thus would only use the 6 and 12 month results from Aubin *et al*; Pfizer had defended the use of 12 week quit rates by stating that the NHS used 4 week quit rates as a target so 12 weeks was substantially longer than this. The NHS recognised the limitations of the reliance on 4 week quit rates, and ideally would use longer term outcomes. However, the surrogate marker of 4 week quit rates was used as a compromise (Ferguson *et al*, 2005).

The overall impression created was that Champix was more effective than NiQuitin Clear Patch, which although true for the short term end of treatment result, was not true for the more clinically relevant longer term results. GlaxoSmithKline alleged that the claims were misleading.

The detailed response from Pfizer is given below.

The Panel considered that it was clear that the data comparing quit success for Champix (55.9%) and NRT (43.2%) ($p<0.001$) was at 12 weeks (the primary endpoint of the study). The data for one year was included as the final bullet point and it was clear that the difference in quit success between Champix (26.1%) and NiQuitin (20.3%) was not statistically significant ($p=0.056$). The Panel did not accept that the data from Aubin *et al* had been presented in a misleading manner. The 12 week and 52 week data had been accurately reported and the statistical significance of the results stated. It was clear that the numerical difference in favour of Champix at 52 weeks was not statistically significant. Both the 12 week and the one year data would be of interest to prescribers. No breach of the Code was ruled.

Page 7 was headed 'Champix – numbers needed to treat in smoking cessation'. Beneath which data from the Cochrane Review was presented. The NNT to achieve each additional successful quitter compared with placebo was 20 for all types of NRT, 15 for bupropion and 8 for Champix,

GlaxoSmithKline alleged that the discussion on page 7 of the NNT in smoking cessation was misleading as it was not an up-to-date evaluation of all the evidence since the publication of Aubin *et al* of Champix vs NiQuitin Clear Patch; the NNTs had been calculated by others on the basis of these results. There were shortcomings to the use of the Cochrane review as all types of NRT were pooled in this comparison, when it was clear there were differences between the different dosage forms and combinations (patch, gum, lozenge, nasal spray, combination), doses, support methods, analyses, patient groups and health professional intervention

(eg over the counter NRT use without the intervention of a health professional vs GP-led prescribing).

On the basis of Aubin *et al*, it had been calculated that to get one extra quitter over and above that gained by using NiQuitin Clear Patch, the NNT was 18 extra Champix patients giving an incremental cost of £1,155 per patient. This was clearly at odds with the claim which did not present an up-to-date evaluation of all the evidence.

The Panel noted that page 7 reported the NNT to achieve each additional successful quitter with, *inter alia*, all types of NRT (20) and Champix (8) vs placebo. Updated NNT data vs placebo had been published by Cochrane on 16 July 2008. The complaint from GlaxoSmithKline was received on 15 July 2008.

The Panel noted Pfizer's submission that the Champix NNT data that could be derived from Aubin *et al* would be compared with NiQuitin Clear Patch and not placebo.

The Panel considered that at the time the complaint was made the NNT data compared to placebo was up-to-date. The publication of the updated Cochrane data on 16 July meant that from that date the data in the detail aid was not up-to-date. However this was after the complaint was made. Thus the Panel ruled no breach of the Code. The Panel did not consider that the NNT data vs placebo had to be updated following publication of Aubin *et al* and thus no breach was ruled.

The claim 'Added benefit of cost-effectiveness' appeared on page 7 of the detail aid as a subheading followed by the claim 'Champix was more cost-effective than NRT patches or bupropion (using indirect and direct comparisons respectively)' which was referenced to O'Regan *et al* (2007).

GlaxoSmithKline alleged that the claim was misleading as it did not reflect up-to-date evidence fairly. Aubin *et al* showed no significant difference in long term quit rates and should be used in any cost-effectiveness models rather than older, indirect comparisons which also had the limitations outlined above.

The Panel noted that O'Regan *et al* was a brief abstract which had calculated cost effectiveness data for Champix, NRT patch and bupropion based on quit rates at 1 year of 22.5%, 15.5% and 15.7% respectively.

The Panel had little information about the methods used but assumed that the data from Aubin *et al* could be fed into it. It was true that Aubin *et al* was not a cost effectiveness study but it had provided data on quit rates that might be relevant to the cost-effectiveness claim. The Panel noted, however, that although Aubin *et al* post-dated O'Regan *et al*, there was no data to show that even if the later results had been added to the model used by O'Regan *et al* they would have changed the overall, broad conclusion that Champix was more cost-effective than NRT patches or bupropion. On the basis of the data before it the Panel ruled no breach of the Code.

GlaxoSmithKline alleged that patient safety was paramount and the safety and tolerability page falsely reassured prescribers about the lack of serious events associated with Champix. It referred to the claim 'Favourable safety profile in approximately 4,000 treated smokers'. A similar claim appeared on the key messages summary page. Using this type of wording did not give the reader a true picture of the safety issues. Page 11 did not make clear that there had been a number of reports of myocardial infarction (MI) as itemised in the Champix summary of product characteristics (SPC), and neither was this listed in the prescribing information.

Whether or not a causal relationship had been established or the reports were infrequent or most patients had underlying risk factors, the EMEA required a statement about MI to be added to the side-effects section of the SPC. The EMEA concluded that 'the presence of cardiovascular risk factors cannot exclude the possibility of an additional contributory risk from the use of varenicline'. As such, the risk of MI should be included in the prescribing information as this was a serious side-effect. The fact that the MHRA had accepted Pfizer's rationale for not including MI in the prescribing information did not mean that there was not a breach of the Code. The prescriber was not able to make an informed appraisal of the medicine.

The Panel noted that in July 2007 the statement 'Post marketing cases of myocardial infarction, depression and suicidal ideation have been reported in patients taking varenidine (see section 4.4)' had been added to the Champix SPC. The statement appeared beneath a table listing all adverse reactions which occurred at an incidence greater than placebo. Section 4.4 included additional information about depression and suicidal ideation but gave no additional information about MI. The prescribing information in the detail did not mention MI. A statement to see the SPC for less commonly reported side effects was included.

The Panel did not consider that in the circumstances the failure to include in the prescribing information the post marketing surveillance data in relation to MI meant that the prescribing information did not meet the requirements of the Code that a succinct statement of common side-effects likely to be encountered in clinical practice, serious side-effects and precautions and contra-indications, relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of products characteristics, together with a statement that prescribers should consult the summary of products characteristics in relation to other side-effects be included. No breach of the Code was ruled.

The Panel did not consider that the absence of information about MI on the page detailing the safety and tolerability of Champix, on the key messages page or in the prescribing information meant that the prescriber was not in a position to make an informed appraisal of the medicine. No breach of the Code was ruled.

GlaxoSmithKline Consumer Healthcare complained about a Champix (varenicline) detail aid issued by Pfizer Limited. GlaxoSmithKline marketed NiQuitin Clear Patch (nicotine), a nicotine replacement therapy (NRT). Both Champix and NiQuitin were indicated for smoking cessation.

This case was considered under the 2008 Constitution and Procedure. The clauses cited, 4.2, 7.2, 7.3 and 7.9, were the same in the 2006 Code as the 2008 Code.

1 Claims 'Champix at 12 weeks – significantly higher quit success vs NRT' and 'Champix at 12 weeks enables significantly more smokers to quit than NRT'

The claims at issue appeared on page 6 of the detail aid. They were referenced to Aubin *et al* (2008) which was the first direct comparison of varenicline with a specific type of NRT.

COMPLAINT

GlaxoSmithKline was concerned that although Aubin *et al* showed significantly higher end of treatment (12 week) quit rates for Champix compared with NiQuitin, there was no significant difference in long term (52 week) quit rates between the two. This new evidence needed to be incorporated in any comparison of Champix and NRT to ensure that the promotional material was up-to-date and reflected all available evidence clearly.

In this area of emerging scientific opinion, previous discussions on the relative efficacy of the two treatment types had been based on indirect comparisons where results for all different types of NRT had been pooled so that 'apples' were not compared to 'pears' but to 'fruit'. This newly published direct comparison gave a clearer picture of the relative efficacies of NiQuitin Clear Patch and Champix.

GlaxoSmithKline did not dispute that the primary endpoint of the study showed a significantly greater quit success at the end of treatment with Champix than with NiQuitin Clear Patch. This difference was no longer significant at six and twelve months.

However, the impression created was that Champix was more effective overall than NiQuitin Clear Patch which was not true. This impression was created by:

- the headline 'Champix at 12 weeks – significantly higher quit success rate vs NRT' which set the tone for the page,
- the emphasis of the bar chart that only described the end of treatment (12 week) results,
- the prominent '2x' in the claim 'approximately 2x greater odds of quitting smoking with Champix at 12 weeks vs NRT patch (odds ratio 1.70; p<0.001)',
- the strap line at the bottom of the page, 'Champix at 12 weeks enables significantly more smokers to quit than NRT',
- the inclusion of the unqualified claim 'Significantly higher quit success at 12 weeks vs NRT patch, bupropion or placebo' as a key message on the back page.

The Code required comparisons to be accurate, balanced, fair, objective and unambiguous and based on an up-to-date evaluation of all evidence and reflect that evidence clearly. They must not mislead directly or by implication, by distortion, exaggeration or undue emphasis. Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. This was particularly true for issues where clinical opinion was evolving. As such GlaxoSmithKline considered that the longer term results must be given equal (if not greater) prominence to the short term results in an effort to balance the material.

The six and twelve month results were highly clinically relevant, with long term quit being the goal of all smoking cessation interventions. The fact that the short term results were the primary endpoint of Aubin *et al* did not negate this, and were likely to have been chosen simply for regulatory expediency. The real health benefits of smoking cessation required continued long term cessation, and because of this, the European Medicines Evaluation Agency's (EMEA's) draft guidelines on smoking cessation products were clear that it should be persistent abstinence rates one year post treatment that were the primary endpoint, with end of treatment abstinence rates a secondary endpoint. The Cochrane collaboration, the National Institute for Health and Clinical Excellence (NICE) and the Thorax smoking cessation guidelines for health professionals all used trials with a minimum of six months' follow up on which to base their recommendations, and would only use the 6 and 12 month results from Aubin *et al* when they next updated; they would not use the end of treatment data-point, even if it was the primary endpoint as it was not as clinically relevant as the longer term results. Pfizer defended the use of 12 week quit rates by stating that the NHS used 4 week quit rates as a target so 12 weeks was substantially longer than this. However, the NHS did not have the capacity to follow patients long term, and 4 week quit rates were used as a measure of success of their overall intervention. They were not intended as a robust comparison between treatments, but a target set by the NHS for it to monitor progress within a locality on a rolling basis. The NHS recognised the limitations of the reliance on 4 week quit rates, and ideally would use longer term outcomes. However, because their collection could be expensive and time-consuming, detracting from the delivery of core services, it relied on the surrogate marker of 4 week

quit rates as a useful compromise (Ferguson *et al*, 2005).

The overall impression created was that Champix was more effective than NiQuitin Clear Patch, which although true for the short term end of treatment result, was not true for the more clinically relevant longer term results. The omission of any reference to the head-to-head long term quit rate results on the back page (key messages) clearly demonstrated Pfizer's intent to persuade prescribers that Champix was significantly more effective than the NRT patch when this was not so in the long term. It was vital that prescribers were given adequate and balanced information to enable them to form their own opinion about the value of medicines, particularly when new data such as this might challenge their current beliefs. GlaxoSmithKline alleged that the detail aid was misleading and in breach of Clause 7.2.

RESPONSE

Pfizer explained that the primary objective of Aubin *et al* was to compare a 12 week standard regimen of Champix with a 10 week standard regimen of transdermal NRT, and it was the primary endpoint result that was the focus of this section of the detail aid. As detailed in Section 3.2.2.4 of the ICH General Considerations for Clinical Trials, a primary endpoint should reflect clinically relevant effects and was typically selected based on the principal objective of the study. Pfizer also included a longer term secondary endpoint, notably the 52 week data, despite its understanding that secondary endpoints were regarded as for further exploratory use only. Inclusion of the 52 week data in the detail aid facilitated more in-depth discussion with the health professional.

Pfizer submitted that it clearly stated that the difference between Champix and the NRT patch at 52 weeks was not significant and showed the p value. The study was powered for the primary endpoint and not at 52 weeks, giving a scientific rationale as to why Champix was numerically but not statistically superior at 52 weeks. Furthermore, in the pre-specified sensitivity analysis looking at the 'all randomised' population at 52 weeks, Champix was both numerically and statistically superior to the NiQuitin Clear patch [25.9% vs 19.8%, OR 1.44 (1.02–2.03), p=0.040].

Pfizer noted GlaxoSmithKline's concern that the 'impression' created by this section of the detail aid was that Champix was more effective overall than NiQuitin Clear patch.

Pfizer disagreed that its approach created a misleading impression. The page in the detail aid had a headline and strapline that represented the primary endpoint of the study presented, and it was explicitly clear that the treatment significance was at 12 weeks only (ie short term quit rate). Similarly, the bar chart demonstrated this primary endpoint in a balanced manner, which helped the representative discuss the data with a health professional. Furthermore it was reasonable to highlight the primary endpoint within the text as it was the principal aim of the study. Finally, the comment around the alleged unqualified claim 'Significantly higher quit success at 12 weeks vs NRT patch, bupropion or placebo' in the key messages page was invalid, since this was clearly referenced to clinical papers. It was not misleading as it clearly referred to the correct time span within the clinical studies. Pfizer therefore did not believe that the presentation of this information was in breach of Clause 7.2.

Pfizer also disagreed that the longer term results should be given equal (if not greater) prominence to the short-term results in an 'effort to balance the material'; the page represented a balanced overview of Aubin *et al*. The study was not powered for the longer term result, it was a secondary endpoint, evaluated for exploratory means only. It was consistently made explicitly clear that the significant difference in quit rates between Champix and NiQuitin Clear patch was seen in the primary endpoint, at end-of-treatment.

Pfizer noted that GlaxoSmithKline had included information from the draft 'Guideline on the development of medicinal products for the treatment of nicotine dependence' that was sent on 19 July 2007 by the EMEA for consultation. Pfizer would review the document in its entirety once it had been finalised, and incorporate this information into its thinking around future clinical trials with Champix.

Pfizer noted that GlaxoSmithKline also referred to the Cochrane collaboration using only 6 and 12 month results. This update was recently published online in 'Nicotine receptor partial agonists for smoking cessation' on 16 July 2008 (Issue 3, 2008). The authors included Aubin *et al* in their review and stated that 'One open-label trial of varenicline versus nicotine replacement therapy demonstrated a modest benefit of varenicline over NRT with a RR at week 52 of 1.31 (95%CI 1.01 to 1.71)'. The results within this Cochrane review were in keeping with the overall presentation of Aubin *et al* within the detail aid.

Pfizer disagreed that the overall impression in the detail aid of the head-to-head study of Champix vs NiQuitin Clear patch was misleading (Clause 7.2). Throughout the material the timeframe was clearly stated with the inclusion of the primary endpoint of the study and details of the 52 week secondary endpoint were provided to facilitate a more in-depth discussion with the health professional.

PANEL RULING

The Panel examined page 6 of the detail aid. It was clear that the data comparing quit success for Champix (55.9%) and NRT (43.2%) (p<0.001) was at

12 weeks (the primary endpoint of the study). The data for one year was included as the final bullet point and it was clear that the difference in quit success between Champix (26.1%) and NiQuitin (20.3%) was not statistically significant (p=0.056). The Panel did not accept that the data from Aubin *et al* had been presented in a misleading manner. The 12 week and 52 week data had been accurately reported and the statistical significance of the results stated. It was clear that the numerical difference in favour of Champix at 52 weeks was not statistically significant. Both the 12 week and the one year data would be of interest to prescribers. No breach of Clause 7.2 was ruled.

2 Number Needed to Treat (NTT)

Page 7 was headed 'Champix – numbers needed to treat in smoking cessation'. Beneath which data from the Cochrane Review was presented. The NNT to achieve each additional successful quitter compared with placebo was 20 for all types of NRT, 15 for bupropion and 8 for Champix,

COMPLAINT

GlaxoSmithKline alleged that the discussion on the this page of the NNT in smoking cessation was misleading as it was not an up-to-date evaluation of all the evidence since the publication of Aubin *et al* of Champix vs NiQuitin Clear Patch; the NNTs had been calculated by others on the basis of these results. There were shortcomings to the use of the Cochrane review as all types of NRT were pooled in this comparison, when it was clear there were differences between the different dosage forms and combinations (patch, gum, lozenge, nasal spray, combination), doses, support methods, analyses, patient groups and health professional intervention (eg over the counter NRT use without the intervention of a health professional vs GP-led prescribing).

However, leaving that aside, the publication of Aubin *et al* meant that there was more and relevant evidence that needed to feed in to any NNT calculation and this was not done in the detail aid.

On the basis of Aubin *et al*, it had been calculated that to get one extra quitter over and above that gained by using NiQuitin Clear Patch, the NNT was 18 extra Champix patients giving an incremental cost of £1,155 per patient. This was clearly at odds with the claim which did not present an up-to-date evaluation of all the evidence, in breach of Clauses 7.2 and 7.3.

RESPONSE

Pfizer submitted that the NNT evidence was from the original Cochrane Review – 'Nicotine receptor partial agonists for smoking cessation', which was published online in January 2007 as part of the Cochrane Library. Since this information source provided high-quality, independent evidence Pfizer considered that it was an appropriate reference. The primary objective of this Cochrane Review was to assess the efficacy and tolerability of nicotine receptor partial agonists for smoking cessation. As part of this evaluation, the NNT to achieve each additional successful quitter was derived from the pooled difference between placebo and treatment quit rates. For comparison with Champix, the Cochrane Review estimated NNTs from recent meta-analyses of NRT and bupropion. The values reported were for 'all types of NRT', and Pfizer therefore could not include values for different dosage forms and combinations, different doses/support methods and so on, as this level of information was not available.

Pfizer noted that NNT data had not been published for Aubin *et al* and NNTs derived from this study would compare Champix with the NRT patch rather than placebo.

Since April 2008, when the Champix detail aid was printed, as described above the Cochrane Collaboration had updated the original 'Nicotine receptor partial agonists for smoking cessation' document, including updated NNT values (published 16 July 2008). The original values for NNT to achieve each additional successful quitter compared with placebo were: all types of NRT, 20; bupropion, 15 and Champix, 8. In the updated document, the values have been revised: all types of NRT 23, bupropion, 18 and Champix 10. Pfizer stated that it could use these updated NNT values in future materials, now that they had been published.

Pfizer did not agree that the presentation of the original NNT values from the Cochrane review was misleading and therefore denied breaches of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that page 7 reported the NNT to achieve each additional successful quitter with, *inter alia*, all types of NRT (20) and Champix (8) vs placebo. Updated NNT data vs placebo had been published by Cochrane on 16 July 2008. The complaint from GlaxoSmithKline was received on 15 July 2008.

The Panel noted Pfizer's submission that the Champix NNT data that could be derived from Aubin *et al* would be compared with NiQuitin Clear Patch and not placebo.

The Panel considered that at the time the complaint was made the NNT data compared to placebo was up-to-date. The publication of the updated Cochrane data on 16 July meant that from that date the data in the detail aid was not up-to-date. However this was after the complaint was made. Thus the Panel ruled no breach of Clauses 7.2 and 7.3. The Panel did not consider that the NNT data vs placebo had to be updated following publication of Aubin *et al*. Thus no breach of Clauses 7.2 and 7.3 was ruled.

3 Claim 'Added benefit of cost-effectiveness'

The claim appeared on page 7 of the detail aid as a subheading followed by the claim 'Champix was more cost-effective than NRT patches or bupropion (using indirect and direct comparisons respectively)' which was referenced to O'Regan *et al* (2007).

COMPLAINT

GlaxoSmithKline alleged that the claim was misleading as it did not reflect up-to-date evidence fairly. As noted above, Aubin *et al* showed no significant difference in long term quit rates and should be used in any cost-effectiveness models rather than older, indirect comparisons which also had the limitations outlined above. O'Regan *et al* was out of date since the publication of the new head-to-head data in Aubin *et al*. GlaxoSmithKline alleged breaches of Clauses 7.2 and 7.3.

RESPONSE

Pfizer stated that O'Regan *et al* was a relevant and up-to-date reference for the claim 'Champix was more cost-effective than NRT patches or bupropion (using indirect and direct comparisons respectively)'. GlaxoSmithKline had not provided a more up-to-date cost-effectiveness reference. The results of Aubin *et al* did not include a cost-effectiveness analysis. Thus Pfizer denied breaches of Clauses 7.2 and 7.3 as the claim was an up-to-date evaluation of the evidence.

PANEL RULING

The Panel noted that O'Regan *et al* was a brief abstract which had calculated cost effectiveness data for Champix, NRT patch and bupropion based on quit rates at 1 year of 22.5%, 15.5% and 15.7% respectively. Efficacy was based on biochemically confirmed quit rates at one year taken from pooling the results of published clinical trials.

The data had been produced by a Pfizer team using a model which calculated the cost and benefits that would accrue from smoking cessations over a 20 year period. The model calculated savings in direct healthcare costs in Scotland.

The Panel had little information about the methods used in the cost effectiveness model but assumed that the data from Aubin *et al* could be fed into it. It was true that Aubin *et al* was not a cost effectiveness study but it had provided data on quit rates that might be relevant to the cost-effectiveness claim. The Panel noted, however, that although Aubin *et al* post-dated O'Regan *et al*, there was no data to show that even if the later results had been added to the model used by O'Regan *et al* they would have changed the overall, broad conclusion that Champix was more cost-effective than NRT patches or bupropion. On the basis of the data before it the Panel ruled no breach of Clauses 7.2 and 7.3.

4 Claim 'Favourable safety profile in approximately 4,000 treated smokers' and prescribing information

The claim appeared on page 11 of the detail aid and was referenced to the Champix SPC.

COMPLAINT

GlaxoSmithKline submitted that patient safety was paramount and the safety and tolerability page falsely reassured prescribers about the lack of serious events associated with Champix. A similar claim appeared on the key messages summary page. As highlighted in the recent Drug and Therapeutics Bulletin article using this type of wording did not give the reader a true picture of the safety issues surrounding Champix. The page did not make clear that there had been a number of reports of myocardial infarction (MI) as itemised in the Champix summary of product characteristics (SPC), and neither was this listed in the prescribing information. The Code clearly stated that the prescribing information should contain 'a succinct statement of common side-effects likely to be encountered in clinical practice, serious side-effects and precautions and warnings … giving, in abbreviated form, the substance of the relevant information in the summary of product characteristics, together with …'.

Whether or not a causal relationship had been established or the reports were infrequent or most patients had underlying risk factors, the EMEA required a statement about MI to be added to the side-effects section of the SPC. The EMEA concluded that 'the presence of cardiovascular risk factors cannot exclude the possibility of an additional contributory risk from the use of varenicline'. As such, the risk of MI should be included in the prescribing information as this was a serious side-effect. The fact that the MHRA had accepted Pfizer's rationale for not including MI in the prescribing information did not mean that there was not a breach of Clause 4.2. The prescriber was not able to make an informed appraisal of the medicine and as such this breached Clause 7.9.

RESPONSE

Pfizer noted that section 4.8 of the SPC stated:

> 'Clinical trials included approximately 4,000 patients treated with CHAMPIX for up to 1 year (average exposure 84 days). In general, when adverse reactions occurred, onset was in the first week of therapy; severity was generally mild to moderate and there were no differences by age, race or gender with regard to the incidence of adverse reactions.

In patients treated with the recommended dose of 1mg BID following an initial titration period the adverse event most commonly reported was nausea (28.6%). In the majority of cases nausea occurred early in the treatment period, was mild to moderate in severity and seldom resulted in discontinuation.

The treatment discontinuation rate due to adverse events was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse events in varenicline treated patients were as follows: nausea (2.7% vs. 0.6% for placebo), headache (0.6% vs. 1.0% for placebo), insomnia (1.3% vs. 1.2% for placebo), and abnormal dreams (0.2% vs. 0.2% for placebo).'

Based on both the treatment discontinuation rates reported in the clinical trial data, and the fact that when adverse reactions occurred their severity was generally mild to moderate, Pfizer considered that the claim 'Favourable safety and tolerability profile in approximately 4,000 treated smokers' was justified. Although nausea was the most common adverse effect of Champix it appeared to be generally well tolerated as only 2.7% of those experiencing nausea discontinued treatment. This rationale had recently been accepted by the MHRA which had accepted Pfizer's use of the claim 'Favourable safety and tolerability profile in approximately 4,000 treated smokers' in recent correspondence on this subject. Pfizer did not believe that the claim was in breach of Clause 7.9.

Pfizer noted GlaxoSmithKline's concern that reports of MI were not listed in the Champix prescribing information. However, Pfizer considered that it had taken all necessary steps to ensure that the Champix prescribing information was updated in a timely manner to include all safety information. The statement regarding post-marketing reports of MI was added to section 4.8 of the Champix SPC, effective July 2007:

– 'Post-marketing cases of myocardial infarction have been reported in patients taking varenicline.'

This information did not warrant inclusion within the table of very common, common, uncommon or rare side-effects outlined in section 4.8 of the SPC. No causal relationship between Champix and these cases of MI had been established. These reports were infrequent and most patients had additional pre-existing cardiovascular disease and/or other risk factors. In 2007 Pfizer thus took the view that the statement regarding post-marketing reports of MI did not warrant inclusion in the Champix prescribing information.

Subsequent reviews of the SPC had not led to any further changes to the information regarding MI. Therefore Pfizer still considered that inclusion in the prescribing information at this stage was not necessary. In recent correspondence the MHRA had agreed that Pfizer acted appropriately. Pfizer denied breaches of Clauses 4.2 or 7.9.

PANEL RULING

The Panel noted that in July 2007 the statement 'Post marketing cases of myocardial infarction, depression and suicidal ideation have been reported in patients taking varenicline (see section 4.4)' had been added to the Champix SPC. The statement appeared beneath a table listing all adverse reactions which occurred at an incidence greater than placebo. Section 4.4 included additional information about depression and suicidal ideation but gave no additional information about MI. The prescribing information in the detail did not mention MI. A statement to see the SPC for less commonly reported side effects was included.

The Panel did not consider that in the circumstances the failure to include in the prescribing information the post marketing surveillance data in relation to MI meant that the prescribing information did not meet the requirements of Clause 4.2 that a succinct statement of common side-effects likely to be encountered in clinical practice, serious side-effects and precautions and contra-indications, relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of products characteristics, together with a statement that prescribers should consult the summary of products characteristics in relation to other side-effects be included. No breach of Clause 4.1 was ruled.

The Panel did not consider that the absence of information about MI on the page detailing the safety and tolerability of Champix, on the key messages page or in the prescribing information meant that the prescriber was not in a position to make an informed appraisal of the medicine. No breach of Clause 7.9 was ruled.

During its consideration of the case, the Panel noted that section 4.8 of the Champix SPC included the statement 'Clinical trials included approximately 4,000 patients treated with Champix for up to 1 year (average exposure 84 days). In *general*, [emphasis added] when adverse reactions occurred, onset was in the first week of therapy; severity was *generally* [emphasis added] mild to moderate and there were no differences by age, race or gender with regard to the incidence of adverse reactions'. In that regard the Panel queried whether the claim 'Favourable safety profile in approximately 4,000 treated smokers' was an accurate reflection of the SPC statement. The statement in the SPC appeared to be more qualified in tone than the claim in the detail aid. The Panel requested that Pfizer be advised of its concerns in this regard.

Complaint received **15 July 2008**

Case completed **29 August 2008**

CASE AUTH/2143/7/08

NURSE v SYNER-MED

Promotion of Ferinject

A nurse complained about what she had been told about Ferinject (ferric carboxymaltose), an injectable iron preparation, at a Syner-Med exhibition stand. She also referred to a detail aid.

The complainant had been told that Ferinject was an IV iron and 1,000mg could be given in a single dose over 15 minutes. The complainant asked about safety concerns worldwide and was informed that Ferinject was safe.

The complainant had since discovered that the maximum dose was 1,000mg iron per week, but should not exceed 15mg/kg of body weight. This was included on page 9 of the detail aid 'The next generation of intravenous iron'. The complainant alleged that the detail aid was misleading as patients might need more than one dose.

The Food and Drug Administration (FDA) had refused to approve Ferinject in the US because of safety issues; 10 deaths occurred during trials. The complainant was concerned that as a nurse she had been misled over safety issues and the single dosage of Ferinject.

The detailed response from Syner-Med is given below.

On the basis of the parties' submissions the Panel did not consider that there was sufficient evidence to show that on the balance of probabilities any of the representatives on Syner-Med's stand had described Ferinject as safe. The Panel ruled no breach of the Code.

With regard to the maximum infusible the Panel noted that the summary of product characteristics (SPC) stated 'Ferinject may be administered by intravenous infusion up to a maximum single dose of 20ml of Ferinject (1000mg of iron) but not exceeding 0.3ml of Ferinject (15mg of iron) per kg body weight or the calculated cumulative dose. Do not administer 20ml (1000mg of iron) as an infusion more than once a week'. The adequate cumulative dose required by a patient had to be calculated for each patient individually according to a formula in the SPC and must not be exceeded. The dosing of Ferinject was thus not straightforward.

Page 5 of the detail aid stated simply 'Ferinject, Up to 1000mg, Single Infusion, Dose in 15 mins'. The headline to page 6 (which faced page 5) stated 'Ferinject… the only intravenous iron that allows for 1000mg to be given in 15 mins'. Page 9, in a footnote to a table detailing administration by drip infusion, stated 'The maximum dose by infusion is 1000mg iron per week, but should not exceed 15mg/kg'.

The Panel considered that, given the details regarding dosage in the SPC, the dosage statements in the detail aid were too simple and important information was omitted. It was not acceptable to refer to the maximum permitted single dose by infusion on one page but give the qualifying information (ie the dose should not exceed 15mg/kg) on another. It was only in the prescribing information that it was stated that the cumulative dose must be calculated for each patient individually and must not be exceeded. The Panel considered that the detail aid was misleading with regard to the dosage particulars for Ferinject and a breach of the Code was ruled.

A nurse complained about what she had been told about Ferinject (ferric carboxymaltose), an injectable iron preparation from Syner-Med (Pharmaceutical Products) Limited, when she visited the company's stand at a meeting in May 2008. The complainant also referred to a detail aid.

COMPLAINT

The complainant explained that she had enquired at the Syner-Med stand about Ferinject and was told that it was an IV iron and 1,000mg could be given in single dose over 15 minutes. The complainant asked about safety concerns worldwide and was informed that Ferinject was safe.

The complainant had since discovered that the maximum dose was 1,000mg iron per week, but should not exceed 15mg/kg of body weight. This was written in smaller print on page 9 of the detail aid 'The next generation of intravenous iron' (ref F07/01-05-08-039). The complainant considered the detail aid and the representation of the usage of Ferinject was misleading as patients might need more than one dose.

The complainant had since discovered that the Food and Drug Administration (FDA) had refused to approve Ferinject in the US because of safety issues; 10 deaths occurred during trials.

The complainant was concerned that as a nurse she had been misled over safety issues and the single dosage of Ferinject.

When writing to Syner-Med, the Authority asked it to respond in relation to Clauses 7.2, 7.9 and 7.10 of the 2006 Code which were the same as the 2008 Code. This case was considered under the 2008 Constitution and Procedure.

RESPONSE

Syner-Med submitted that it was very difficult to investigate the circumstances surrounding the conversation about safety as there were very few details given and the complaint was made more than two months after the incident. There was no precise date, no specified time and no named company employee with whom to verify this conversation. The exhibition spanned three days, with more than a thousand delegates and fourteen Syner-Med employees on the stand at different times. None of them recalled a conversation as described by the complainant. From the information provided it was unclear as to how long the conversation lasted, whether other people were involved and the circumstances (eg whether the exhibition stand was crowded and there were distractions, whether everything was audible to both parties).

There was no information as to what was said by either party and therefore no context in which Syner-Med could make specific comments. The complainant's phrase 'Ferinject was safe' appeared to be a summary statement. Given the complainant's open question ie 'I asked about safety concerns worldwide' the answer given had to be a summary; if the answer was taken as a verbatim statement, then it neither answered the question nor made sense.

Syner-Med knew that it was inappropriate to imply that a product had no side-effects or to use the word 'safe' in the promotion of medicines under both guidance from the Medicines and Healthcare products Regulatory Agency (MHRA) and Clause 7.9 of the Code. All the company's sales representatives had successfully passed the ABPI examination and equally knew that the use of the term was inappropriate. The Ferinject detail aid, to which the complainant referred, made no such statement, and, in line with the requirements to encourage rational use of a medicine by presenting it objectively and without exaggeration (Clause 7.10), the company had conveyed the 'benefit/risk' profile clearly in the text. Syner-Med noted that a whole A4 page was devoted to the issue of adverse events with Ferinject. Thirteen specific adverse events were reported with their relative frequency. Reference was also made to the frequency of life threatening anaphylactic reactions. On Page 9 reproduced, in bold print, a warning/precaution from the summary of product characteristics (SPC): 'Parenterally administered iron preparations can cause hypersensitivity reactions. Therefore facilities for cardio-pulmonary resuscitation must be available'.

Given that the complainant made detailed reference to the specifics contained in the detail aid it seemed unreasonable to ignore all the safety information contained therein, and claim that the company had misrepresented the safety issue.

At the exhibition stand there was other information relating to safety contained in the Ferinject SPC. The medical information department was also represented on the stand and many written questions were left for follow up. All these opportunities were available to the complainant yet they were not taken up. Syner-Med considered that they were all important considerations in the context of the complaint.

Regarding the supply of safety information on Ferinject, Syner-Med noted that the product was licensed in eighteen European countries but had only been launched in Germany, the UK and Switzerland. The time period from launch in each country was such that Periodic Safety Data had only been submitted from one country to date. In the context of the discussion between the complainant and the representative this information would not be known to the representative.

In conclusion, the company had thoroughly investigated the complainant's comments and was unable to identify anyone who remembered being involved in a conversation of this nature. In line with the regulations, the company did not allow staff to use the word 'safe' in the promotion of any medicine, either verbally or written.

With regard to the dosing of Ferinject, Syner-Med was again unable to identify anyone who remembered the specific details of the conversation described. However, the verbal statement that Ferinject was an IV iron preparation and 1,000mg could be given in a single dose over 15 minutes was correct and in line with the product licence.

Page 5 of the detail aid cited by the complainant stated:

'Ferinject
Up to 1000mg
Single Infusion
Dose in 15 mins.'

This statement complied with the product licence as a dose of 'Ferinject may be administered by intravenous infusion up to a maximum single dose of 20ml (1000mg) of iron …' (ref SPC).

As identified by the complainant, page 9 of the detail aid stated: 'The maximum single dose by infusion is 1000mg iron per week, but should not exceed '15mg/Kg'.

This also complied with the licence and occurred at a very relevant place in the brochure. This came under the heading 'Administration by drip infusion'. This section contained information about vial sizes, volumes of saline to be used, and administration time. To include detailed information about maximum doses and the frequency of dosing was highly relevant to this section. Thus, the company refuted the suggestion that there was some attempt to be misleading in the layout of the information in the detail aid.

Syner-Med submitted that the complainant made a

different point when she stated that the information was 'misleading as patients might need more than one dose'. The detail aid did not claim that the total dose required could be administered in any one visit (for example, the phrase 'total dose infusion' was not used). The wording used was 'Up to 1000mg Single Infusion' which simply meant that there was flexibility in dosing from 100mg up to 1,000mg. This was not a statement about frequency of dosing.

Syner-Med strenuously refuted the allegation that it had breached Clauses 7.2, 7.9 and 7.10.

PANEL RULING

The provisions of Clauses 7.2, 7.9 and 7.10 of the 2008 Code were considered. These clauses were the same in the 2006 Code.

With regard to the question about the safety of Ferinject, the Panel noted that the parties' accounts differed; it was difficult in such cases to know what had transpired. A judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually necessary on the part of an individual before he or she was moved to actually submit a complaint.

The complainant had submitted that she was told that Ferinject was safe. Syner-Med had been unable to find anyone who had been on the company stand who remembered the alleged conversation. The company had submitted that it knew it could not describe Ferinject as safe; the detail aid did not describe Ferinject as safe.

On the basis of the parties' submissions the Panel did not consider that there was sufficient evidence to show that on the balance of probabilities any of the representatives on Syner-Med's stand had described Ferinject as safe. The Panel ruled no breach of Clauses 7.9 and 7.10.

With regard to the maximum infusible dose of Ferinject the Panel noted that the SPC stated 'Ferinject may be administered by intravenous infusion up to a maximum single dose of 20ml of Ferinject (1000mg of iron) but not exceeding 0.3ml of Ferinject (15mg of iron) per kg body weight or the calculated cumulative dose. Do not administer 20ml (1000mg of iron) as an infusion more than once a week'. The adequate cumulative dose required by a patient could be calculated according to a formula given in the SPC; the dose must be calculated for each patient individually and must not be exceeded. The dosing of Ferinject was thus not straightforward.

Page 5 of the detail aid stated simply 'Ferinject, Up to 1000mg, Single Infusion, Dose in 15 mins'. The headline to page 6 (which faced page 5) stated 'Ferinject… the only intravenous iron that allows for 1000mg to be given in 15 mins'. Page 9, in a footnote to a table detailing administration by drip infusion, stated 'The maximum dose by infusion is 1000mg iron per week, but should not exceed 15mg/kg'.

The Panel considered that, given the details regarding dosage in the SPC, the dosage statements in the detail aid were too simple and important information was omitted. It was not acceptable to refer to the maximum permitted single dose by infusion on one page but give the qualifying information (ie the dose should not exceed 15mg/kg) on another. It was only in the prescribing information that it was stated that the cumulative dose must be calculated for each patient individually and must not be exceeded. The Panel considered that the detail aid was misleading with regard to the dosage particulars for Ferinject and a breach of Clause 7.2 was ruled.

Complaint received **17 July 2008**

Case completed **28 August 2008**

NURSE v SYNER-MED

Question at a meeting

A nurse complained about a meeting organised by Syner-Med at the recent British Renal Society meeting.

The complainant stated that one of the speakers gave a talk on giving Syner-Med's product Venofer, an injectable iron preparation (iron sucrose), in the community. A delegate asked about the safety issues of giving intravenous (iv) iron in the community. In reply another delegate from the audience stated that they had got around this by sending people away with an EpiPen (adrenaline injection). The speaker and several representatives from Syner-Med made no comment which gave the impression that cardio-pulmonary resuscitation procedures could be replaced with an EpiPen.

The detailed response from Syner-Med is given below.

The Panel noted that Syner-Med had sponsored the meeting in question; one of the speakers acted as a consultant to Syner-Med on a part-time basis. Syner-Med had supplied two of the speakers with slide templates and ten of Syner-Med's staff had attended the meeting. Syner-Med submitted that although the meeting was about chronic renal disease and the future of iv iron treatment, it was not about Venofer in particular. One of a speaker's slides referred to iv iron sucrose but the presentation appeared to be about anaemia management and not Venofer *per se*. The question and answer at issue had occurred in the open session of the meeting. It appeared that in response to a question from a delegate about the safety issues of giving iv iron in the community another delegate had referred to the use of an EpiPen. It was impossible for the Panel to know the exact question and answer or the context in which they had occurred. Nonetheless it appeared that the discussion was general and not about Venofer in particular. Syner-Med had submitted that the question was not specifically directed at Syner-Med's consultant and so she had had no reason to intervene.

The Panel noted that the Venofer summary of product characteristics (SPC) stated that parenterally administered iron preparations could cause allergic or anaphylactoid reactions which might be potentially fatal. Therefore treatment for serious allergic reactions and facilities with the established cardio-pulmonary resuscitation procedures should be available.

Given the implications for patient safety the Panel considered that it might have been helpful if someone had reminded the audience about cardio-pulmonary resuscitation during the discussion of the EpiPen. (EpiPen was injectable adrenalin for use in allergic emergencies). Given the lack of details, however, the Panel was satisfied that, on the balance of probabilities, the audience was not left with the impression that EpiPen could replace cardio-pulmonary resuscitation as alleged. No breach of the Code was ruled.

A nurse complained about a meeting organised by Syner-Med (Pharmaceutical Products) Limited at the recent British Renal Society (BRS) meeting.

COMPLAINT

The complainant stated that one of the speakers gave a talk on giving Syner-Med's product Venofer, an injectable iron preparation (iron sucrose), in the community. A delegate asked about the safety issues of giving intravenous (iv) iron in the community. In reply another delegate from the audience stated that they had got around this legality by sending people away with an EpiPen (adrenaline injection). The speaker and several representatives from Syner-Med made no comment which gave the impression that cardio-pulmonary resuscitation procedures could be replaced with an EpiPen.

When writing to Syner-Med, the Authority asked it to respond in relation to Clauses 7.2, 7.9 and 7.10 of the 2006 Code. The case was considered under the 2008 Constitution and Procedure.

RESPONSE

The Syner-Med symposium (100 plus delegates) was listed in the programme of the BRS Conference on Thursday,15 May. The lunchtime educational meeting, entitled 'Anaemia in chronic kidney disease: The future of iv iron treatment', lasted 60 minutes and was chaired by a leading UK renal consultant. Three presentations of approximately 15 minutes were given, followed by questions.

The presentations were: anaemia in chronic kidney disease (renal consultant); prediction of iron requirements in pre-dialysis patients (clinical scientist) and how the latest evidence can support changes in clinical practice (nurse advisor). The last presentation was given by a former nurse consultant at a London hospital who had worked as a research nurse in anaemia management. She was well qualified to lecture on the subject and to answer relevant questions. Her talk covered aspects of her work at the hospital.

There were Syner-Med representatives in the audience as noted by the complainant.

Syner-Med explained that in the open session (last 10 minutes of meeting) there were a number of questions that were answered by different members of the panel under the direction of the chairman. The panel members were sat together at the front of the meeting. The speaker in question was not at the podium, but sat with the panel members and took questions as requested of her.

During the open discussion, the chairman raised the issue with the audience that the Department of Health agenda for future chronic kidney disease management required that consideration should be given to the administration of iv iron nearer to the patient's home. This prompted a very general question from a delegate 'What about safety issues of giving iv iron in the community?' As noted by the complainant the questioner did not specify a product and it was not directed to anyone specifically. Also as noted a nurse delegate answered the question and referred to her own experience relating to the provision of EpiPens to patients on home haemodialysis. Her answer went no further than providing a short headline statement about a product used locally in the home haemodialysis setting, and a statement that there had not been any problems over a number of years. The answer did not explain the details of this practice but it was a valid interjection and an appropriate response to the question. The complainant was of the opinion that the statement regarding the use of an EpiPen was inadequate and that either the nurse advisor in question or Syner-Med personnel should have intervened. The company disagreed. The original question was not addressed to the nurse advisor so she had no reason to intervene. The provision of an EpiPen in the community was not inappropriate as it was first line treatment in the event of an anaphylactic reaction in the community in line with the Resuscitation Council's Guideline 2008, so Syner-Med had no reason to intervene. Also, it was not appropriate for Syner-Med to comment either on other medicines or the clinical practice of health professionals.

If the complainant, or any other delegate, thought that the meeting would have benefited from a more detailed explanation on the use of an EpiPen or of cardio-pulmonary resuscitation then there was opportunity to ask a follow-up question. To suggest that the meeting was left with the impression that cardio-pulmonary resuscitation could be replaced with an EpiPen was a subjective interpretation which the company refuted. There was no discussion about cardio-pulmonary resuscitation.

Syner-Med rejected the view that it had been negligent, or that it had a duty to supply additional corrective information to the meeting. There was nothing that required correction and the audience requested no additional information. All the information, claims and comparisons at the meeting over which the company had control were accurate, balanced and fair and did not mislead. Syner-Med strenuously refuted the allegation that it had breached Clauses 7.2, 7.9 or 7.10.

Syner-Med provided details of the three speakers and their presentations and of the company employees who were present.

None of the slides presented by the speakers were provided by the company. A background template was supplied that was used by two speakers. Each speaker's presentation represented their own area of experience, knowledge or clinical research. The company did not contribute to the content of the presentations. Each presenter was invited to speak at the symposium based on the expert knowledge they could share with the audience.

As was very evident from the slides, the symposium was educational and not promotional. The focus was on iv iron management and was not product specific. There were no brand names used in any of the three sets of slides.

The presentation referred to by the complainant was entitled 'Using evidence to inform change in practice: Anaemia management' and covered recognition that evidence was required to change clinical practice and identification of the need to change current practice to facilitate a growing need to treat patients with iv iron infusions. All data referred to by the speaker was collected whilst she was employed as a nurse consultant. The tone of the presentation was educational with emphasis on changing practice to meet the needs of patients and changing service delivery.

PANEL RULING

The Panel noted that Syner-Med had sponsored the lunchtime meeting in question; one of the speakers acted as a consultant to Syner-Med on a part-time basis. Syner-Med had supplied two of the speakers with slide templates and ten of Syner-Med's staff had attended the meeting. Syner-Med submitted that although the meeting was about chronic renal disease and the future of iv iron treatment, it was not about Syner-Med's product Venofer in particular. One of a speaker's slides referred to iv iron sucrose but the presentation appeared to be about anaemia management and not Venofer *per se*. The question and answer at issue had occurred in the open session of the meeting in the last 10 minutes. It appeared that a delegate had asked about the safety issues of giving iv iron in the community and another delegate had stated that they had got around this legality by sending people away with an EpiPen. It was impossible for the Panel to know the exact question and answer or the context, ie the wider discussion, in which they had occurred. Nonetheless it appeared that the discussion was a general one and not about Venofer in particular. Syner-Med had submitted that the question was not specifically directed at Syner-Med's consultant and so she had had no reason to intervene.

The Panel noted that the Venofer summary of product characteristics (SPC) stated in Section 4.4, Special warnings and precautions for use, that parenterally administered iron preparations could cause allergic or anaphylactoid reactions which might be potentially fatal. Therefore treatment for serious allergic reactions and facilities with the established cardio-pulmonary resuscitation procedures should be available.

Given the implications for patient safety the Panel considered that it might have been helpful if someone had reminded the audience about cardio-pulmonary resuscitation during the discussion of the EpiPen. (EpiPen was injectable adrenalin for use in allergic emergencies). Given the lack of details, however, the Panel was satisfied that, on the balance of probabilities, the audience was not left with the impression that EpiPen could replace cardio-pulmonary resuscitation as alleged. No breach of Clauses 7.2, 7.9 and 7.10 was ruled.

Complaint received **17 July 2008**

Case completed **16 September 2008**

CASE AUTH/2146/7/08

PRIMARY CARE TRUST CHIEF PHARMACIST v SANOFI-AVENTIS

Plavix leavepiece and conduct of a representative

The chief pharmacist at a primary care trust complained about the promotion of Plavix (clopidogrel) by Sanofi-Aventis and about the conduct of its representative. Materials at issue were a leavepiece and a reply paid card.

The complainant was very concerned that the representative had left the leavepiece with a GP practice and in a meeting had verbally linked The Reduction of Atherothrombosis for Continued Health (REACH) registry study with a lifelong need for Plavix. The complainant submitted that the output from the REACH registry gave no grounds for choosing one antiplatelet over another.

The complainant rather suspected that the detail aid should have been withdrawn from use as she had received a later version via the co-marketer, Bristol-Myers Squibb. This did not refer to Plavix whereas the earlier version contained the SPC despite not naming the product in the body of the text. However, the complainant did not feel that it was an innocent mistake in view of the conversations.

The complainant considered that it was an example of misleading and unwarranted promotion.

The detailed response from Sanofi-Aventis is given below.

The Panel noted that the REACH registry sought to compile an international data set to extend knowledge of atherothrombotic risk factors and ischaemic events in the outpatient setting. The registry, supported by Sanofi-Aventis and Bristol-Myers Squibb, provided an opportunity to measure both ischaemic events rates and use of risk reduction therapies in a large population.

The Panel examined the detail aid used by the representative. The front page described the protection offered by Plavix compared with aspirin. The next two pages (double page spread) described the REACH registry and data relating to the risk of cardiovascular death, myocardial infarction (MI), stroke or hospitalisation for other atherothrombotic events within the first year. The next double page spread set out details of a patient and asked how that patient should be treated followed by information from CAPRIE which showed a relative risk reduction of 23% in the subgroup of patients who had peripheral arterial disease or stroke and previous MI. The detail aid stated that these benefits were maintained for up to 3 years and that 26% of patients in CAPRIE fitted the REACH registry profile, with vascular disease in more than one location. A red line ran across the bottom of all of the pages of the detail aid seemingly linking them together. One each right hand page and on the front and back pages, the line incorporated the Plavix product logo. In that regard the Panel considered that the double page spread detailing the REACH registry could be seen as linking that study to the use of Plavix.

The Panel noted that in his presentation the representative had introduced himself and stated that he wanted to talk about Plavix in atherothrombosis. The representative then referred to the REACH registry using the detail aid which featured the Plavix product logo, he then described the CAPRIE trial and concluded the presentation by referring back to the REACH registry data in the detail aid, confirming that patients with vascular disease in two or three locations would be ideal targets for Plavix. Each attendee was given a REACH leavepiece which included the prescribing information for Plavix.

The Panel noted that the representatives' briefing document stated under key messages that 'REACH supports the use of Plavix within the current strategy in the management of the multi-vascular patient with established atherothrombosis'. In the Panel's view this was misleading as it directly associated the REACH registry with Plavix. The REACH registry established the need for treatment in general whilst the CAPRIE study supported the use of Plavix in particular. The briefing document mixed up these two messages and thus 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 it was impossible to know exactly what had been said at the meeting. Nonetheless, bearing in mind the briefing material and given the structure and content of the Plavix detail aid and of the representative's presentation, the Panel considered that on the balance of probabilities, attendees at the meeting would be left with the impression that the REACH registry supported the use of Plavix *per se*. This impression would be strengthened by the use of the REACH leavepiece which incorporated the prescribing information for Plavix. The Panel considered that it was misleading to link the REACH registry data to the use of Plavix in particular. A breach of the Code was ruled.

The Panel considered that the representative had,

by following the briefing material and using the detail aid and leavepiece, structured his presentation such that a misleading impression had been given with regard to the REACH registry and Plavix. Although the representative had used material provided by the company and followed company instructions all the relevant requirements of the Code had not been complied with. Thus a further breach was ruled.

The chief pharmacist at a primary care trust complained about the promotion of Plavix (clopidogrel) by Sanofi-Aventis and about the conduct of its representative. Materials at issue were a leavepiece and a reply paid card (both referenced PLA07/1081).

Plavix was an antiplatelet medicine indicated for the prevention of atherothrombotic events in patients suffering from myocardial infarction (MI) (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. It was also indicated for patients suffering from acute coronary syndrome in line with the conditions set out in the summary of product characteristics (SPC).

COMPLAINT

The complainant was very concerned that a Sanofi-Aventis representative had left the leavepiece with a GP practice. He also verbally linked The Reduction of Atherothrombosis for Continued Health (REACH) registry study with a lifelong need for Plavix. The complainant had confirmed that this was the impression given by the representative at a practice meeting with all five doctors. The output from the REACH registry gave no grounds for choosing one antiplatelet over another.

The complainant rather suspected that the detail aid should have been withdrawn from use as she had received a later version via the co-marketer, Bristol-Myers Squibb. This did not refer to Plavix whereas the earlier version contained the SPC despite not naming the product in the body of the text. However, the complainant did not feel that it was an innocent mistake in view of the conversations.

The complainant considered that it was an example of misleading and unwarranted promotion.

When writing to Sanofi-Aventis, the Authority asked it to respond in relation to Clauses 7.2, 15.2 and 15.9 of the 2008 Code which were the same as the 2006 Code.

RESPONSE

Sanofi-Aventis submitted that the REACH registry was an epidemiological study that explored the risk of events and management of patients with atherothrombosis. The registry was independently run and sponsorship was provided by Sanofi-Aventis and Bristol-Myers Squibb. Baseline prevalence data were published in JAMA in 2006 and one-year follow-up data in early 2007 (also in JAMA). This registry was of major importance as it was the largest and most current assessment of the burden of atherothrombotic disease. It was not designed to investigate the effectiveness of any individual therapeutic agent and no such data had been reported from the registry.

The representative had been a pharmaceutical sales representative for many years including ten years with Sanofi-Aventis. He was trained on the Code at his initial training course with Sanofi-Aventis and via the company 'I-Learn' training system, to which he had continuous access as a reference tool. He had passed his ABPI examination and it was understood that there had been no previous history connected with his conduct against the Code, either in Sanofi-Aventis or with his previous employer.

The representative had been trained on Plavix in two days of on-line coursework with an on-line assessment, three days of classroom tuition with a written assessment and a series of practical role play assessments taking into account a variety of scenarios and customer groups. He completed his training successfully. In addition, he attended a two day refresher course at which he received additional training around clinical data relating to Plavix. He had successfully passed the course assessments.

The representative attended the practice to provide lunch and deliver a presentation, prior to its internal weekly meeting. According to the representative, the meeting was attended by five GPs, two nurses, the practice pharmacist, the practice manager and his assistant. The representative started his presentation at about 1.05pm and, after introducing himself, he explained that he wanted to talk about Plavix and its use in atherothrombosis using the Plavix primary care detail aid (PLA07/1601) to support his talk. From his recollection, the group was positive towards Plavix and one doctor explained his satisfaction towards its lack of side effects. The doctor also confirmed that the hospital requested that patients stayed on Plavix for 12 months before being discharged. The representative continued the discussion by highlighting the two indications for Plavix: acute coronary syndrome for which 12 month treatment was appropriate and atherothrombosis which was what he wanted to discuss.

The representative then introduced the REACH registry data from the sales aid. From recollection he explained that from the data, those patients with disease in one vascular location, had a 1 in 10 likelihood of a further event or hospitalisation within the next 12 months. This, however, increased to a 1 in 5 chance when a patient had disease in two locations. He confirmed that patients within the REACH registry were on conventional therapy including ACE inhibitors, beta blockers, statins and

aspirin, and despite this, these patients went on to have further events or were hospitalised in the next 12 months.

The representative then introduced the CAPRIE trial, a comparison of Plavix and aspirin in 19,185 patients. From recollection, he explained that the outcome of the study was that there was a 9% relative risk reduction in favour of Plavix over aspirin in preventing further MI, stroke or vascular death. He recalled that the group felt that these were reasonable results but was concerned about the cost of Plavix compared with aspirin in a large group of patients.

The representative then explained that in a subgroup analysis of the CAPRIE trial looking at patients with peripheral arterial disease or stroke and previous MI that the relative risk reduction was significantly greater than in the overall trial. This information received a positive response from those at the meeting.

He concluded the presentation by referring back to the REACH registry data in the sales aid, confirming that patients with vascular disease in two or three locations would be ideal targets for the use of Plavix, which the group confirmed it would consider. He then thanked the group for attending and gave each doctor a copy of the REACH leavepiece (PLA07/1081), which included prescribing information for Plavix. The representative left the surgery at about 1.15pm.

Overall, the account of the presentation given by the representative was very much in line with his previously observed customer interactions. His usual style of customer communication contained a high level of information delivery, in the structure set out within the sales aid with a consistent approach of maintaining the discussion in line with the marketing brief.

All sales representatives who promoted Plavix were comprehensively trained and briefed on the product and therapy area.

As stated previously the REACH registry was an epidemiological study that explored the risk of events and use of several therapies in patients with atherothrombosis. It did not, as the complainant rightly stated, give grounds for one antiplatelet to be used over another as it neither captured the use of specific agents nor was designed to explore therapeutic effect. This had been communicated clearly and consistently in the material used by the representatives and in the training they had received. This was supported by the information contained in the leavepiece and memorandum and in all subsequent briefing material: training material (PLA07/1502), section 8-9; key message brief (PLA07/1245), May 07; key message brief (CV07/1177), Nov 07; resource guide (PLA07/1578), Dec 07 and brand book (CV08/1041), May 08.

The basis for the promotion of the efficacy of Plavix in patients with atherothrombosis was the CAPRIE study, as explicitly included in all the above materials. Throughout these materials, REACH was used as the substantiation for statements on the burden of disease and it was never used to back up claims or statements regarding Plavix. The briefing document on the publication of REACH 1-year results commented that 'REACH supports the use of Plavix…' immediately prior to presenting the registry results and then followed this, separately, by referring to Plavix efficacy in the CAPRIE study. The need to 'tie back' the results of the registry to 'how Plavix can help protect these patients' was specifically referred to in the concluding section – which would clearly be unnecessary if the registry was presented as having itself incorporated Plavix data or usage.

The leavepiece left by the representative and the supporting briefing memorandum (PLA07/1147) were reviewed, approved and certified in March 2007. The theme of this item was that the REACH registry provided evidence of the burden of disease and the increasing risk of atherothrombotic events in patients with atherothrombosis in relation to number of vascular beds affected. This item was no longer in use and had not been superseded.

The promotional aid used in the meeting was a Plavix primary care detail aid (PLA07/1601) and the content clearly distinguished between the burden of disease, as shown by REACH, and the effect of Plavix on patients with atherothrombosis, as shown by CAPRIE.

Sanofi-Aventis explained that the reason one leavepiece had prescribing information [referred to as 'the SPC' by the complainant] and one subsequently presented by Bristol-Myers Squibb (PLA07/1361) did not, was that they were developed for two very different audiences. The leavepiece left by the representative was for use with prescribers during detailed discussion on Plavix, to provide more detail on REACH and the burden of disease, and also to allow them to request additional information if so desired. When the leavepiece was developed, it was considered that prescribing information would be appropriate as it was to be used in a detailed Plavix sales call with prescribers. In this context, and given that prescribing information was by its nature, non-promotional and contained no product claims, this was a conservative view taken with the intention of providing appropriate information in keeping with the spirit of the Code. Sanofi-Aventis noted that the rest of the leavepiece did not refer to Plavix, nor was Plavix livery or typography used in this item.

The separate REACH item with no prescribing information was developed for use by Sanofi-Aventis/Bristol-Myers Squibb market access/healthcare teams for use with non-prescribers to stimulate a dialogue on the burden of disease at a population level and it was deemed that prescribing information was not necessary due to the different context in which this item was to be

used.

In summary, Sanofi-Aventis took great care to appropriately train and brief its representatives and develop materials which accurately reflected the content and implications of the REACH registry. Active consideration was given to the context and audience for each of the materials in question, with reference to both the letter and spirit of the Code. The detailed account of the meeting from the representative did not support the complainant's allegations that he misled his audience. Overall, Sanofi-Aventis believed that high standards had been maintained, both by the representative and the company in general, and the materials used in the relevant training, briefing and sales activities had been constructed to avoid misleading the recipient and/or customers. Any allegation of breaches of Clauses 7.2, 15.2 and 15.9 was refuted.

PANEL RULING

The Panel noted that the REACH registry sought to compile an international data set to extend knowledge of atherothrombotic risk factors and ischaemic events in the outpatient setting. Patients aged ≥45 years with at least 3 atherothrombotic risk factors or documented cerebrovascular coronary artery or peripheral arterial disease were to be involved. The REACH registry offered an opportunity to provide a better understanding of the prevalence and clinical consequences of atherothrombosis in the outpatient setting in a wide range of patients from different parts of the world. The REACH registry provided an opportunity to measure both ischaemic events rates and use of risk reduction therapies in a large population. Sanofi-Aventis and Bristol-Myers Squibb supported the registry.

The Panel examined the detail aid used by the representative (PLA07/1601). The front page described the protection offered by Plavix compared with aspirin. The next two pages (double page spread) described the REACH registry and data relating to the risk of cardiovascular death, MI, stroke or hospitalisation for other atherothrombotic events within the first year. The next double page spread set out details of a patient and asked how that patient should be treated followed by information from CAPRIE which showed a relative risk reduction of 23% in the subgroup of patients who had peripheral arterial disease or stroke and previous MI. The detail aid stated that these benefits were maintained for up to 3 years and that 26% of patients in CAPRIE fitted the REACH registry profile, with vascular disease in more than one location. A red line ran across the bottom of all of the pages of the detail aid seemingly linking them together. One each right hand page and on the front and back pages, the line incorporated the Plavix product logo. In that regard the Panel considered that the double page spread detailing the REACH registry could be seen as linking that study to the use of Plavix.

The Panel noted the structure of the presentation given by the representative. Sanofi-Aventis had submitted that the representative had introduced himself and stated that he wanted to talk about Plavix in atherothrombosis. The representative then referred to the REACH registry using the detail aid which featured the Plavix product logo, he then described the CAPRIE trial and concluded the presentation by referring back to the REACH registry data in the detail aid, confirming that patients with vascular disease in two or three locations would be ideal targets for Plavix. Each attendee was given a REACH leavepiece which included the prescribing information for Plavix.

The Panel noted that the representatives' briefing document (PLA-07/1147) stated under key messages that 'REACH supports the use of Plavix within the current strategy in the management of the multi-vascular patient with established atherothrombosis'. In the Panel's view this was misleading as it directly associated the REACH registry with Plavix. The REACH registry established the need for treatment in general whilst the CAPRIE study supported the use of Plavix in particular. The briefing document mixed up these two messages and thus 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 it was impossible to know exactly what had been said at the meeting. It appeared that the complainant had not been present. Nonetheless, bearing in mind the briefing material and given the structure and content of the Plavix detail aid and of the representative's presentation, the Panel considered that on the balance of probabilities, attendees at the meeting would be left with the impression that the REACH registry supported the use of Plavix *per se*. This impression would be strengthened by the use of the REACH leavepiece which incorporated the prescribing information for Plavix. The Panel considered that it was misleading to link the REACH registry data to the use of Plavix in particular. A breach of Clause 7.2 was ruled.

The Panel considered that the representative had, by following the briefing material and using the detail aid and leavepiece, structured his presentation such that a misleading impression had been given with regard to the REACH registry and Plavix. Although the representative had used material provided by the company and followed company instructions all the relevant requirements of the Code had not been complied with. Thus a breach of Clause 15.2 was ruled.

Complaint received **23 July 2008**

Case completed **1 October 2008**

CASE AUTH/2147/7/08

GLAXOSMITHKLINE v SANOFI PASTEUR MSD

Gardasil press release and agency emails

GlaxoSmithKline complained about materials issued by Sanofi Pasteur MSD and activities undertaken on behalf of the company following the Department of Health's (DoH) announcement to use Cervarix (GlaxoSmithKline's human papillomavirus (HPV) vaccine) for the national HPV immunisation programme for the prevention of cervical cancer, instead of Sanofi Pasteur MSD's vaccine, Gardasil. Cervarix and Gardasil were the only two vaccines licensed for the prevention of cervical cancer. At issue were a press release, entitled 'School girls in the UK will not benefit from the World's leading four type human papillomavirus (HPV) vaccine, Gardasil', issued on 18 June following the DoH's announcement about its choice of vaccine, and an email containing press coverage sent by Sanofi Pasteur MSD's public relations (PR) agency.

GlaxoSmithKline alleged that the claim in the press release that Gardasil provided 'unmatched cervical cancer protection' invited a comparison of Gardasil with Cervarix, was all embracing and there was no evidence from head-to-head studies to substantiate it. GlaxoSmithKline's head-to-head study was still ongoing and results were not yet available. The cross-study comparisons cited to support the claim were fundamentally flawed as it was not possible to directly compare the individual results as the populations, methodology and analyses varied between the studies.

In clinical trials, the two vaccines had shown similar, efficacy against cervical pre-cancerous lesions and this was reflected in the Cervarix summary of product characteristics (SPC).

The detailed response from Sanofi Pasteur MSD is given below.

The Panel noted that the press release stated 'We regret that school girls in the UK, unlike most of their peers in Western Europe, the USA, Australia, New Zealand and Canada, will not benefit from the unmatched cervical cancer protection and additional benefits provided by the World's leading HPV vaccine, Gardasil'. The Panel considered that, within the context of the press release, the claim implied that Gardasil had been unequivocally proven to be clinically superior to Cervarix with regard to cervical cancer protection. The SPCs for Gardasil and Cervarix reported high percentage efficacy rates for both products. There was no head-to-head data, however, and so it was not known if any of the differences between the products, based on the figures published in their respective SPCs, were clinically or statistically significant.

The Panel considered that the claim for unmatched cervical cancer protection was misleading, unsubstantiated and exaggerated. Breaches of the Code were ruled.

GlaxoSmithKline made three allegations regarding the claim 'In addition to protection from cervical cancer, Gardasil provides protection from precancerous cervical, vulval and vaginal lesions (an extension to the licence following a recent Commitee for Medicinal Products for Human Use (CHMP) positive opinion) and from genital warts caused by virus types targeted by the vaccine. The four HPV types 6, 11, 16 and 18 together cause the vast majority of cervical cancer and other HPV-related genital disease'.

Firstly GlaxoSmithKline noted that Gardasil was not licensed for the prevention of vaginal pre-cancerous lesions as implied by the claim; a CHMP positive opinion did not equate to a licence extension.

Secondly GlaxoSmithKline submitted that the second sentence of the claim, and indeed the whole press release, was intended to make the reader believe that enhanced cervical cancer protection was offered by choosing a vaccine with four antigens compared with a vaccine with two, when in fact the additional two HPV types (6 and 11) had no impact on cervical cancer protection. The word 'together' perpetuated the misconception. This grouping of HPV types was continued throughout the press release, misleading readers into believing all four types had an impact on cervical cancer.

Thirdly GlaxoSmithKline alleged that the implication that Gardasil could prevent the 'vast majority' of cervical cancer was falsely reassuring, exaggerated the potential benefits of Gardasil in cervical cancer protection, and could affect future uptake of the UK cervical screening programme. HPV 16 and 18 – the two cancer-causing HPV types that Gardasil protected against – did not account for the 'vast majority' of cervical cancer. HPV 16 and 18 caused 70% of cervical cancers, which although substantial did not equate to the vast majority; the common understanding of 'vast majority' would lead people to believe that HPV 16 and 18 caused over 90% of cervical cancers. Sanofi Pasteur MSD had attempted to justify the use of 'vast majority' since it 'related to the diseases, not the vaccine'. However, it was naïve to suggest that the reader would not link this statement with the protection offered by the 'four type (HPV 6, 11, 16, 18) HPV vaccine, Gardasil'. Furthermore, regardless of whether or not the sentence related to the vaccine or the disease, it was inaccurate to say that '6, 11, 16 and 18 together caused the vast majority of cervical cancers…'.

GlaxoSmithKline alleged that the claim, in the context of the rest of the press release, was misleading and exaggerated.

The Panel noted that GlaxoSmithKline was concerned that the claim 'In addition to protection from cervical cancer, Gardasil provides protection from precancerous cervical, vulval and vaginal lesions (an extension to the licence following a recent CHMP positive opinion) …' implied that Gardasil was licensed for the prevention of vaginal pre-cancerous lesions which was not so. Sanofi Pasteur MSD submitted that the matter was satisfactorily dealt with in inter-company dialogue and the archived copy of the press release had been altered. The sentence in the amended copy was the same as the original version except that the text in brackets stated '(the subject of a CHMP positive opinion)'.

In the Panel's view the amended copy of the press release did not substantially change the message; some readers would continue to assume that Gardasil could be used to provide protection from pre-cancerous vaginal lesions and that the product was so authorized. This was not so. Such an implication was inconsistent with the Gardasil SPC and misleading and a breach was ruled. The Panel noted that a press release should not be promotion of a medicine and thus on these narrow grounds the Panel ruled no breach of the Code.

In the Panel's view the second sentence at issue 'The four HPV types 6, 11, 16 and 18 together cause the vast majority of cervical cancer and other HPV-related genital disease' was ambiguous. Some readers might assume that the claim implied that all four HPV types played a role in cervical cancer which was not so. In that regard the claim was misleading and a breach was ruled.

The second sentence stated that the four HPV types together caused the vast majority of cervical cancer and other HPV-related genital disease. In the Panel's view the claim was ambiguous; some readers would assume that the four HPV types caused the vast majority of cervical cancer. GlaxoSmithKline had submitted that HPV 16 and 18 caused 70% of cervical cancers and Sanofi Pasteur MSD submitted it was 75%. In the Panel's view the use of 'vast majority' to describe 70% or 75% was exaggerated as alleged. It was difficult to know exactly what figure constituted a 'vast majority' but in this instance the 30% or 25% of cervical cancers which were not caused by HPV 16/18 was a sizable minority. The Panel ruled a breach of the Code.

GlaxoSmithKline noted that the press release contained a number of statements relating to choice of HPV vaccine by governments/health authorities and health professional preferences, which were inaccurate, misleading and disparaged Cervarix and the DoH's choice of vaccine for the UK immunisation programme. The press release had six footnotes, three of which related to the following claims:

'In all other tenders awarded to date in Western Europe†, health authorities have chosen Gardasil for about 80% of the population covered'. (The footnote† stated 'Regional tenders in Italy, Spain, Sweden; a national tender in Switzerland'.)

GlaxoSmithKline submitted that the word 'chosen' in relation to tenders in this claim was of key importance. In order for there to be a choice, both vaccines had to have been licensed and able to submit a tender application.

Since it received its marketing authorization Cervarix had been awarded nearly two thirds of EU regional and national tenders that had occurred. At the time of the UK tender announcement, Cervarix had been awarded 19 of 29 EU tenders, excluding the UK and Denmark.

Even if one used the countries 'selected' by Sanofi Pasteur MSD and highlighted in the footnote, Cervarix had been awarded the majority; winning 16 out of 23 tenders in Italy, Spain and Sweden. Cervarix was not licensed in Switzerland and so it was inappropriate to use it to support a statement where choice was explicit. Furthermore, GlaxoSmithKline did not agree that it was appropriate to clarify the regulatory status in Switzerland in a footnote to another statement.

Although Sanofi Pasteur MSD had stated that it considered it more accurate not to quote the number of tenders awarded (as some were local or regional and covered small populations) but rather to quantify in terms of the proportion of the population covered, this was at stark odds with the press release which was very much focussed on 'choice'; indeed 'choice' was used four more times.

- **'Two years after its first launch in June 2006, Gardasil is today the HPV vaccine of choice across the world…'.**
- **'…Gardasil will continue to be the HPV vaccine of choice for girls and women worldwide'.**
- **'Where doctors can choose between the two vaccines, more than 9 out of 10 doctors worldwide choose Gardasil'.**
- **'The tender decision made by the UK authorities choosing a two-type (16/18) HPV vaccine for their immunisation campaign means that the girls in this campaign will not benefit from…'.**

GlaxoSmithKline suggested that Sanofi Pasteur MSD selected 'population covered' because the statement 'in all other tenders awarded to date in Western Europe, health authorities have chosen Cervarix', would have been less appealing for the purposes of the press release.

This claim used by Sanofi Pasteur MSD could not be substantiated and was misleading; and although the company claimed to have 'robust evidence' to support it, it had not been provided.

'Gardasil is, or will be, used exclusively for campaigns in the USA, Australia, New Zealand,

Canada and Switzerland‡'. (The footnote‡ stated 'The two-type vaccine has not yet been approved in Canada and Switzerland to the best of our knowledge'.)

GlaxoSmithKline submitted that the claim implied that health service providers in all five countries had actively selected Gardasil over Cervarix, when in fact Cervarix was not actually licensed in three of the countries; following inter-company dialogue, Sanofi Pasteur MSD had stated that it would correct the footnote to include the USA. Nevertheless, to attempt to clarify the regulatory situation, and the true meaning of the statement, by the use of a footnote (positioned eight paragraphs away) was inadequate.

Sanofi-Pasteur MSD had noted that unlike the previous claim which had used the word 'chosen', this claim used '*used*' which did not imply any process of selection. However, a similarly misleading claim occurred earlier in the press release: 'Countries like Australia, New Zealand, *Canada*, France and *Switzerland* have *chosen* Gardasil preferentially or exclusively for their vaccination campaigns' (emphasis added). Again, Canada and Switzerland were cited as countries that had chosen Gardasil, when in fact no choice was available as Cervarix was not licensed in either. GlaxoSmithKline submitted that Sanofi Pasteur MSD's contradictory explanation exposed its clear intention to mislead.

'Where doctors can choose between the two vaccines§, more than 9 out of 10 doctors worldwide choose Gardasil'. (The footnote§ read 'Germany, France and Belgium in Western Europe'.)

Sanofi-Pasteur MSD had stated that although the footnote referred to only three countries, the claim was not confined to Germany, France and Belgium – these were cited as examples in Western Europe, Sanofi Pasteur MSD's territory. This was misleading and exaggerated. Again no evidence had been provided to support individual doctor choice in a global context.

GlaxoSmithKline alleged that the claims were misleading, exaggerated and incapable of substantiation. Furthermore, their use in the context of the press release about the 'UK authorities choosing a two-type (16/18) HPV vaccine', disparaged Cervarix and the DoH choice of vaccine.

The Panel noted that the selection of vaccine by a country/region for use was complicated. The basis of choice could be one of a number of options depending on the regulatory status of the vaccines in the country. Firstly a choice between two licensed products Gardasil and Ceravix, secondly a choice between a licensed product (Gardasil) and an unlicensed product (Ceravix) and thirdly a choice between the only licensed vaccine (Gardasil) or nothing. A fourth factor was also relevant given the differences in indications for the products ie did the country/region only want to vaccinate against cervical cancer or against cervical cancer and genital warts. The Panel did not consider that the press release was sufficiently clear about the options available and the regulatory status of the products at the time the tender decisions were made. The Panel considered it was really important to include very clear information about the factors that might have influenced the tendering decisions round the world. Simple claims were not sufficient given the complexity of the situation.

The three other claims at issue all relied on footnotes to provide clarification. The supplementary information to the Code stated '… that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like'.

In the claim 'In all other tenders awarded to date in Western Europe, health authorities have chosen Gardasil for about 80% of the population covered', Western Europe was asterisked to a footnote 'Regional tenders in Italy, Spain, Sweden; a national tender in Switzerland'. The Panel considered that this was misleading as Italy, Spain, Sweden and Switzerland were a small part of Western Europe. Further, Cervarix was not licensed in Switzerland and so in that country Gardasil was chosen instead of nothing; in the Panel's view the majority of readers would not realise this. The Panel considered that the claim was misleading and in that regard could not be substantiated. Breaches of the Code were ruled.

The claim 'Gardasil is, or will be, used exclusively for campaigns in the USA, Australia, New Zealand, Canada and Switzerland' relied upon the footnote 'The two-type vaccine has not yet been approved in Canada and Switzerland to the best of our knowledge'. The Panel noted its comments above regarding choice and the reader's knowledge of product availability. As above the Panel considered that the claim was misleading and a breach of the Code was ruled.

The claim 'Where doctors can choose between the two vaccines, more than 9 out of 10 doctors worldwide choose Gardasil' relied on the footnote 'Germany, France and Belgium in Western Europe'. The Panel considered that the claim was misleading in its reliance upon a footnote for clarity. The Panel further considered that it was exaggerated to use data from only Germany, France and Belgium in a worldwide claim. Breaches of the Code were ruled. The claim had not been substantiated by the data relating solely to Germany, France and Belgium. Further, as this data was confidential and not to be provided to GlaxoSmithKline it could not be considered by the Panel. A breach of the Code was ruled.

The Panel considered that the claims at issue undermined the DoH's choice of Cervarix and thus disparaged both the product and the DoH. Breaches

of the Code were ruled.

GlaxoSmithKline noted that there was no direction on the Sanofi Pasteur MSD's website or press release itself that it was intended for medical journalists only; it appeared to have been distributed widely to both medical and consumer press. Although company press releases could be distributed to the consumer media when appropriate, particular care must be taken not to promote prescription only medicines to the public and the information presented must be factual and balanced. This was clearly not the case. The purpose of the press release appeared to be to encourage the public to question the choice of vaccine by the DoH and invite them to specifically request Gardasil, which was mentioned 13 times.

In defence of this allegation, Sanofi Pasteur MSD had stated that HPV vaccination was not available outside the national programme. However, Sanofi Pasteur MSD would know that both vaccines were prescribed privately and, although the DoH's Green Book stated that 'vaccination is not routinely recommended for those aged 18 years or over', HPV vaccination could be prescribed on a case-by-case basis to individual women who might benefit.

GlaxoSmithKline alleged the distribution of the press release to consumer media, and therefore the public, was in breach of the Code.

In addition to the press release Sanofi Pasteur MSD distributed, via a PR agency, two emails following the DoH announcement. The first email contained the press release and was sent on 18 June, the day of the DoH announcement; the second contained a summary of the press coverage relating to the tender announcement and was sent the following day. Although the email covered a broad range of media types and publications, GlaxoSmithKline disagreed with Sanofi Pasteur MSD's statement '…the synthesis of the media coverage was not selective'.

Only statements from patient advocacy groups who would be expected to have an interest in protection from genital warts were included: BASHH (British Association for Sexual Health and HIV), Brook (the UK's leading provider of sexual health services and advice for the under 25s) and the Terrence Higgins Trust; the absence of a cervical cancer/cancer advocacy group statement was striking and significant.

Furthermore, the PR agency was careful to note the negative media coverage: 'a number of publications have raised concerns about the Department's decision including The Times, BBC Online, PA News, Reuters, Channel Four, Yorkshire Post, Newcastle Chronicle, Cheshire News'. It was clear that the email was intended to reinforce the messages in the press release.

In addition, of the 21 national and regional articles highlighted in the email, 16 appeared to have been significantly influenced by the Sanofi Pasteur MSD press release, containing direct content/quotes or similar misinformed and misleading messages to those discussed earlier.

In addition to the media, the PR agency distributed the Sanofi Pasteur MSD press release and press coverage in unsolicited emails to health professionals. Due to their surprise at receiving such a press release from Sanofi Pasteur MSD, and their concerns of the impact that this might have on the national immunisation programme, a number of health professionals had contacted GlaxoSmithKline anonymously.

The way in which both emails were used by the PR agency made them promotional and thus subject to the Code. Sanofi Pasteur MSD claimed the distribution was limited to a small group of individuals and organisations who received regular media updates about HPV vaccination. However, this was at odds with GlaxoSmithKline's understanding, and Sanofi Pasteur MSD had not provided any evidence in support of the explicit prior permission which it had received from the health professional recipients. GlaxoSmithKline alleged that the unsolicited distribution of these emails to health professionals breached the Code.

The Panel noted that the press release had been issued to the consumer press. It was not unacceptable to issue press releases about prescription only medicines to the consumer press providing that the information contained therein was factual and balanced. Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine.

The Panel considered that, *inter alia*, describing Gardasil as the World's leading four-type HPV vaccine, with unmatched cervical cancer protection, would encourage patients to ask for the medicine. A breach of the Code was ruled.

With regard to whether the emails were unsolicited, the Panel noted Sanofi Pasteur MSD's submission that a relationship existed between it and the recipients and that they had all received correspondence of a similar nature before. The company had further submitted that the emails were sent to specific individuals because of their role in providing Sanofi Pasteur MSD with advice as well as being experts in handling the media. The Panel was concerned that no explanation had been given in the emails that the PR agency sending the material was acting on behalf of Sanofi Pasteur MSD. Nor did the email state that the audience were those who had a role in providing Sanofi Pasteur MSD with advice. It appeared from Sanofi Pasteur MSD's response that the emails were sent to health professionals who were, in some capacity, acting as consultants to the company. On that basis the Panel considered that the emails were not unsolicited promotional material as alleged. No breach of the Code was ruled.

During its consideration of this matter, the Panel noted with concern Sanofi Pasteur MSD's submission that emails had been sent out by its PR agency without formal copy approval by the company. This was wholly unacceptable; pharmaceutical companies could not delegate their responsibilities under the Code to a third party.

GlaxoSmithKline submitted that Sanofi Pasteur MSD's activities and materials provided evidence of the coordinated campaign, designed to question the robustness of the DoH's decision in its choice of vaccine for the immunisation programme and leave the reader believing that the UK government, unlike most other health authorities, had chosen a less effective vaccine to protect UK girls and women. The widespread distribution of material to the medical and consumer media, health professionals and other organisations would encourage health professionals and the public to question the DoH's vaccine choice and ask for Gardasil, which was mentioned by name 13 times.

GlaxoSmithKline stated that Sanofi Pasteur MSD's campaign had a number of potentially serious consequences. Firstly, the uptake of immunisation was likely to be affected, reducing the number of girls who could benefit from vaccination to prevent cervical cancer. Secondly, for those who had been vaccinated against HPV 16 and 18, the mistaken belief that they would be protected against the 'vast majority' of cervical cancers might lead to a false sense of security and reduce future cervical screening attendance, which was already in decline in younger age groups. This would increase the chances of a pre-cancerous lesion progressing to cervical cancer.

In addition to the clauses cited above GlaxoSmithKline alleged that Sanofi Pasteur MSD had breached the Code in that high standards had not been maintained to the extent that its activities brought discredit upon, and seriously undermined confidence in the pharmaceutical industry and its ability to self-regulate in breach of Clause 2.

The Panel noted that GlaxoSmithKline had requested that Sanofi Pasteur MSD issue a corrective letter. This was not a sanction available to the Panel. It was only available to the Appeal Board.

The Panel noted its rulings of breaches of the Code above. It considered that Sanofi Pasteur MSD had not been sufficiently clear about the situation and thus would cause further confusion in a complicated matter. Taking all the circumstances into account the Panel decided that high standards had not been maintained and a breach of the Code was ruled. On balance the Panel did not consider that the circumstances were in breach of Clause 2 which was used as a sign of particular censure.

GlaxoSmithKline UK Ltd complained about materials issued by Sanofi Pasteur MSD and activities undertaken on behalf of the company following the Department of Health's (DoH) announcement to use Cervarix (GlaxoSmithKline's human papillomavirus (HPV) vaccine) for the national HPV immunisation programme for the prevention of cervical cancer, instead of Sanofi Pasteur MSD's vaccine, Gardasil. Cervarix and Gardasil were the only two vaccines licensed for the prevention of cervical cancer. At issue were a press release, entitled 'School girls in the UK will not benefit from the World's leading four type human papillomavirus (HPV) vaccine, Gardasil', issued on 18 June following the DoH's announcement about its choice of vaccine, and an email containing press coverage sent by Sanofi Pasteur MSD's public relations (PR) agency. Inter-company dialogue had failed to resolve the issues.

By way of background, Sanofi Pasteur MSD submitted that HPV was a ubiquitous virus, with four genotypes (6, 11, 16 and 18) together known to cause approximately 75% of cervical cancers in Europe, 90% of genital warts, at least 50% of cases of high and low-grade cervical pre-cancerous lesions, and 43-62% of cases of vulval and vaginal pre-cancerous lesions. Cervical cancer was usually preceded by identifiable, pre-cancerous stages – CIN (cervical intraepithelial neoplasia). CIN was classified according to the extent of the penetration of abnormal epithelial cells into the cervical mucosa, where CIN 1 was the least severe with abnormal cells occupying the first third of the cervical mucosa and CIN 3 was the most severe with abnormal cells occupying the full thickness of the cervical mucosa. The CIN 3 label denoted severe dysplasia or carcinoma in situ (CIS). When the disease had penetrated the basement membrane of the cervical epithelium and moved into the underlying tissue, the cancer was termed 'invasive'. In practice, histologically it could be difficult to separate CIN 2 and 3; hence they were often considered together.

HPV vaccines stimulated the immune system, providing protection against diseases caused by the targeted HPV types. It was well recognised, for example by the World Health Organization (WHO), that there was no immunological correlate of short or long term protection for any HPV vaccine type. Therefore no correlation existed between immune response, in particular antibody levels, and efficacy against clinical disease due to HPV. Given the long time delay in the development of cervical cancers (up to 10 years or more from initial HPV infection), efficacy against cervical cancer was neither a feasible nor an ethical endpoint in clinical trials. The Gardasil phase 3 trials were designed to show efficacy against CIN 2/3 and CIS with high precision. This surrogate endpoint was recommended by a number of official bodies, including the WHO and the Food and Drug Administration (FDA), as the means to demonstrate vaccine efficacy since these lesions were the obligate and immediate precursors to invasive cancer.

The complaint was considered under the 2006 Code using the 2008 Constitution and Procedure.

Press release

1 'Unmatched cervical cancer protection'

COMPLAINT

The press release stated that Gardasil provided 'unmatched cervical cancer protection'. The claim invited a comparison of Gardasil with Cervarix, when there was no evidence from head-to-head studies to substantiate this all-embracing claim. GlaxoSmithKline's head-to-head study was still ongoing and results were not yet available.

GlaxoSmithKline acknowledged the data provided by Sanofi Pasteur MSD to justify this claim. However, the cross-study comparisons cited were fundamentally flawed as it was not possible to directly compare the individual results as the populations, methodology and analyses varied between the studies.

In clinical trials, the two vaccines had shown similar, excellent efficacy against cervical pre-cancerous lesions and this was reflected in the Cervarix summary of product characteristics (SPC). The primary end point analysis from a large study involving over 18,000 girls and women was tabulated in section 5.1: Cervarix provided 90.4% protection against HPV 16 and/or 18 cervical pre-cancerous lesions. However, this was an area of emerging scientific knowledge and several of the lesions were found to contain multiple HPV types (including non-vaccine types), which was unexpected and it was difficult to determine which HPV type had actually caused the lesion. Therefore, an additional analysis was conducted to determine vaccine efficacy against lesions likely to have been caused by HPV 16 and/or 18 and the SPC stated 'Based on this analysis there were no cases in the vaccine group and 20 cases in the control group (Efficacy 100%; 97.9% CI: 74.2; 100)'. In another study, involving approximately 750 girls and women, Cervarix had demonstrated similar efficacy (100%) which had been sustained for at least 6.4 years to date; this was the longest duration of protection reported for any HPV 16/18 vaccine.

GlaxoSmithKline alleged that the claim breached Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

Sanofi Pasteur MSD submitted that the extensive clinical trials programme for Gardasil had involved more than 30,000 subjects and contributed data that, in 2006, resulted in its fast track approval in the US and rapid approval in Europe. The pivotal phase 3 FUTURE studies were terminated early once it became clear that it was unethical for placebo recipients to remain unprotected when such an efficacious vaccine was available. In light of the high and sustained efficacy demonstrated by Gardasil, the independent Data and Safety Monitoring Board (DSMB) for the FUTURE studies recommended that all women receiving placebo should be offered the benefit of Gardasil. In contrast, Cervarix was licensed in Europe in late 2007 and, despite having been filed in the US in early 2007, the evaluation by the FDA was still on-going after GlaxoSmithKline had responded only very recently to a complete response letter sent by the FDA in December 2007.

Sanofi Pasteur MSD acknowledged that direct comparisons were not possible since populations, methodologies and analyses varied between studies, however it was also true that only Gardasil had robust and complete phase 3 data that was currently unmatched by any other cervical cancer vaccine.

Sanofi Pasteur MSD disagreed with GlaxoSmithKline that clinical trials had shown similar, excellent efficacy against cervical pre-cancerous lesions. GlaxoSmithKline referred to data from a study of 18,000 girls and women. However, to date it had only been able to communicate 15 month interim data from this phase 3 study, which were included in the Ceravix SPC. In the primary analysis, the observed efficacy of Cervarix against HPV 16/18-related CIN 2+ was 90.4% [95% CI: 53.4, 99.3]. Statistically significant efficacy was demonstrated against HPV 16-related CIN 2+ but not against HPV 18-related CIN 2+. Efficacy against HPV 16-related CIN 2+ was 93.3% (95% CI: 47.0, 99.9). Point estimate for efficacy against HPV 18-related CIN 2+ was 83.3% (95% CI: <0.0, 99.9).

In combined clinical trials, Gardasil had demonstrated a consistently high level of protection against high grade cervical cancer precursors that no other vaccine had been able to match. Data from three years of follow up were included in the SPC which showed that in the per protocol population the observed efficacy of Gardasil against HPV 16/18-related CIN 2/3 and CIS was 100% (95% CI: 92.9, 100).

Four year follow-up data was also available and, in the per protocol population, the observed efficacy of Gardasil against HPV 16/18-related CIN 2/3, CIS or worse was 98.2% (95% CI: 93.5, 99.8). Statistically significant efficacy was demonstrated against HPV 16-related CIN 2/3, 97.9% (95% CI: 92.3, 99.8) as well as against HPV 18-related CIN 2/3, 100% (95% CI: 86.6, 100).

Far from being an area of emerging scientific knowledge, as submitted by GlaxoSmithKline, Sanofi Pasteur MSD stated that there was now a wealth of clinical experience with Gardasil with more than 30 million doses distributed worldwide (by the end of June 2008), building on the strong data from large multinational trials. Sanofi Pasteur MSD also noted with interest that in its complaint, and which also formed the main content of a recent GlaxoSmithKline press release, GlaxoSmithKline referred to a phase 2 study which involved approximately 750 girls and women to attempt to

demonstrate a duration of sustained efficacy of at least 6.4 years. This was a small study which was insufficiently powered to demonstrate efficacy against the individual vaccine HPV types. This was in comparison to more than 20,000 women followed in combined studies of Gardasil that yielded the results described above. In addition, the Cervarix SPC stated that 'duration of protection has not fully been established'. In the absence of true head-to-head results, based on clinically meaningful efficacy endpoints, it was surprising that GlaxoSmithKline considered it permissible to claim that its study demonstrated the longest duration of protection reported for any vaccine against HPV 16 and 18. This was in itself misleading since, not only was the study inadequately powered, but it also inferred a comparison between the Cervarix phase 2 data and Gardasil phase 3 data which was not valid.

Considering the above data, Sanofi Pasteur MSD considered that the claim was fair, balanced and factual, readily substantiated and not exaggerated. Sanofi Pasteur MSD considered it was beyond dispute that the protection afforded by Gardasil was indeed unmatched. Consequently it refuted the allegation of breaches of Clauses 7.2, 7.4 and 7.10.

PANEL RULING

The Panel noted that the second paragraph of the press release stated 'We regret that school girls in the UK, unlike most of their peers in Western Europe, the USA, Australia, New Zealand and Canada, will not benefit from the unmatched cervical cancer protection and additional benefits provided by the World's leading HPV vaccine, Gardasil'. The Panel considered that, within the context of the press release, the claim implied that Gardasil had been unequivocally proven to be clinically superior to Cervarix with regard to cervical cancer protection.

The Panel noted that the SPCs for Gardasil and Cervarix reported high percentage efficacy rates for both products. There was no head-to-head data, however, and so it was not known if any of the differences between the products, based on the figures published in their respective SPCs, were clinically or statistically significant.

The Panel considered that the claim for unmatched cervical cancer protection was misleading, unsubstantiated and exaggerated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

2 Claim 'In addition to protection from cervical cancer, Gardasil provides protection from precancerous cervical, vulval and vaginal lesions (an extension to the licence following a recent CHMP positive opinion) and from genital warts caused by virus types targeted by the vaccine. The four HPV types 6, 11, 16 and 18 together cause the vast majority of cervical cancer and other HPV-related genital disease.'

COMPLAINT

GlaxoSmithKline noted that Gardasil was not licensed for the prevention of vaginal pre-cancerous lesions as implied by the claim; a CHMP positive opinion did not equate to a licence extension.

GlaxoSmithKline submitted that the second sentence of the claim, and indeed the whole press release, was intended to make the reader believe that enhanced cervical cancer protection was offered by choosing a vaccine with four antigens compared with a vaccine with two, when in fact the additional two HPV types (6 and 11) had no impact on cervical cancer protection. The word 'together' perpetuated the misconception. This grouping of HPV types was continued throughout the press release, misleading readers into believing all four types had an impact on cervical cancer.

Sanofi Pasteur MSD would know that the role of the specific HPV types in cervical cancer was poorly understood by health professionals and the public and so it was vital that any media messages intended for these audiences made it clear that HPV 6 and 11 in Gardasil did not add to the cervical cancer protection afforded by HPV 16 and 18.

Although Sanofi Pasteur MSD claimed there was no intention to suggest types 6 and 11 caused cervical cancer, and that it had simply referred to them in numerical order, it was the lack of a clear and explicit statement that HPV 6 and 11 caused genital warts and HPV 16 and 18 caused cervical cancer that made the claim misleading by omission. The paragraph could easily have been constructed to be clear and unambiguous by adding an introductory sentence such as 'HPV 16 and 18 cause cervical cancer and HPV 6 and 11 are responsible for genital warts'. This fundamental point was not clarified anywhere, despite the HPV types being repeatedly mentioned throughout.

GlaxoSmithKline alleged that the implication that Gardasil could prevent the 'vast majority' of cervical cancer was falsely reassuring, exaggerated the potential benefits of Gardasil in cervical cancer protection, and could affect future uptake of the UK cervical screening programme.

HPV 16 and 18 – the two cancer-causing HPV types that Gardasil protected against – did not account for the 'vast majority' of cervical cancer. HPV 16 and 18 caused 70% of cervical cancers, which although substantial did not equate to the vast majority; the common understanding of 'vast majority' would lead people to believe that HPV 16 and 18 caused over 90% of cervical cancers.

GlaxoSmithKline noted that Sanofi Pasteur MSD had attempted to justify the use of 'vast majority' since it 'related to the diseases, not the vaccine'. However, it was naïve to suggest that the reader would not link this statement with the protection offered by the 'four type (HPV 6, 11, 16, 18) HPV vaccine, Gardasil'. Furthermore, regardless of

whether or not the sentence related to the vaccine or the disease, it was inaccurate to say that '6, 11, 16 and 18 together caused the vast majority of cervical cancers…'.

GlaxoSmithKline alleged that the claim, in the context of the rest of the press release, was misleading and exaggerated in breach of Clauses 3.2, 7.2 and 7.10.

RESPONSE

Sanofi Pasteur MSD noted that, as agreed during inter-company dialogue, it had clarified the wording in the archive copy of the press release to distinguish that pre-cancerous vaginal lesions were the subject of a positive CHMP opinion and so the company was surprised that the allegation remained in the complaint.

Sanofi Pasteur MSD agreed that a positive CHMP opinion did not equate to a licence extension, but was the step before the licence extension was granted. However, the claim at issue did not state that this was the indication of Gardasil. Furthermore, in the notes to editors below, the precise regulatory status of the indication extension was described. Notwithstanding, inclusion of the fact that Gardasil could protect against pre-cancerous lesions of the vagina was acceptable in accordance with Clause 20.2 (2006 Code). Sanofi Pasteur MSD therefore also refuted this allegation of a breach of Clause 3.2.

With regard to the final sentence of the claim, there was no intention to suggest that HPV types 6 and 11 caused cervical cancer. The sentence was carefully constructed in order to state that the four types together caused the vast majority of HPV-related genital diseases, including cervical cancer which was specifically mentioned as it was the primary target for vaccination. When the four types were referred to together, logically, they were always referred to in numerical order (6, 11, 16 and 18); the order stated nothing about which types caused which diseases.

Sanofi Pasteur MSD submitted that the press release did not imply that Gardasil could prevent the vast majority of cervical cancer. The sentence describing its licensed indications was factual and stood alone. In addition, further detail was provided in the notes to editors. The sentence containing 'vast majority' came afterwards and clearly related to the diseases, not the vaccine.

Sanofi Pasteur MSD considered that the claim at issue was factual, capable of substantiation and did not imply anything about Gardasil, let alone exaggerate its potential benefits.

Sanofi Pasteur MSD noted that GlaxoSmithKline's final point regarding the statement focused on the phrase 'vast majority', alleging that it implied that Gardasil protected against the vast majority of cervical cancer. As stated above, the claim did not imply this. When taken together, however, Sanofi Pasteur MSD considered that in preventing 75% of cervical cancer and over 90% of genital warts, it was reasonable to state that 'The four HPV types 6, 11, 16 and 18 together cause the vast majority of cervical cancer and other HPV-related genital diseases'.

Consequently the company considered that that the claim did not refer to unauthorised indications, was not misleading and did not use superlatives. Sanofi Pasteur MSD therefore denied breaches of Clauses 3.2, 7.2 and 7.10.

PANEL RULING

The Panel noted that GlaxoSmithKline was concerned that the statement 'In addition to protection from cervical cancer, Gardasil provides protection from precancerous cervical, vulval and vaginal lesions (an extension to the licence following a recent CHMP positive opinion) …' implied that Gardasil was licensed for the prevention of vaginal pre-cancerous lesions which was not so. Sanofi Pasteur MSD had submitted that the matter was satisfactorily dealt with in inter-company dialogue and the archived copy of the press release had been altered. The Panel noted that the sentence in the amended copy was the same as the original version except that the text in brackets stated '(the subject of a CHMP positive opinion)'. GlaxoSmithKline had not referred to the inter-company dialogue on this point.

In the Panel's view the amended copy of the press release did not substantially change the message; some readers would continue to assume that Gardasil could be used to provide protection from pre-cancerous vaginal lesions and that the product was so authorized. This was not so. Such an implication was inconsistent with the particulars listed in the Gardasil SPC and misleading; a breach of Clause 7.2 was ruled. The Panel noted that Clause 3 related to the promotion of a medicine. A press release should not be promotional. Thus on these narrow grounds the Panel ruled no breach of Clause 3.2.

In the Panel's view the second sentence at issue 'The four HPV types 6, 11, 16 and 18 together cause the vast majority of cervical cancer and other HPV-related genital disease' was ambiguous. Some readers might assume that the claim implied that all four HPV types played a role in cervical cancer which was not so. In that regard the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that the second sentence stated that the four HPV types together caused the vast majority of cervical cancer and other HPV-related genital disease. In the Panel's view the claim was ambiguous; some readers would assume that the four HPV types caused the vast majority of cervical cancer. GlaxoSmithKline had submitted that HPV 16

and 18 caused 70% of cervical cancers and Sanofi Pasteur MSD submitted it was 75%. In the Panel's view the use of 'vast majority' to describe 70% or 75% was exaggerated as alleged. It was difficult to know exactly what figure constituted a 'vast majority' but in this instance the 30% or 25% of cervical cancers which were not caused by HPV 16/18 was a sizable minority. The Panel ruled a breach of Clause 7.10.

3 Tender awards and health professional preferences

COMPLAINT

GlaxoSmithKline alleged that the press release contained a number of statements relating to choice of HPV vaccine by governments/health authorities and health professional preferences, which were inaccurate, misleading and disparaged Cervarix and the DoH's choice of vaccine for the UK immunisation programme. The press release had six footnotes, three of which related to the following claims:

- **'In all other tenders awarded to date in Western Europe†, health authorities have chosen Gardasil for about 80% of the population covered'**

The footnote† stated 'Regional tenders in Italy, Spain, Sweden; a national tender in Switzerland'.

GlaxoSmithKline submitted that the word 'chosen' in relation to tenders in this claim was of key importance. In order for there to be a choice, both vaccines had to have been licensed and able to submit a tender application.

Since it received its marketing authorization Cervarix had been awarded nearly two thirds of EU regional and national tenders that had occurred. At the time of the UK tender announcement, Cervarix had been awarded 19 of 29 EU tenders, excluding the UK and Denmark.

Even if one used the countries 'selected' by Sanofi Pasteur MSD and highlighted in the footnote, Cervarix had been awarded the majority; winning 16 out of 23 tenders in Italy, Spain and Sweden. Cervarix was not licensed in Switzerland and so it was inappropriate to use it to support a statement where choice was explicit. Furthermore, GlaxoSmithKline did not agree that it was appropriate to clarify the regulatory status in Switzerland in a footnote to another statement.

Although Sanofi Pasteur MSD had stated that it considered it more accurate not to quote the number of tenders awarded (as some were local or regional and covered small populations) but rather to quantify in terms of the proportion of the population covered, this was at stark odds with the press release which was very much focussed on 'choice'; indeed 'choice' was used four more times.

- 'Two years after its first launch in June 2006, Gardasil is today the HPV vaccine of choice across the world…'.
- '…Gardasil will continue to be the HPV vaccine of choice for girls and women worldwide'.
- 'Where doctors can choose between the two vaccines, more than 9 out of 10 doctors worldwide choose Gardasil'.
- 'The tender decision made by the UK authorities choosing a two-type (16/18) HPV vaccine for their immunisation campaign means that the girls in this campaign will not benefit from…'.

GlaxoSmithKline suggested that Sanofi Pasteur MSD selected 'population covered' because the statement 'in all other tenders awarded to date in Western Europe, health authorities have chosen Cervarix', would have been less appealing for the purposes of the press release.

This claim used by Sanofi Pasteur MSD could not be substantiated and was misleading; and although Sanofi Pasteur MSD claimed to have 'robust evidence' to support it, it had not been provided.

- **'Gardasil is, or will be, used exclusively for campaigns in the USA, Australia, New Zealand, Canada and Switzerland‡'**

The footnote‡ stated 'The two-type vaccine has not yet been approved in Canada and Switzerland to the best of our knowledge'.

GlaxoSmithKline submitted that the claim implied that health service providers in all five countries had actively selected Gardasil over Cervarix, when in fact Cervarix was not actually licensed in three of the countries; following inter-company dialogue, Sanofi Pasteur MSD had stated that it would correct the footnote to include the USA. Nevertheless, to attempt to clarify the regulatory situation, and the true meaning of the statement, by the use of a footnote (positioned eight paragraphs away) was inadequate.

Sanofi-Pasteur MSD had noted that unlike the previous claim which had used the word 'chosen', this claim used '*used*' which did not imply any process of selection. However, a similarly misleading claim occurred earlier in the press release: 'Countries like Australia, New Zealand, *Canada*, France and *Switzerland* have *chosen* Gardasil preferentially or exclusively for their vaccination campaigns' (emphasis added). Again, Canada and Switzerland were cited as countries that had chosen Gardasil, when in fact no choice was available as Cervarix was not licensed in either. GlaxoSmithKline submitted that Sanofi Pasteur MSD's contradictory explanation exposed its clear intention to mislead.

- **'Where doctors can choose between the two vaccines§, more than 9 out of 10 doctors worldwide choose Gardasil'**

The footnote§ read 'Germany, France and Belgium in Western Europe'.

Sanofi-Pasteur MSD had stated that although the footnote referred to only three countries, the claim was not confined to Germany, France and Belgium – these were cited as examples in Western Europe, Sanofi Pasteur MSD's territory. This statement was misleading and exaggerated. Again no evidence had been provided to support individual doctor choice in a global context.

GlaxoSmithKline alleged that the claims were misleading, exaggerated and incapable of substantiation in breach of Clauses 7.2, 7.4 and 7.10. Furthermore, their use in the context of the press release about the 'UK authorities choosing a two-type (16/18) HPV vaccine', disparaged Cervarix and the DoH choice of vaccine in breach of Clauses 8.1 and 8.2.

RESPONSE

Sanofi Pasteur MSD noted that, since the tender award was announced, it had had a number of face-to-face meetings with the DoH and no complaint had been made about its activities, in particular relating to its response to the tender award. Had the DoH considered that Sanofi Pasteur MSD had disparaged its choice of vaccine, it was sure the DoH would have informed it.

- **'In all other tenders awarded to date in Western Europe†, health authorities have chosen Gardasil for about 80% of the population covered'.**

† 'Regional tenders in Italy, Spain, Sweden; a national tender in Switzerland'.

Sanofi-Pasteur MSD noted that GlaxoSmithKline had implied that this claim was in the main body of the press release whereas it was actually in the notes to the editors. Sanofi Pasteur MSD disagreed with GlaxoSmithKline's selective and flawed interpretation of the meaning of the word 'chosen' in this context; both vaccines did not have to be licensed and able to submit a tender application for a choice to be possible.

If Cervarix had been precluded from a tendering process because it did not have a marketing authorization, then clearly it could not be part of the selection process; however authorities still had to make a choice. Where there was only one product an authority could choose that product (eg US, Switzerland) or wait for competition (eg UK). Hence, the fact that Cervarix might not have had a marketing authorization when a tender was awarded in a particular region or country was irrelevant to the fact that Gardasil was chosen.

Sanofi Pasteur MSD noted that it was a joint venture between Sanofi Pasteur, the vaccine division of Sanofi-Aventis, and Merck & Co Inc and it was present in 19 Western European countries. A worldwide picture of HPV vaccine use could only be drawn including data from Sanofi Pasteur MSD and its parent company Merck, which marketed Gardasil in other countries. Furthermore, Sanofi Pasteur MSD did not believe it was valid to compare numbers of tenders won (as some were local or regional and covered small populations) but rather to quantify tender awards in terms of the proportion of the population covered. GlaxoSmithKline had supplied figures for EU HPV vaccine tenders as of 18 June 2008, but it was not valid to only consider tenders that had been granted since Cervarix received its marketing authorization. In addition, some of the recent tenders were awarded on a regional basis. For example, Italy had 26 separate tenders and so simply adding up the number of tenders won around the world would be relatively meaningless and give a distorted, misleading impression. Gardasil's world leading position was further underlined by the fact that according to GlaxoSmithKline's own press release of 18 June 2008, the UK was the first major national tender for which it had bid.

Sanofi Pasteur MSD maintained its position that Gardasil was the world's leading HPV vaccine and vaccine of choice for girls and women worldwide. This was not only on the basis of number of doses distributed worldwide (more than 30 million compared with 1 million doses of Cervarix), but also on share of tender markets by population covered; Gardasil had 80% share according to the recommendations per region/country. Furthermore, Gardasil also had 90% share in prescriptions in its home territory (data on this point was provided in confidence and was not to be shared with GlaxoSmithKline), as well as a 90% global market share. The press releases which included details of quarter 1 2008 financial reports from both Merck and GlaxoSmithKline were provided, where Gardasil global sales were $390M and Cervarix global sales were £12M.

Sanofi Pasteur MSD considered that the claim had been robustly substantiated and was not misleading; the company refuted any alleged breaches.

- **'Gardasil is, or will be, used exclusively for campaigns in the USA, Australia, New Zealand, Canada and Switzerland‡.'**

‡ 'The two-type vaccine has not yet been approved in Canada and Switzerland to the best of our knowledge.'

Sanofi-Aventis MSD noted that this claim was not in the main body of the press release; it was a clarifying note to the editors and an unambiguous statement of fact. During inter-company dialogue it was agreed, however, to correct an omission from the footnote, namely that Cervarix was also not approved in the US. The claim itself did not imply that health service providers in all five countries had actively selected Gardasil over Cervarix. Sanofi Pasteur MSD repeated its views regarding the word 'chosen' and whilst not specifically mentioned in this statement, reiterated the principle that regardless of Cervarix not having a licence in 3 of the 5 countries, the authorities in those countries still had to make a choice to use the vaccine or not.

Furthermore, in the above statement, the word 'used' did not imply any process of selection and consequently the company denied breaches of Clauses 7.2 and 8.1.

With regard to GlaxoSmithKline's comments about the claim 'Countries like Australia, New Zealand, Canada, France and Switzerland have chosen Gardasil preferentially or exclusively for their vaccination campaigns or recommendations', Saudi Pasteur MSD explained that Australia, New Zealand and France had chosen Gardasil preferentially and Canada and Switzerland had chosen it exclusively. The company disagreed that the statement was misleading since it stated 'preferentially **or** exclusively' (emphasis added). Furthermore it was clear in the notes to editors that Cervarix was not licensed in Canada or Switzerland.

- **'Where doctors can choose between the two vaccines[§], more than 9 out 10 doctors worldwide choose Gardasil.'**

§ 'Germany, France and Belgium in Western Europe.'

Sanofi Pasteur MSD submitted that this claim was not confined to Germany, France and Belgium – they were cited as examples in Western Europe, Sanofi Pasteur MSD's territory. The data was based on a 90% market share in the company's home market by prescriptions (Sanofi Pasteur MSD supplied data in confidence which was not to be shared with GlaxoSmithKline).

Sanofi Pasteur MSD submitted that all of the above statements were factual, had been substantiated, were not misleading or exaggerated and consequently the company denied any breach of Clauses 7.2, 7.4 and 7.10, 8.1 or 8.2.

PANEL RULING

The Panel considered that the selection of vaccine by a country/region for use was complicated. The basis of choice could be one of a number of options depending on the regulatory status of the vaccines in the country. Firstly a choice between two licensed products Gardasil and Ceravix, secondly a choice between a licensed product (Gardasil) and an unlicensed product (Ceravix) and thirdly a choice between the only licensed vaccine (Gardasil) or nothing. A fourth factor was also relevant given the differences in indications for the products ie did the country/region only want to vaccinate against cervical cancer or against cervical cancer and genital warts. The Panel did not consider that the press release was sufficiently clear about the options available and the regulatory status of the products at the time the tender decisions were made.

The Panel considered it was really important to include very clear information about the factors that might have influenced the tendering decisions round the world. Simple claims were not sufficient given the complexity of the situation.

The Panel noted that the three other claims at issue all relied on footnotes to provide clarification. The supplementary information to Clause 7 stated 'It should be borne in mind that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like'.

In the claim 'In all other tenders awarded to date in Western Europe, health authorities have chosen Gardasil for about 80% of the population covered', Western Europe was asterisked to a footnote 'Regional tenders in Italy, Spain, Sweden; a national tender in Switzerland'. The Panel considered that this was misleading as Italy, Spain, Sweden and Switzerland were a small part of Western Europe. Further, Cervarix was not licensed in Switzerland and so in that country Gardasil was chosen instead of nothing; in the Panel's view the majority of readers would not realise this. The Panel considered that the claim was misleading and in that regard could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled. In making its ruling the Panel did not consider the data which had been provided in confidence and which could not be given to GlaxoSmithKline. The claim 'Gardasil is, or will be, used exclusively for campaigns in the USA, Australia, New Zealand, Canada and Switzerland' relied upon the footnote 'The two-type vaccine has not yet been approved in Canada and Switzerland to the best of our knowledge'. The Panel noted its comments above regarding choice and the reader's knowledge of product availability. As above the Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that the claim 'Where doctors can choose between the two vaccines, more than 9 out of 10 doctors worldwide choose Gardasil' relied on the footnote 'Germany, France and Belgium in Western Europe'. The Panel considered that the claim was misleading in its reliance upon a footnote for clarity. The Panel further considered that it was exaggerated to use data from only Germany, France and Belgium in a worldwide claim. Breaches of Clauses 7.2 and 7.10 were ruled. The claim had not been substantiated by the data relating solely to Germany, France and Belgium. Further, as this data was confidential and not to be provided to GlaxoSmithKline it could not be considered by the Panel. A breach of Clause 7.4 was also ruled.

With regard to the alleged breaches of Clauses 8.1 and 8.2, the Panel considered that the claims at issue undermined the DOH's choice of Cervarix and thus disparaged both the product and the DOH. Breaches of Clauses 8.1 and 8.2 were ruled.

4 Distribution of materials

COMPLAINT

GlaxoSmithKline noted that the press release was

distributed to the media through the usual channels and also added to Sanofi Pasteur MSD's website. However, there was no direction on the website or press release itself that the press release was intended for medical journalists only; it appeared to have been distributed widely to both medical and consumer press. Although company press releases could be distributed to the consumer media when appropriate, particular care must be taken not to promote prescription only medicines to the public and the information presented must be factual and balanced. This was clearly not the case with this concerted campaign. The purpose of the press release appeared to be to encourage the public to question the choice of vaccine by the DoH and invite them to specifically request Gardasil, which was mentioned 13 times.

In defence of this allegation, Sanofi Pasteur MSD had stated that HPV vaccination was not available outside the national programme. However, Sanofi Pasteur MSD would know that both vaccines were prescribed privately and, although the DoH's Green Book stated that 'vaccination is not routinely recommended for those aged 18 years or over', HPV vaccination could be prescribed on a case-by-case basis to individual women who might benefit.

GlaxoSmithKline alleged the distribution of the press release to consumer media, and therefore the public, was a breach of Clause 20.2.

GlaxoSmithKline noted that in addition to the press release Sanofi Pasteur MSD distributed, via a PR agency, two emails following the DoH announcement. The first email contained the press release and was sent on 18 June, the day of the DoH announcement; the second contained a summary of the press coverage relating to the tender announcement and was sent the following day. Although the email covered a broad range of media types and publications, GlaxoSmithKline disagreed with Sanofi Pasteur MSD's statement '…the synthesis of the media coverage was not selective'.

Only statements from patient advocacy groups who would be expected to have an interest in protection from genital warts were included: BASHH (British Association for Sexual Health and HIV), Brook (the UK's leading provider of sexual health services and advice for the under 25s) and the Terrence Higgins Trust; the absence of a cervical cancer/cancer advocacy group statement was striking and significant.

Furthermore, the PR agency was careful to note the negative media coverage: 'a number of publications have raised concerns about the Department's decision including The Times, BBC Online, PA News, Reuters, Channel Four, Yorkshire Post, Newcastle Chronicle, Cheshire News'. It was clear that the email was intended to reinforce the messages in the press release.

In addition, of the 21 national and regional articles highlighted in the email, 16 appeared to have been significantly influenced by the Sanofi Pasteur MSD press release, containing direct content/quotes or similar misinformed and misleading messages to those discussed earlier.

In addition to the media, the PR agency distributed the Sanofi Pasteur MSD press release and press coverage in unsolicited emails to health professionals. Due to their surprise at receiving such a press release from Sanofi Pasteur MSD, and their concerns of the impact that this might have on the national immunisation programme, a number of health professionals had contacted GlaxoSmithKline anonymously.

The way in which both emails were used by the PR agency made them promotional and thus subject to the Code. Sanofi Pasteur MSD claimed the distribution was limited to a small group of individuals and organisations who received regular media updates about HPV vaccination. However, this was at odds with GlaxoSmithKline's understanding, and Sanofi Pasteur MSD had not provided any evidence in support of the explicit prior permission which it had received from the health professional recipients. GlaxoSmithKline alleged that the unsolicited distribution of these emails to health professionals breached Clause 9.9.

RESPONSE

Sanofi Pasteur MSD noted that GlaxoSmithKline was concerned about the content of the press coverage email, although a specific breach of the Code had not been alleged. GlaxoSmithKline was concerned that the press coverage was selective and that only statements from patient advocacy groups which would be expected to have an interest in protection from genital warts were included. Sanofi Pasteur MSD was surprised that GlaxoSmithKline had stated that the complete absence of a cervical cancer/cancer advocacy statement was striking and significant. To the contrary, Sanofi Pasteur MSD found it striking and significant that GlaxoSmithKline had not mentioned that the fourth hyperlink on the page (the second hyperlink in the Newswires section) was a press release from Jo's Trust, the UK's leading cervical cancer charity (the item was also included in the press clippings that GlaxoSmithKline had supplied to the Authority). Furthermore this was an entirely positive press release relating to the DoH's choice of vaccine.

To further substantiate that the content of the emails was not selective or promotional, the PR agency had told Sanofi Pasteur MSD that between 17 June 2008 and the beginning of July Google news alerts (using the search terms 'HPV vaccine' and 'tender announcement') were used in addition to Factiva (an alert service to which the agency subscribed) and in house scanning of all the national daily newspapers and weekly/monthly medical publications. In addition, the agency had an

ongoing Google alert set up for 'HPV' and 'Gardasil'.

All articles forwarded in the email were unbiased in that the PR agency was not selective over which coverage was sent. All tender-related coverage to that date from a broad range of media types was forwarded regardless of which product it mentioned, including articles that were positive for GlaxoSmithKline.

Sanofi Pasteur MSD noted that GlaxoSmithKline was also concerned that the emailing of the press release, which GlaxoSmithKline alleged to be misleading, had influenced the national and regional articles that were included in the email. Sanofi Pasteur MSD had already responded to the allegations regarding the content of the press release above and so refuted the allegation that misinformed and misleading messages were picked up by the press coverage. The company therefore denied the allegation of a breach of Clause 20.2.

Sanofi Pasteur MSD noted that GlaxoSmithKline was concerned about the distribution by the agency of the Sanofi Pasteur MSD press statement and press coverage by email, alleging that the emails had been sent unsolicited to health professionals. Sanofi Pasteur MSD denied this allegation and thus a breach of Clause 9.9.

The emails were not unsolicited. A relationship existed and previous correspondence of a similar nature had taken place with all those who received the emails. The recipients of the emails had a legitimate interest in receiving such information so they were well placed to offer Sanofi Pasteur MSD advice when required and also to remain adequately informed so that they might handle media enquiries in a responsible manner. As part of the ongoing dialogue no one had ever complained or asked to stop receiving information. In the context of the DoH announcement, it was therefore in keeping with previous practice with this group to provide them with both a copy of the company's statement and a synthesis of media coverage.

This was further supported by a letter and slides from an advisory board where it was made clear that Sanofi Pasteur MSD intended to provide email updates of licence application news and data communications (with copies of abstracts/papers/media coverage of interest). Those involved at an early stage therefore had the opportunity face to face in these meetings to opt out. The emails were found to be of relevance – demonstrated by recipients' responses when they were called upon to give comment to the media at short notice.

Sanofi Pasteur MSD therefore refuted the allegations that the sending of these emails breached Clause 9.9.

With regard to the emails from its PR agency, Sanofi Pasteur MSD knew that the agency intended to send these types of emails and did not object since they were deemed to be a legitimate part of the ongoing dialogue that had taken place since working with the recipients. The emails were not formally copy approved by Sanofi Pasteur MSD. The agency knew about, received regular training on, and was committed to complying with, the Code and reviewed the emails as part of its own approval process.

Sanofi Pasteur MSD disagreed with the allegation that the purpose of the press statement was to encourage the public to question the choice of vaccine by the DoH and to invite them to specifically request Gardasil. The company thus denied a breach of Clause 20.2. The press statement was fair, balanced, factual and well substantiated. The brand name was used for clarity since the generic name was long and unwieldy and might have confused readers.

A recent editorial in the BMJ further highlighted the controversial nature of the decision, stating that 'The decision to select the bivalent vaccine implies that the Department of Health is willing to accept foregone health benefits (and additional cost savings) from averting cases of genital warts for the reduced financial outlay, which may be allocated to other priority investments in health'. This was a hugely topical area for both health professionals and consumers.

Given the above, it was beyond dispute that the issue was clearly a significant public health issue and very relevant for a consumer audience as well as health professionals. In fact a government minister had recently stated that the national immunisation campaign was one of the biggest public health campaigns in recent history.

The press release was distributed to the media via the usual channels, following releases by both the DoH and GlaxoSmithKline on 18 June 2008. The company website contained an archive of previous releases to which this was also added. This was in the section of the website that was clearly marked as being for journalists, both on the homepage and on the page containing the release itself. Nonetheless, it was entirely appropriate for the press release to be accessible to consumer journalists.

Clause 20.2 allowed non-promotional information about prescription only medicines to be provided to the public including via press announcements. The press statement was factual, fair, balanced and would not encourage the public to specifically request Gardasil. In fact the opposite was true since the press statement actually reinforced the fact that girls in the national immunisation programme would not be able to receive Gardasil and consequently Sanofi Pasteur MSD believed that people would actually be deterred from asking for Gardasil. Furthermore, the DoH's Green Book stated that the HPV vaccine was not routinely recommended for those outside of the national

programme. There was no mention in the press release that the vaccine could be prescribed on a case-by-case basis.

PANEL RULING

The Panel noted that the press release had been issued to the consumer press. It was not unacceptable to issue press releases about prescription only medicines to the consumer press providing that the information contained therein was factual and balanced. Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine.

The Panel considered that, *inter alia*, describing Gardasil as the World's leading four-type HPV vaccine, with unmatched cervical cancer protection, would encourage patients to ask for the medicine. It was irrelevant that they might not be able to get it on the NHS. A breach of Clause 20.2 was ruled.

With regard to the allegations of breaches of Clauses 9.9 and 9.10, the Panel noted Sanofi Pasteur MSD's submission that such allegations had not been discussed in inter-company dialogue. A letter to Sanofi Pasteur MSD, however, was headed 'Unsolicited emails to health professionals, patient organisations and charities'. The Panel considered that, in that regard, the issue of whether the emails were sent unsolicited had been raised. There was no mention in the inter-company correspondence, however, of whether the material needed to include a declaration of sponsorship (Clause 9.10) and so this aspect of the complaint was not considered.

With regard to whether the emails were unsolicited, the Panel noted Sanofi Pasteur MSD's submission that a relationship existed between it and the recipients and that they had all received correspondence of a similar nature before. The company had further submitted that the emails were sent to specific individuals because of their role in providing Sanofi Pasteur MSD with advice as well as being experts in handling the media. The Panel was concerned that no explanation had been given in the emails that the PR agency sending the material was acting on behalf of Sanofi Pasteur MSD. Nor did the email state that the audience were those who had a role in providing Sanofi Pasteur MSD with advice. It appeared from Sanofi Pasteur MSD's response that the emails were sent to health professionals who were, in some capacity, acting as consultants to the company. On that basis the Panel considered that the emails were not unsolicited promotional material as alleged. No breach of Clause 9.9 was ruled.

During its consideration of this matter, the Panel noted with concern Sanofi Pasteur MSD's submission that emails had been sent out by its PR agency without formal copy approval by the company. This was wholly unacceptable; pharmaceutical companies could not delegate their responsibilities under the Code to a third party.

5 High standards and alleged breach of Clause 2 of the Code

COMPLAINT

GlaxoSmithKline submitted that Sanofi Pasteur MSD's activities and materials provided evidence of the coordinated campaign, designed to question the robustness of the DoH's decision in its choice of vaccine for the immunisation programme and leave the reader believing that the UK government, unlike most other health authorities, had chosen a less effective vaccine to protect UK girls and women. The widespread distribution of material to the medical and consumer media, health professionals and other organisations would encourage health professionals and the public to question the DoH's vaccine choice and ask for Gardasil, which was mentioned by name 13 times.

Sanofi Pasteur MSD's campaign had a number of potentially serious consequences. Firstly, the uptake of immunisation was likely to be affected, reducing the number of girls who could benefit from vaccination to prevent cervical cancer. Secondly, for those who had been vaccinated against HPV 16 and 18, the mistaken belief that they would be protected against the 'vast majority' of cervical cancers might lead to a false sense of security and reduce future cervical screening attendance, which was already in decline in younger age groups. This would increase the chances of a pre-cancerous lesion progressing to cervical cancer.

In addition to the clauses cited above GlaxoSmithKline alleged that Sanofi Pasteur MSD had breached Clause 9.1 in that high standards had not been maintained to the extent that its activities brought discredit upon, and seriously undermined confidence in the pharmaceutical industry and its ability to self-regulate in breach of Clause 2.

Given the widespread distribution of these misleading, inaccurate and damaging materials to media organisations, health professionals and patient groups, GlaxoSmithKline requested that a corrective letter, with the Authority's and GlaxoSmithKline's prior agreement, be issued to all parties on the original press release and email distribution lists. In addition, the letter should be sent to all media that had published inaccurate information taken from the press release in order to address the inaccuracies and minimise the damage caused to the national immunisation programme.

RESPONSE

Sanofi Pasteur MSD believed that it and its PR agency had acted responsibly and appropriately in

light of the DoH's decision to select Cervarix for the national immunisation programme. Sanofi Pasteur MSD strongly refuted all allegations of breaches of the Code. Sanofi Pasteur MSD was a responsible company, dedicated to vaccines and public health, and believed that it had maintained high standards throughout and consequently denied breaching Clause 9.1. Furthermore it disagreed with the allegation that its activities had brought discredit upon and seriously undermined confidence in the pharmaceutical industry and its ability to self-regulate. Sanofi Pasteur MSD thus refuted the alleged breach of Clause 2.

Sanofi Pasteur MSD did not believe that any of its activities or content of materials had been misleading, inaccurate or damaging. To the contrary it believed that its materials and activities had conformed to the highest standards. During the inter-company dialogue, it agreed to correct the omission of the US from a footnote and also to clarify the wording in the archive copy of the press release to distinguish that pre-cancerous vaginal lesions were the subject of a positive CHMP opinion. It did not agree with GlaxoSmithKline's request to issue a corrective statement for widespread distribution.

PANEL RULING

The Panel noted that GlaxoSmithKline had requested that Sanofi Pasteur MSD issue a corrective letter. This was not a sanction available to the Panel. It was only available to the Appeal Board following a ruling by the Appeal Board (Paragraph 10.6 of the Constitution and Procedure) or when it was considering a report (Paragraph 11.3).

The Panel noted its rulings of breaches of the Code above. It considered that Sanofi Pasteur MSD had not been sufficiently clear about the situation and thus would cause further confusion in a complicated matter. Taking all the circumstances into account the Panel decided that high standards had not been maintained and a breach of Clause 9.1 was ruled.

On balance the Panel did not consider that the circumstances were in breach of Clause 2 which was used as a sign of particular censure.

Complaint received **22 July 2008**

Case completed **22 September 2008**

ASTRAZENECA V TRINITY-CHIESI

Fostair cost comparison chart

AstraZeneca complained that a cost comparison chart used by Trinity-Chiesi to promote Fostair (beclometasone 100mcg formoterol 6mcg) inhaler for asthma was incomplete, unfair and misleading. The chart compared the cost of Fostair, two puffs twice daily, with Seretide (GlaxoSmithKline's combination inhaler) two puffs twice a day, and AstraZeneca's combined corticosteroid/long-acting ß-agonist inhaler Symbicort. Symbicort was available in three strengths but only one (budesonide 200mcg plus salmeterol 6mcg (Symbicort 200/6)) was included in the chart – also at a dose of two puffs twice daily. For each inhaler the chart gave the NHS price for 30 days, the NHS price per patient per year, the annual NHS inhaler cost saving per patient with Fostair and the percentage annual inhaler cost saving per patient with Fostair. It was stated that there was a 23% annual saving if Fostair (two puffs bd) was used instead of Symbicort 200/6 (two puffs bd), and a 20% annual saving compared with Seretide. Despite ongoing inter-company correspondence about it, the chart appeared in a detail aid which had been prepared in April 2008, and contrary to assurances that it would be amended, in an advertisement in Pulse in June 2008

The cost comparison in Pulse was headed 'Fostair is less expensive than comparable doses of Symbicort or Seretide' referenced to Papi *et al* (2007a/b). Papi *et al* (2007a) compared Fostair with Symbicort 200/6. The claim was also referenced to MIMS May 2008. The cost comparison in the detail aid was headed '20% less expensive than other fixed combinations' and referenced to MIMS, March 2008.

The chart showed that Fostair was 23% cheaper than Symbicort in the doses chosen over a year. AstraZeneca considered that the chart was incomplete and misleading as it only showed one presentation and one dosing regimen for Symbicort, which happened to be more expensive than the Fostair comparator dose. Readers would be unaware that Symbicort was available in different presentations (eg 100/6 and 400/12) or that there were other dosing regimens including using Symbicort as maintenance and reliever therapy and that some of these regimens or presentations were cheaper than Fostair.

The detail aid produced in April 2008 contained the disputed chart when inter-company discussions about it were ongoing. The detail aid was not withdrawn as agreed as a representative gave it to a GP in mid-June 2008. The advertisement was not published until 25 June 2008 which gave Trinity-Chiesi ample time to change the chart before final copy was required. However it seemed that Trinity-Chiesi failed to do so and the chart was reproduced unaltered. AstraZeneca considered that this illustrated, at best, systematic failure of internal recall procedures and processes within Trinity-Chiesi to update material, or at worst, a blatant disregard for inter-company dialogue and failure to adhere to agreed undertakings.

The detailed response from Trinity-Chiesi is given below.

The Panel noted that the advertisement in Pulse had appeared as a double page spread. The left-hand page detailed the results of Papi *et al* (2007a) and showed that at a dose of two puffs twice daily Fostair and Symbicort (200/6), over a twelve week treatment period, resulted in comparable morning peak expiratory flows. The published paper concluded that the two products produced equivalent benefits in lung function and clinical symptoms and led to a significant decrease in the use of rescue medicines. No significant differences were observed in terms of rates of asthma exacerbations and/or the need for additional prevention therapy. The cost comparison chart appeared on the right-hand page under the heading 'Fostair is less expensive than comparable doses of Symbicort or Seretide' which was referenced to Papi *et al* (2007a/b) and to MIMS, May 2008. The strengths and doses cited in the chart were the same as those used in Papi *et al* (2007a).

The Panel considered that in the context of an advertisement which had discussed the results of Papi *et al* (2007a), it was not unreasonable to use a cost comparison chart based on those results. In that regard the Panel did not consider it was necessary to include other strengths or dosage regimens for Symbicort. The Panel noted AstraZeneca's submission with regard to Symbicort SMART (Symbicort as maintenance and reliever therapy). The Symbicort (200/6) summary of product characteristics (SPC) stated that SMART treatment should be especially considered for, *inter alia*, asthmatics with exacerbations in the past requiring medical intervention. One of the exclusion criteria in Papi *et al* (2007a) was three or more courses of oral corticosteroids or hospitalisation due to asthma in the previous 6 months. The Panel did not consider that, given the context in which it appeared, the chart was incomplete, unfair or misleading as alleged; it was clear that the figures cited were based on the results of Papi *et al* (2007a). The Panel ruled no breach of the Code.

With regard to the detail aid, the Panel noted that it

had detailed the results of the Papi *et al* studies. The Panel noted its comments regarding the cost comparison in the advertisement. The heading in the detail aid ('20% less expensive than other fixed combinations') was different to the heading in the advertisement. However taking all the circumstances into account the Panel did not consider that the cost comparison in the detail aid was incomplete, unfair or misleading as alleged. No breach was ruled.

AstraZeneca UK Limited complained about a cost comparison chart used by Trinity-Chiesi Pharmaceuticals Ltd to promote Fostair, its combined corticosteroid (beclometasone 100mcg) and long-acting ß-agonist (formoterol 6mcg) inhaler for asthma. The chart compared the cost of Fostair, two puffs twice daily, with Seretide (GlaxoSmithKline's combination inhaler) two puffs twice a day, and AstraZeneca's combined corticosteroid/long-acting ß-agonist inhaler Symbicort. Symbicort was available in three strengths but only one (budesonide 200mcg plus salmeterol 6mcg (Symbicort 200/6)) was included in the chart – also at a dose of two puffs twice daily. For each inhaler the chart gave the NHS price for 30 days, the NHS price per patient per year, the annual NHS inhaler cost saving per patient with Fostair and the percentage annual inhaler cost saving per patient with Fostair. It was stated that there was a 23% annual saving if Fostair (two puffs bd) was used instead of Symbicort 200/6 (two puffs bd), and a 20% annual saving compared with Seretide. The chart had appeared in an advertisement in Pulse in June 2008 (ref TRF0S20080298) and a detail aid (ref TRF0S20080198) which had been prepared in April 2008.

The cost comparison in Pulse was headed 'Fostair is less expensive than comparable doses of Symbicort or Seretide' referenced to Papi *et al* (2007a/b). Papi *et al* (2007a) had compared Fostair with Symbicort 200/6. The claim was also referenced to MIMS May 2008. The cost comparison in the detail aid was headed '20% less expensive than other fixed combinations' and referenced to MIMS, March 2008.

This case was considered under the 2008 Constitution and Procedure. The clauses cited by AstraZeneca, 7.2 and 7.3 were the same in the 2008 Code as in the 2006 Code.

COMPLAINT

AstraZeneca alleged that the cost comparison chart which compared acquisition costs for Fostair, Seretide and Symbicort was incomplete, unfair and misleading in breach of Clauses 7.2 and 7.3 of the Code. Following inter-company dialogue AstraZeneca had been reassured by Trinity-Chiesi that the chart would be amended and no longer used in its current format. However, AstraZeneca had evidence that Trinity-Chiesi had continued to use the offending chart despite this agreement and this now justified complaining to the Authority.

Both the advertisement and the detail aid contained the cost comparison chart that AstraZeneca had discussed with Trinity-Chiesi previously. The table showed the 30-day and one-year NHS acquisition costs for Fostair 100/6, Seretide 125/25 and Symbicort 200/6, all taken as two inhalations twice daily. The table showed that Fostair was 23% cheaper than Symbicort in the doses chosen over a year. AstraZeneca considered that the chart was incomplete and misleading as it only showed one presentation and one dosing regimen for Symbicort, which happened to be more expensive than the Fostair comparator dose. Readers would be unaware that Symbicort was available in different presentations (eg 100/6 and 400/12) or that there were other dosing regimens including using Symbicort as maintenance and reliever therapy (Symbicort SMART) and that some of these regimens or presentations were cheaper than Fostair.

The cost comparison chart was included in a document entitled 'Information for drugs and therapeutics committees' (ref TRFOS20070581) which was discussed in recent inter-company dialogue; AstraZeneca believed agreement was reached that the chart was incomplete and would be amended. In a letter dated 14 May, Trinity-Chiesi accepted AstraZeneca's rationale that the chart, if taken in isolation, might be considered incomplete and the company agreed to change it to show that the doses used were those taken from the randomised comparative studies and the chart was therefore able to stand in isolation of the document.

Having admitted that the chart was incomplete, AstraZeneca assumed that Trinity-Chiesi would comply with the spirit of the Code and withdraw not only the drugs and therapeutics document, but also all other potentially misleading materials promptly whilst it revised the chart.

The detail aid now at issue was produced in April 2008 and contained the disputed chart during the period where inter-company discussions about it were ongoing. It was clear that the detail aid was not withdrawn as agreed as it was given to a GP by a sales representative in mid-June 2008. The advertisement was not published until 25 June 2008 which gave Trinity-Chiesi ample time to change the chart before final copy was required. However it seemed that Trinity-Chiesi failed to do so and the chart was reproduced unaltered. AstraZeneca felt strongly that this illustrated, at best, systematic failure of internal recall procedures and processes within Trinity-Chiesi to update material, or at worst, a blatant disregard for the process of inter-company dialogue and failure to adhere to agreed undertakings.

RESPONSE

Trinity-Chiesi stated that the comparable dosages

used in the chart came from two published head-to-head studies, one which compared Fostair two puffs bd with Seretide 125/25 two puffs bd (Papi *et al* 2007b) and the other Fostair (n=109) two puffs bd with Symbicort 200/6 (n=110) two puffs bd (Papi *et al* 2007a). Both studies had similar design; phase III, multinational, multicentre, double-blinded, randomised, two-arm parallel groups and controlled trial lasting 12 weeks in moderate-to-severe asthmatics. The non-inferiority primary end-point of both studies was morning peak expiratory flow in the last two weeks of treatment and it showed no difference between the treatments for both studies. There were also no differences in the results for the secondary end-points measured in Papi *et al* (2007a) (Fostair vs Symbicort). Papi *et al* (2007a) was published in the official journal of the European Respiratory Society. Trinity-Chiesi believed that the comparable dosages used in the chart were scientifically and clinically validated and therefore complied with Clauses 7.2 and 7.3.

Furthermore, following inter-company dialogue in May 2008, Trinity-Chiesi agreed to amend the chart, as evident in the advertisement, by adding superscripts of the references of the two head-to-head studies in the heading above the table as follows: 'Fostair is less expensive than comparable doses of Symbicort or Seretide', referenced to Papi *et al* (2007a/b).

Trinity-Chiesi noted AstraZeneca's assertion that the chart should have included other available strengths of Symbicort (100/6 and 400/12) or other dosing regimens like Symbicort SMART. Trinity-Chiesi did not undertake to do this firstly because it was not incumbent for a company to include strengths or dosing regimen of competitors' products in its promotional materials without valid reasons to do so; secondly to have included these other strengths and dosing regimen of Symbicort could have misled the reader into thinking that Fostair had similar strengths and dosing regimen, which it did not. This was possible as both Fostair and Symbicort contained formoterol with a corticosteroid and finally Trinity-Chiesi mentioned only the doses of Fostair 100/6 and Symbicort 200/6 as used in Papi *et al* (2007a).

Trinity-Chiesi noted that the detail aid obtained by AstraZeneca was prepared in April 2008, ie before inter-company dialogue was concluded. Given that dialogue was only offered for closure by AstraZeneca on 27 May (by email), it was only reasonable that AstraZeneca allowed Trinity-Chiesi sufficient time to amend and re-print the detail aid. The April detail aid was re-issued by 12 June and the cost comparison chart was amended to be similar to that used in the advertisement. Given AstraZeneca's allegation that the April detail aid was used in mid-June, it would be helpful if it would give more details about exactly when and where the item was used. Trinity-Chiesi could investigate the matter and take the necessary action if one of its representatives had been proved to use the April detail aid after 12 June.

Trinity-Chiesi submitted that the cost comparison chart was fair, complete and was not misleading, and therefore did not breach Clauses 7.2 and 7.3.

Trinity-Chiesi stated that it had fulfilled its side of the inter-company agreement by amending the chart and the detail aid. Trinity-Chiesi wrote to AstraZeneca on 14 May with its undertakings but did not receive an acknowledgement until 27 May when it considered the complaint closed. Hence, it was reasonable for Trinity-Chiesi to use the April version of the detail aid until it instituted a change by 12 June. With regard to the chart itself, in a letter to AstraZeneca of 14 May Trinity-Chiesi undertook to change the chart to show that the doses cited were taken from the randomised comparative studies and the chart was therefore able to stand alone. As explained above, Trinity-Chiesi did not undertake to include information about other strengths of Symbicort (100/6 and 400/12) or other dosing regimens like Symbicort SMART. Trinity-Chiesi only mentioned the respective doses of Fostair and Symbicort 200/6 as used in Papi *et al* (2007a).

Trinity-Chiesi took inter-company undertakings seriously and in this instance it maintained that it fulfilled all its undertakings to AstraZeneca. Trinity-Chiesi believed that the amended cost comparison chart was fair, not misleading, and not in breach of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that the advertisement in Pulse had appeared as a double page spread. The left-hand page detailed the results of Papi *et al* (2007a) and showed that at a dose of two puffs twice daily Fostair and Symbicort (200/6), over a twelve week treatment period, resulted in comparable morning peak expiratory flows. The published paper concluded that the two products produced equivalent benefits in lung function and clinical symptoms and led to a significant decrease in the use of rescue medicines. No significant differences were observed in terms of rates of asthma exacerbations and/or the need for additional prevention therapy. The cost comparison chart appeared on the right-hand page under the heading 'Fostair is less expensive than comparable doses of Symbicort or Seretide' which was referenced to Papi *et al* (2007a/b) and to MIMS, May 2008. The strengths and doses cited in the chart were the same as those used in Papi *et al* (2007a).

The Panel considered that in the context of an advertisement which had discussed the results of Papi *et al* (2007a), it was not unreasonable to use a cost comparison chart based on those results. In that regard the Panel did not consider it was necessary to include other strengths or dosage regimens for Symbicort. The Panel noted AstraZeneca's submission with regard to Symbicort SMART (Symbicort as maintenance and reliever therapy). The Symbicort (200/6) summary of

product characteristics (SPC) stated that SMART treatment should be especially considered for, *inter alia*, asthmatics with exacerbations in the past requiring medical intervention. One of the exclusion criteria in Papi *et al* (2007a) was three or more courses of oral corticosteroids or hospitalisation due to asthma in the previous 6 months. The Panel did not consider that, given the context in which it appeared, the chart was incomplete, unfair or misleading as alleged; it was clear that the figures cited were based on the strengths, dosages and clinical results of Papi *et al* (2007a). The Panel ruled no breach of Clauses 7.2 and 7.3.

With regard to the detail aid the Panel noted that the cost comparison chart appeared on page 9; pages 6, 7 and 8 had detailed the results of the Papi *et al* studies. The Panel noted its comments regarding the cost comparison in the advertisement. The heading in the detail aid ('20% less expensive than other fixed combinations') was different to the heading in the advertisement. However taking all the circumstances into account the Panel did not consider that the cost comparison in the detail aid was incomplete, unfair or misleading as alleged. No breach of Clauses 7.2 and 7.3 was ruled.

During its consideration of this case the Panel noted that the annual cost savings cited in the chart were based on patients taking a constant dose of Symbicort (200/6) and Fostair two puffs twice a day. This was the maximum dose for Symbicort (200/6) when used as maintenance therapy and the maximum dose for Fostair. The Symbicort (200/6) SPC stated for maintenance therapy 'In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include Symbicort given once daily …'. The Fostair SPC stated 'The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When control of symptoms is maintained with the lowest recommended dose, then the next step could include a test dose of inhaled corticosteroid alone'. The Panel thus queried the validity of extrapolating three month clinical data, using the maximum dose of each product, to one year financial data. The cost comparison chart implied that patients would take two puffs twice daily continuously and this would not necessarily be so. The Panel requested that Trinity-Chiesi be advised of its concerns in this regard.

Complaint received **28 July 2008**

Case completed **5 September 2008**

CASE AUTH/2149/8/08

FREELANCE MEDICAL WRITER v SYNER-MED

Promotion of Ferinject

A freelance medical writer complained about the promotion of Ferinject (ferric carboxymaltose) by Syner-Med at the British Renal Society meeting in May 2008. The materials at issue were a detail aid, a two page brochure and a leavepiece.

The detailed response from Syner-Med is given below.

In relation to the detail aid, the complainant was mainly concerned about the claim in small print at the foot of page 9 that 'The maximum dose by infusion is 1000mg iron per week, but should not exceed 15mg/kg'. This was essential information because it meant that the maximum dose by infusion (1000mg) should not be given to a patient with a body weight of less than 67kg. However, the statement did not appear with the dosage information earlier in the brochure and might easily be missed. In the interests of patient safety, and to provide a clear and accurate statement of the dosage of Ferinject by infusion, the complainant thought that this information should be incorporated in context, on pages 5/6, for example.

The Panel noted that the summary of product characteristics (SPC) stated 'Ferinject may be administered by intravenous infusion up to a maximum single dose of 20ml of Ferinject (1000mg of iron) but not exceeding 0.3ml of Ferinject (15mg of iron) per kg body weight or the calculated cumulative dose. Do not administer 20ml (1000mg of iron) as an infusion more than once a week'. The adequate cumulative dose required by a patient could be calculated according to a formula given in the SPC; the dose must be calculated for each patient individually and must not be exceeded. The dosing of Ferinject was thus not straightforward.

Page 5 of the detail aid stated simply 'Ferinject, Up to 1000mg, Single Infusion, Dose in 15 mins'. The headline to page 6 (which faced page 5) stated 'Ferinject… the only intravenous iron that allows for 1000mg to be given in 15 mins'. Page 9, in a footnote to a table detailing administration by drip infusion, stated 'The maximum dose by infusion is 1000mg iron per week, but should not exceed 15mg/kg'.

The Panel considered that it was not acceptable to refer to the maximum permitted single dose by infusion on one page but give the qualifying information (ie the dose should not exceed 15mg/kg) on another. It was only in the prescribing information that it was stated that the cumulative dose must be calculated for each patient individually and must not be exceeded. The Panel considered that the detail aid was misleading with regard to the dosage particulars for Ferinject and a breach of the Code was ruled.

The complainant alleged that the claim 'reduces infusion time… 6hrs to 15mins' referenced to a competitor product's SPC (CosmoFer) was unreasonable given that the infusion time stated in the CosmoFer SPC was 4-6 hours.

The Panel considered that the claim 'Reduces infusion time … 6 hours to 15 minutes was misleading as it only referred to the maximum length of time over which a total dose infusion of CosmoFer could be given. A breach of the Code was ruled. The Panel considered that, for similar reasons, its ruling in this regard also applied to claims made in the brochure and the leavepiece.

The complainant alleged that in the detail aid there was no reference as to where the prescribing information appeared. It did not include a statement that prescribers should consult the SPC in relation to other side-effects. The line length of the prescribing information was much longer than the 100 characters recommended in the Code. There was no date of preparation.

The Panel noted that the detail aid was 12 pages in total and did not include a reference as to where the prescribing information could be found. A breach of the Code was ruled as acknowledged by Syner-Med. This ruling also applied to the leavepiece, again as acknowledged by Syner-Med.

The Panel noted that the side effects listed in the prescribing information were the complete list from the SPC. Thus there was no need for the prescribing information to include a statement that prescribers should consult the SPC in relation to other side effects. No breach of the Code was ruled in this regard. This ruling also applied to the brochure and the leavepiece.

The Panel noted that with regard to prescribing information the Code's supplementary information gave recommendations to assist legibility. The Panel considered that although the line length of the prescribing information at issue (around 150 characters) was more than the recommended 100 characters, this did not necessarily mean that it was not legible. The spacing between the lines and emboldening of the headings were helpful. The Panel decided that although on the limits of acceptability the prescribing information was legible and no breach of the Code was ruled. This ruling also applied to the brochure.

The Code required that the date that the prescribing information was drawn up or last revised was given. This was given as December 2007. In addition promotional material other than advertisements appearing in professional publications must include the date on which the promotional material was drawn up or last revised. The company submitted that the reference code for the detail aid included the date of preparation. However, as this was not obvious or understandable to the reader the Panel ruled a breach of the Code. This ruling also applied to the brochure and the leavepiece.

A freelance medical writer complained about promotional material for Ferinject (ferric carboxymaltose) distributed by Syner-Med (Pharmaceutical Products) Limited at the British Renal Society (BRS) meeting in Glasgow, 13/14 May 2008.

The materials at issue were a detail aid, 'The next generation intravenous iron' (ref F07/01-05-08-039), a two page brochure 'Anaemia Service… Redesigning Provision' (ref F09/07-05-08-045) and a leavepiece, 'The next generation intravenous iron' (ref F08/06-05-08-044).

When writing to Syner-Med, the Authority asked it to respond in relation to Clauses 4.1, 4.8, 4.9 and 7.2 which were the same in the 2008 Code as in the 2006 Code.

A Detail aid 'The next generation intravenous iron'

1 Dosage information

COMPLAINT

The complainant was mainly concerned about the claim in small print at the foot of page 9 that 'The maximum dose by infusion is 1000mg iron per week, but should not exceed 15mg/kg'. Clearly this information was absolutely essential for the safe prescribing of Ferinject because it meant that the maximum dose by infusion (1000mg) should not be given to a patient with a body weight of less than 67kg. However, the statement did not appear where the dosage information was boldly displayed earlier in the brochure and might easily be missed by the reader. In the interests of patient safety, and to provide a clear and accurate statement of the dosage of Ferinject by infusion, the complainant thought that this information should be incorporated in context, on pages 5/6, for example.

RESPONSE

Syner-Med submitted that pages 5/6 of the brochure complied with the Ferinject summary of product characteristics (SPC) Section 4.2 Posology and Method of Administration: a maximum single dose of Ferinject up to 1000mg might be administered over 15 minutes once a week. There was no reference to variable dosing or individual patient dosing, the two statements referred to nothing other than the maximum weekly dose and the convenience to patients of a short infusion time. No other claims about specific product dosing had been made.

Page 9 of the detail aid headed 'Ferinject Administration' clearly contained information about vial sizes, volumes of saline to be used, administration time and different methods of administration. The statement regarding the maximum single dose by infusion of 1000mg iron per week, stated that this should not exceed 15mg/kg and was correctly documented on the relevantly titled page.

PANEL RULING

With regard to the dosing information the Panel considered its ruling in another case, Case AUTH/2143/7/08 also applied here.

The Panel noted that the SPC stated 'Ferinject may be administered by intravenous infusion up to a maximum single dose of 20ml of Ferinject (1000mg of iron) but not exceeding 0.3ml of Ferinject (15mg of iron) per kg body weight or the calculated cumulative dose. Do not administer 20ml (1000mg of iron) as an infusion more than once a week'. The adequate cumulative dose required by a patient could be calculated according to a formula given in the SPC; the dose must be calculated for each patient individually and must not be exceeded. The dosing of Ferinject was thus not straightforward.

Page 5 of the detail aid stated simply 'Ferinject, Up to 1000mg, Single Infusion, Dose in 15 mins'. The headline to page 6 (which faced page 5) stated 'Ferinject… the only intravenous iron that allows for 1000mg to be given in 15 mins'. Page 9, in a footnote to a table detailing administration by drip infusion, stated 'The maximum dose by infusion is 1000mg iron per week, but should not exceed 15mg/kg'.

The Panel considered that, given the details regarding dosage in the SPC, the dosage statements in the detail aid were too simple and important information was omitted. It was not acceptable to refer to the maximum permitted single dose by infusion on one page but give the qualifying information (ie the dose should not exceed 15mg/kg) on another. It was only in the prescribing information that it was stated that the cumulative dose must be calculated for each patient individually and must not be exceeded. The Panel considered that the detail aid was misleading with regard to the dosage particulars for Ferinject and a breach of Clause 7.2 was ruled.

2 Comparison with CosmoFer

CosmoFer (iron (III)) was marketed by Vitaline Pharma UK.

COMPLAINT

The complainant alleged that the claim 'reduces infusion time… 6hrs to 15mins' on page 6, referenced to the CosmoFer SPC was unreasonable, in that it compared the maximum infusion time for CosmoFer, whereas the infusion time given in the CosmoFer SPC was 4-6 hours.

RESPONSE

Syner-Med submitted that the claim about reducing the infusion time from 6 hours to 15 minutes was made in the context of reducing the maximum amount of time a patient would spend in a clinic receiving an iron infusion. Including the impact on a patient's travel and waiting time and the overall convenience that reducing the infusion time would confer to the patient. The maximum infusion rate of Cosmofer was 6 hours.

Syner-Med strenuously refuted that it had breached Clause 7.2.

PANEL RULING

The Panel noted that the CosmoFer SPC gave two options for administration by infusion, iv drip infusion or total dose infusion. The dosage instructions for the iv drip infusion (100mg-200mg) were similar to those of the iv bolus injection (up to 200mg) detailed in the Ferinject SPC whilst the total dose infusion (up to 20mg/kg bodyweight) referred to in the CosmoFer SPC was the equivalent of the iv drip infusion (maximum 1000mg not to exceed 15mg/kg) of the Ferinject SPC. The Panel considered that the use of iv drip infusion by two companies to describe two different methods of administration was confusing and as such, given the very different doses involved, any comparison of the different methods of administration for the two products should make it abundantly clear as to which method and dose was being cited for each.

The claim at issue simply stated 'Reduces infusion time … 6 hrs to 15 mins' which was referenced to the CosmoFer SPC. The page was headed 'Ferinject … the only iv iron that allows for 1000mg to be given in 15 mins'. Given the reference to a 1000mg dose the Panel assumed that the claim at issue was about the total dose infusion for CosmoFer which could be administered over 4-6 hours.

The Panel considered that the claim 'Reduces infusion time … 6 hours to 15 minutes was misleading as it only referred to the maximum length of time over which a total dose infusion of CosmoFer could be given. A breach of Clause 7.2 was ruled.

3 Prescribing information

COMPLAINT

The complainant alleged that there was no reference as to where the prescribing information appeared. It did not include a statement that prescribers should consult the SPC in relation to other side-effects. The line length of the prescribing information was much longer than the 100 characters recommended in the Code. There was no date of preparation.

RESPONSE

Syner-Med agreed that there was no reference as to where the prescribing information appeared. The company acknowledged a technical breach of Clause 4.8 which would be corrected.

The prescribing information contained all the currently known side-effects of Ferinject and the incidence of frequency. There were no other side effects referred to in the SPC and therefore no requirement to include a statement referring prescribers to the SPC. The prescribing information was not in breach of Clause 4.2.

Each line of the prescribing information was longer than the recommended 100 characters. However every effort had been made to ensure that the prescribing information was legible. The font was Arial which was clearly legible with black type on a very light background and each section title in bold. The Code required prescribing information to be clear and legible; the 100 characters per line was a recommendation, and not a requirement. The prescribing information met the requirements for clarity and legibility. The company refuted the alleged breach of Clause 4.1.

The detail aid included a company identifiable code, date of preparation and company job number found on the back cover above the box containing the prescribing information. This code F07/01-05-08-039, denoted the code relevant to identify the item (F07), date of preparation (01-05-08) of the brochure and the print code (039). The company refuted a breach of Clause 4.9.

PANEL RULING

The Panel noted that the detail aid was 12 pages in total and did not include a reference as to where the prescribing information could be found. A breach of Clause 4.8 of the Code was ruled as acknowledged by Syner-Med.

The Panel noted that the side effects listed in the prescribing information were the complete list from the SPC. Thus there was no need for the prescribing information to include a statement that prescribers should consult the SPC in relation to other side effects. No breach of Clause 4.1 was ruled in this regard as it was this clause that required the prescribing information to be present

whereas Clause 4.2 set out the elements of the prescribing information.

The Panel noted that Clause 4.2 required prescribing information to include a succinct statement of common side effects, serious side effects and precautions and contra-indications relevant to the indications in the advertisement giving in an abbreviated form the substance of the relevant information in the SPC. The Code did not require all the information in the SPC to be given.

The Panel noted the line length used in the prescribing information was longer than 100 characters. The supplementary information to Clause 4.1, Legibility of Prescribing Information gave recommendations to assist legibility. The Panel considered that although line length at around 150 characters was more than recommended this did not necessarily mean the prescribing information was not legible. The spacing between the lines and emboldening of the headings were helpful. The Panel decided that although on the limits of acceptability the prescribing information was legible and no breach of Clause 4.1 was ruled.

The Code required that the date that the prescribing information was drawn up or last revised was given (Clause 4.2). This was given as December 2007. In addition promotional material other than advertisements appearing in professional publications must include the date on which the promotional material was drawn up or last revised. The Panel noted Syner-Med's submission that the reference code for the item included the date of preparation. However this was not obvious or understandable to the reader. Thus the Panel ruled a breach of Clause 4.9.

B Brochure 'Anaemia Service… Redesigning Provision'

Page 2 of the brochure included a section headed 'Time to Deliver i.v. Iron Dose (incl 10min setup time/visit)'. This was followed by a bar chart which showed that CosmoFer 1000mg took 370 minutes to deliver including 10 minutes to set up. The key beside the barchart stated that CosmoFer was a 6 hour iv infusion.

1 Comparison with CosmoFer

COMPLAINT

The complainant alleged that, as in point A2 above, the 'Time to Deliver' data compared the maximum infusion time for CosmoFer, whereas the infusion time given in the CosmoFer SPC was 4-6 hours.

RESPONSE

Syner-Med referred to its response in point A2 above.

PANEL RULING

The Panel considered that although the brochure was different to the detail aid it was nonetheless misleading for similar reasons stated in point A2 above. A breach of Clause 7.2 was ruled.

2 Prescribing information

COMPLAINT

The complainant alleged that the prescribing information did not include a statement that prescribers should consult the SPC in relation to other side-effects. The lines of the prescribing information were very much longer than the 100 characters recommended in the Code. There was no date of preparation.

RESPONSE

Syner-Med referred to the relevant part of its response in point A3 above.

PANEL RULING

The Panel considered that the relevant part of its rulings in point A3 above applied here ie no breach of the Code regarding the statement to consult the SPC in relation to side-effects and the line length of the prescribing information and a breach of Clause 4.9 with regard to the date of preparation.

C Leavepiece 'The next generation intravenous iron'

1 Comparison with CosmoFer

COMPLAINT

The complainant alleged that, as in point A2 above, the claim 'reduces infusion time… 6hrs to 15mins' compared the maximum infusion time for CosmoFer, whereas the infusion time given in the CosmoFer SPC was 4-6 hours.

RESPONSE

Syner-Med referred to its response in point A2 above.

PANEL RULING

The Panel noted that the leavepiece was very similar to the detail aid and that it was misleading for similar reasons to those stated in point A2 above. A breach of Clause 7.2 was ruled.

2 Prescribing information

COMPLAINT

The complainant alleged that there was no reference as to where the prescribing information appeared. The prescribing information did not include a statement that prescribers should consult the SPC in relation to other side-effects. There was no date of preparation.

RESPONSE

Syner-Med referred to its response in point A3 above.

PANEL RULING

The Panel noted that the leavepiece was 6 pages in total and did not include a reference as to where the prescribing information could be found. A breach of Clause 4.8 was ruled as acknowledged by Syner-Med.

The Panel considered that the relevant part of its rulings in point A3 above applied here ie no breach of the Code regarding the statement to consult the SPC in relation to other side effects and a breach of Clause 4.9 with regard to the date of preparation.

Complaint received	**24 July 2008**
Case completed	**21 August 2008**

CASE AUTH/2150/7/08

GENERAL PRACTITIONER v PFIZER

Toviaz journal advertisements

A general practitioner complained about two advertisements for Toviaz (fesoterodine) issued by Pfizer. One advertisement (published in July 2008) was a revised version of a previous advertisement. At issue were claims comparing the efficacy of Toviaz with tolterodine (Pfizer's product Detrusitol) in the treatment of overactive bladder syndrome (OAB).

The detailed response from Pfizer is given below.

The complainant noted that the phrase 'Article in press' had been used in both advertisements in support of two different, although similar, claims. In the original advertisement this was clearly false as the article in question was not actually in press until 18 July 2008 when it was available online for the first time. The complainant stated that if a journal had agreed to publish a manuscript the usual convention was to state that it had been 'accepted' for publication. The complainant presumed that Pfizer had used 'Article in press' to suggest that this publication, which it had sponsored, had already been accepted by a prestigious peer reviewed journal and so lend gravitas to the claims to which it referred.

The Panel considered that as the article in question, Chapple *et al* (2008), had been accepted for publication in March 2008 it was not unacceptable to describe it as an 'Article in press' in advertisements prepared in May and June 2008; readers would understand that the study was to be published whether such publication was in print or online. The phrase was not misleading or incorrect. No breach of the Code was ruled.

The complainant alleged that the two claims at issue were misleading and not supported by Chapple *et al*. The complainant noted that the claim in the original advertisement 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' did not include p values. The claim in the revised advertisement 'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically, severe urgency with UUI per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours' was asterisked to a footnote in smaller type 'Analysis of Toviaz 8mg vs tolterodine ER was not part of the original study plan. Starting dose 4mg titrated up to 8mg for more efficacy'.

The complainant stated that 'significantly better than' in the revised advertisement invited readers to assume that not only was the significant superiority of Toviaz 8mg clinically relevant but also statistically significant compared with Toviaz 4mg [sic]. This was misleading.

The footnote highlighted that the claim was based on an unplanned retrospective analysis after unblinding data from two studies and which focussed inappropriately on selective outcome variables in the knowledge that the primary efficacy variable showed no difference between Toviaz 4mg and 8mg. Indeed, it appeared that the statistical analysis section described only planned comparisons of Toviaz vs placebo in the individual studies. There was no mention of any intention to pool study data or undertake a planned meta-analysis that would validate the introduction of a specific comparison of Toviaz 8mg vs 4mg. The complainant alleged that this was a blatant example of data massaging.

Whilst the footnote provided additional information, it fundamentally altered the interpretation and message of the claim as it appeared in the original advertisement and revised advertisement but was also not capable of being substantiated. The complainant understood that the Code did not permit misleading headlines to be corrected by a footnote.

The complainant considered that the Authority should address this potentially serious matter with Pfizer and ask why Pfizer should not be subject to an enquiry as to why such shoddy and misleading promotional materials were used. Given Pfizer's propensity to mislead, make false statements and fail to comply with previous undertakings (ie Case AUTH/2130/0/08) the complainant believed Pfizer had brought the ABPI into disrepute and must face appropriate sanctions.

The Panel noted that there was some confusion on the complainant's part as to the claims being made and to the basis of those claims. The Panel considered the claims as written and referenced in the advertisements at issue.

The Panel noted that the study to which the claims were referenced (Chapple *et al* 2008) was a post hoc analysis of a phase 3 study by Chapple *et al* (2007). The original study had investigated the efficacy, tolerability and safety of Toviaz 4mg and 8mg vs placebo in OAB. The study included a tolterodine ER 4mg arm as an active control. Both doses of Toviaz were significantly better than placebo in improving the symptoms of OAB. Efficacy was more pronounced with Toviaz 8mg than with other treatments. The post hoc study

extracted from the original study only the data relating to Toviaz 8mg, tolterodine ER 4mg and placebo and examined the results for the primary endpoint (voids/24h), the two co-primary endpoints (urgency urinary incontinence (UUI) episodes/24h and treatment response), several secondary endpoints and health related quality of life HRQoL. The data showed that by week 12 patients in both active-treatment groups showed significant improvements in most bladder diary variables and treatment response rates compared with placebo. Toviaz 8mg was statistically significantly better than tolterodine ER 4mg for improving UUI episodes, severe urgency plus UUI, mean voided volume and number of continent days/week. In addition the Toviaz and tolterodine groups showed significantly greater improvements in HRQoL than the placebo group. A major improvement in the severity of bladder-related problems was reported by 39% of the Toviaz group and 34% of the tolterodine ER groups v 25% of those on placebo ($p \leq 0.01$). The author stated that one of the limitations of the study was that it was a post hoc analysis of a study which was not powered for a comparison between active treatments or for HRQoL. Prospective studies were under way. The lack of consensus on measurement of the urgency classification was described as another shortcoming.

The Panel noted that the claim in the first advertisement 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' was very general. The Panel was concerned that the post hoc comparison of Toviaz 8mg with tolterodine ER 4mg was not part of the original study plan and that the original study was not powered for such a comparison. The Panel thus considered that the claim was misleading, and ruled a breach of the Code which was accepted by Pfizer. Chapple *et al* (2008) did not substantiate the claim and thus a further breach of the Code was also ruled, which was upheld on appeal by Pfizer.

With regard to the second advertisement the Panel noted that it was a well established principle under the Code that a claim could not be qualified by a footnote. It considered that given the statements in Chapple *et al* (2008) about the limitations of the study, the fact that it was a post hoc analysis and that Chapple *et al* (2007) was not powered for a between treatments comparison meant that the claim 'Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically…' was misleading and not capable of substantiation. Breaches of the Code were ruled, which were upheld on appeal by Pfizer.

The position was further confused by the second part of the footnote 'Starting dose 4mg titrated up to 8mg for more efficacy'. This did not apply to Chapple *et al* (2007) where patients received medicine at the same dose throughout the study. It appeared to be more general information about the use of Toviaz as according to its summary of product characteristics the recommended starting dose of 4mg once daily could, according to individual response, be increased to 8mg once daily (the maximum daily dose).

Overall, the Panel considered that high standards had not been maintained and a breach of the Code was ruled, which was upheld on appeal by Pfizer.

The Panel noted that Clause 2 of the Code was reserved as a sign of particular censure. It considered on balance that the circumstances did not warrant a ruling of a breach of that clause. This ruling was upheld on appeal by the complainant.

A general practitioner complained about the promotion of Toviaz (fesoterodine fumarate) by Pfizer Limited. Pfizer also marketed Detrusitol (tolterodine). Both products were for the symptomatic treatment of overactive bladder syndrome (OAB).

This case was considered under the 2008 Constitution and Procedure. When writing to Pfizer the Authority asked it to comment in relation to Clauses 2, 7.2, 7.4 and 9.1 of the Code which were the same in the 2008 Code as in the 2006 Code.

1 Use of the phrase 'Article in press'

The phrase 'Article in press' appeared as a reference in an advertisement (TOV097b) and in the revised edition of that advertisement (ref TOV162) which was published in Geriatric Medicine (July 2008).

The 'Article in press' (Chapple *et al* 2008) was used as a reference for the claim 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' in the original advertisement (TOV097b). It was also used as a reference to the claim 'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically, severe urgency with [urgency urinary incontinence] UUI per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours' in the updated advertisement (TOV162).

COMPLAINT

The complainant stated the claim 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' did not include p values. It was referenced to Chapple *et al* ('Clinical efficacy, safety, tolerability of once-daily fesoterodine in subjects with an overactive bladder') which was cited as being an 'Article in press' in the British Journal of Urology International. This was clearly false given that it was not actually in press until 18 July 2008 when it was available online for the first time! The

complainant stated that if the journal in question had agreed to publish the manuscript the usual convention was to state that the publication was 'accepted' for publication.

The complainant presumed the reason why Pfizer considered the use of the wording 'Article in press' appropriate, thereby suggesting that this Pfizer sponsored publication had already been accepted by a prestigious peer reviewed journal, was because it lent gravitas to the promotional claims to which it referred.

In the revised advertisement (TOV162) the same misleading wording with regard to the publication status of Chapple *et al* was used in support of a similar claim.

RESPONSE

Pfizer explained that the phase 3 clinical trial program for Toviaz consisted of two key trials. These were both published as primary publications: Chapple *et al* (2007) and Nitti *et al* (2007). As was common with clinical trial programmes, subsequent publications and analysis had been produced. One of these publications was a further analysis of data regarding maximum recommended doses of fesoterodine (8mg) and tolterodine (4mg). This was currently published online as Chapple *et al* (2008) ('Comparison of fesoterodine and tolterodine in subjects with overactive bladder. British Journal of Urology International. (Epub ahead of print)').

The complaint was wrong to state that the claim 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' was referenced to Chapple *et al* (2007) ('Clinical efficacy, safety and tolerability of once-daily fesoterodine in subjects with overactive bladder'). This particular manuscript was accepted for publication by the journal European Urology on 6 July 2007; published online on 17 July 2007 and appeared in Issue 4 of Volume 52 on October 2007 and was referenced as such when used.

The above claim, as used in both advertisements (TOV097b and TOV162) was substantiated from the correctly referenced publication Chapple *et al* (Article in press).

When the advertisements were prepared (May 2008 – TOV097b and June 2008 – TOV162) the term 'Article in press' was accurate as the article had been accepted by the British Journal of Urology International on 28 March 2008 and published online on 21 July 2008. The statement 'Article in press' was an acceptable and common phrase to describe a manuscript that had been submitted and accepted by a journal, but where an imminent date of publication had not been provided by the journal. It was not misleading nor false as the complainant had suggested.

Pfizer therefore, refuted a breach of Clauses 2, 7.4 and 9.1.

PANEL RULING

The Panel noted that when referring to the Chapple *et al* article that was yet to be published, the complainant had cited the title of Chapple *et al* (2007). The Panel considered that as Chapple *et al* (2008) had been accepted for publication it was not unacceptable to describe it as an 'Article in press'; readers would understand that the study was to be published whether such publication was in print or online. The phrase was not misleading or incorrect. No breach of Clause 7.2 was ruled.

2 Claims 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' (TOV097b) and **'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically, severe urgency with UUI per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours'** (TOV162).

Both claims were referenced to Chapple *et al* (2008) (Article in press). The second claim was asterisked to a footnote in smaller type 'Analysis of Toviaz 8mg vs tolterodine ER was not part of the original study plan. Starting dose 4mg titrated up to 8mg for more efficacy'.

COMPLAINT

The complainant alleged that the claims were misleading and not supported by Chapple *et al* (2008). The first claim (in TOV097b) did not include the p values and the footnote to the second claim (in TOV162) was barely legible. The wording 'significantly better than' invited readers to assume that not only was the significant superiority of Toviaz 8mg clinically relevant but also statistically significant compared with Toviaz 4mg [sic]. This was misleading.

The footnote highlighted that the claim was based upon an unplanned retrospective analysis after unblinding data from two studies and which focussed inappropriately on selective outcome variables in the knowledge that the primary efficacy variable showed no difference between Toviaz 4mg and 8mg. Indeed, it appeared that the statistical analysis section described only planned comparisons of Toviaz vs placebo in the individual studies. The publication made no mention of any intention to pool study data or undertake a planned meta-analysis that would validate the introduction of a specific comparison of Toviaz 8mg vs 4mg.

Given the latter, the complainant had discussed the statistical validity of this claim with a pharmacist colleague. They reviewed the two published

primary studies, upon which Chapple *et al* (2008) was based and it was clear that in these studies the statistical analysis plan started off with micturition frequency in what was described as a sequentially rejective closed-test procedure and then moved on to the next specified endpoints only if this was statistically significant. It was therefore logical to assume that micturition frequency was also the primary variable (or one of the primary variables) for Chapple *et al* (2007). In the latter, however, Chapple *et al* failed to show statistical significance of Toviaz 8mg vs 4mg. Therefore it seemed that there was no statistical basis that justified the statistical testing of other endpoints referred to in the publication and in the revised advertisement; this important clarification was completely missing both in Chapple *et al* (2008) and in the advertisement footnote. Indeed, if Chapple *et al* applied the same method as for the individual study protocols, they had to stop testing after the test for micturition frequency had failed and would have had to declare all endpoints were not statistically significant with respect to differences between Toviaz 8mg vs 4mg.

It therefore appeared that these studies had been selected for discussion in this publication on the basis of their results and called into question the validity of this citation as substantiation of the superiority claim for 8mg Toviaz, in both Toviaz advertisements. Indeed, the timing of this retrospective analysis, which clearly occurred after the unblinding of the data, totally nullified the basis for undertaking any comparison. The complainant alleged that this was a blatant example of 'data massaging'.

Whilst the footnote provided additional information, it fundamentally altered the interpretation and message of the promotional claim as it appeared in the original advertisement and revised advertisement but was also not capable of being substantiated. The complainant understood that the Code did not permit misleading headlines to be corrected by a footnote.

The complainant believed that this unsubstantiated claim was cited in many other Toviaz promotional materials including the Toviaz detail aid (which the Pfizer sales representative did not allow the complainant to have a copy of… was this consistent with the Code?) and promotional flyers (TOV096 and TOV095). The complainant believed these documents must be scrutinised to ascertain the above.

The complainant considered that the Authority should address this potentially serious matter with Pfizer and also ask why Pfizer should not be subject to an enquiry as to why such shoddy and misleading materials were used. Given Pfizer's propensity to mislead, make false statements and fail to comply with previous undertakings (ie Case AUTH/2130/0/08) the complainant believed Pfizer had brought the ABPI into disrepute and must face appropriate sanctions.

RESPONSE

Pfizer stated that the initial advertisement (TOV097b), was withdrawn due to lack of prescribing information (Case AUTH/2130/6/08) and the claim, Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' was no longer used. Pfizer therefore refuted a breach of Clause 7.2.

Pfizer stated that although the publication supporting the claim was clearly separate from the primary publication and was specifically about the comparison of fesoterodine and tolterodine (Chapple *et al* 2008), Pfizer included the footnote 'Analysis of Toviaz 8mg vs. tolterodine ER was not part of the original study plan' in the updated advertisement specifically so that readers might obtain a comprehensive and balanced view of the data to form an opinion on the therapeutic value of the medicine. The footnote did not fundamentally alter the interpretation and message of the claim as alleged by the complainant. The footnote was in a clearly legible font size and placed immediately below the claim.

Pfizer therefore, refuted breaches of Clauses 2, 7.2 and 9.1.

In the revised advertisement (TOV162), additional information was included specifically to ensure it was not misleading and clearly reflected the available evidence. The updated advertisement stated 'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically, severe urgency with UUI per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours' which made it clear to the reader which outcomes reached a statistical and clinical relevant result and it was appropriately substantiated by its reference.

The complainant had made some fundamental errors in his statistical assessment of the claim. The claim was not based on a pooled analysis of the two primary studies, nor was there any comparison of Toviaz 4mg vs Toviaz 8mg in the paper or in the claim.

Chapple *et al* (2008) used to substantiate the claim was a post hoc analysis of one phase 3 trial, in which fesoterodine 8mg was compared to tolterodine 4mg (Chapple *et al* 2007). Although statistical methods used in post hoc analyses might be similar to the primary methods used in the study they did not necessarily follow the same approach regarding controlling for error rates.

The closed-testing methodology used in the analysis of the three co-primary endpoints in the original fesoterodine phase 3 trials was appropriate for controlling experiment-wise error rates. The need to use such methodology was, however, unusual for over active bladder (OAB) trials in general, since the overwhelming majority of

published OAB studies had one primary endpoint and multiple secondary endpoints.

When performing post hoc analyses Pfizer typically reported p values without adjustments, in order to help understand treatment differences separately, and not in the context of the overall error rate that also considered other comparisons. Generating individual comparison p values was an accepted and common practice when performing post hoc and secondary analyses.

The statistical methods employed in the Chapple *et al* (2008) post hoc analysis were clearly described in the British Journal of Urology International manuscript, which was accepted for publication following peer review and considered level 1b evidence by the journal. This publication was robust, peer-reviewed and accurately portrayed in promotional materials.

Pfizer had never claimed superiority of Toviaz 8mg in any of its materials and strongly objected to any allegation of data massaging. Pfizer did not consider any of its materials to be in breach of Clauses 7.2 or 7.4.

Pfizer submitted that its representatives were not obliged to distribute promotional materials that were not intended for that purpose. Detail aids, which remained the property of Pfizer, were designed to be retained by the representative and used with the health professional as part of a discussion. Promotional items intended to be left with a health professional were designed with that function in mind. This practice was entirely consistent with the Code.

Pfizer did not consider the promotional items mentioned by the complainant had breached the Code and firmly believed that they were properly referenced, accurate and factually correct without being misleading. Pfizer also had maintained high standards and ensured that its items and activities did not diminish the reputation of the industry. Pfizer firmly believed that upon examination of the complainant's concerns, there were no breaches of the Code.

Pfizer aimed to continually review all its promotional materials to ensure they complied with the Code in word and in spirit. It was keen to ensure the highest standard of professional practice and to safeguard the reputation of the industry.

PANEL RULING

The Panel noted that the study to which the claims were referenced (Chapple *et al* 2008) was a post hoc analysis of a phase 3 study by Chapple *et al* (2007). The original study had investigated the efficacy, tolerability and safety of Toviaz 4mg and 8mg vs placebo in OAB. The study included a tolterodine ER 4mg arm as an active control. Both doses of Toviaz were significantly better than placebo in improving the symptoms of OAB. Efficacy was more pronounced with Toviaz 8mg than with other treatments. The post hoc study extracted from the original study only the data relating to Toviaz 8mg, tolterodine ER 4mg and placebo and examined the results for the primary endpoint (voids/24h), the two co-primary endpoints (urgency urinary incontinence (UUI) episodes/24h and treatment response), several secondary endpoints and health related quality of life HRQoL. The data showed that by week 12 patients in both active-treatment groups showed significant improvements in most bladder diary variables and treatment response rates compared with placebo. Toviaz 8mg was statistically significantly better than tolterodine ER 4mg for improving UUI episodes, severe urgency plus UUI, mean voided volume and number of continent days/week. In addition the Toviaz and tolterodine groups showed significantly greater improvements in HRQoL than the placebo group. A major improvement in the severity of bladder-related problems was reported by 39% of the Toviaz group and 34% of the tolterodine ER groups v 25% of those on placebo ($p \leq 0.01$). The author stated that one of the limitations of the study was that it was a post hoc analysis of a study which was not powered for a comparison between active treatments or for HRQoL. Prospective studies were under way. The lack of consensus on measurement of the urgency classification was described as another shortcoming.

The Panel noted that there appeared to be some confusion. Both advertisements included two claims based on Chapple data. Firstly, that Toviaz was effective in relieving the most bothersome symptoms of OAB at both 4mg and 8mg doses referenced to Chapple *et al* (2007) and secondly, the claims comparing Toviaz 8mg with tolterodine ER 4mg (not Toviaz 4mg as submitted by the complainant) referenced to Chapple *et al* (2008). Chapple *et al* (2008) was based on Chapple *et al* (2007) not two studies as stated by the complainant.

The Panel noted that the original study (Chapple *et al* 2007) had demonstrated more pronounced treatment effects with Toviaz 8mg than with tolterodine ER 4mg or Toviaz 4mg. There was no comparison between treatments. Thus it appeared that the complainant's comments about the statistical analysis, in this regard were misguided.

The Panel considered that some of the complainant's comments about Chapple *et al* (2008) were relevant to the comparison of Toviaz 8mg with tolterodine 4mg.

The Panel noted that the claim in the first advertisement (TOV097b) 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' was very general. The Panel was concerned that the post hoc comparison of Toviaz 8mg with tolterodine ER 4mg was not part of the original study plan and that the original study was not powered for such a comparison. The Panel

thus considered that the claim was misleading, and ruled a breach of Clause 7.2 which was accepted by Pfizer. Chapple *et al* (2008) did not substantiate the claim and thus a breach of Clause 7.4 was also ruled.

With regard to the second advertisement (TOV162) the Panel noted that it was a well established principle under the Code that a claim could not be qualified by a footnote. It considered that given the statements in Chapple *et al* (2008) about the limitations of the study, the fact that it was a post hoc analysis and that Chapple *et al* (2007) was not powered for a between treatments comparison meant that the claim 'Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically…' was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

The position was further confused by the second part of the footnote 'Starting dose 4mg titrated up to 8mg for more efficacy'. This did not apply to Chapple *et al* (2007) where patients received medicine at the same dose throughout the study. It appeared to be more general information about the use of Toviaz as according to its summary of product characteristics the recommended starting dose of 4mg once daily could, according to individual response, be increased to 8mg once daily (the maximum daily dose).

Overall, the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that Clause 2 was reserved as a sign of particular censure. It considered on balance that the circumstances did not warrant a ruling of a breach of that clause.

APPEAL BY PFIZER

Pfizer accepted a breach of Clause 7.2 in relation to the claim 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' in TOV097b, as it agreed that the claim could be viewed as too general. Before the complaint was received, Pfizer had withdrawn TOV097b to provide additional information so that there was no doubt about which treatment endpoints had reached statistical significance. The claim 'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically severe urgency with UUI per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours' in the subsequent advertisement, TOV162, stated that the significant improvements with Toviaz 8mg compared with tolterodine ER 4mg were relevant to a number of defined endpoints. These endpoints were then clearly specified, with no indication that this statistical significance related to all endpoints measured. Furthermore, a footnote was added to provide further information on the analysis and to ensure that the material was sufficiently complete to enable the reader to form their own opinion; the footnote did not qualify the claim.

Pfizer therefore submitted that the claim in the advertisement TOV162 was not misleading, and not in breach of Clause 7.2.

Pfizer noted that the Panel had ruled a breach of Clause 7.4 in relation to both advertisements TOV097b and TOV162. The Panel was concerned that the post hoc comparison of Toviaz 8mg with tolterodine ER 4mg was not part of the original study plan and that the original study was not powered for between-treatment comparisons (Chapple *et al*).

Pfizer submitted that a post hoc analysis was conducted to explore patterns that were not specified at the time of protocol development. Typically, studies were powered for the primary endpoint(s) only, which in this case was the comparison of the two doses of Toviaz with placebo on the three co-primary endpoints. Generally, neither secondary endpoints nor additional analyses might be statistically powered, and should be regarded as exploratory. Such data might still be able to substantiate claims, provided the materials clearly contained this context information on the nature of the data, so as to ensure the reader was not misled.

Whilst the comparison of the two Toviaz doses with tolterodine ER was not the primary endpoint in the phase 3 trial, it was of clinical interest and had been pre-specified in the statistical analysis plan (provided). The comparison was carried out on the full analysis set with the last observation carried forward (LOCF), and the patient populations were not selected, altered or modified compared with those used for the pre-specified analyses (Chapple *et al*). The results for the co-primary endpoint urge incontinence showed that the 95% confidence interval for the treatment difference of 0.48 episodes/day between Toviaz 8mg and tolterodine ER 4mg was (-0.92; -0.05) (Pfizer data on file). Since this did not contain zero this indicated a difference between the two treatments with respect to urge incontinence.

The statistical methods used for the comparison of Toviaz 8mg with tolterodine ER were clearly described in the manuscript which was accepted for publication following peer review and considered level 1b evidence by British Journal of Urology International, a well respected, peer-reviewed journal. Pfizer therefore did not agree that the claims in the advertisements TOV097b and TOV162 were unsubstantiated by the post hoc evidence, and did not agree that these materials were in breach of Clause 7.4.

Pfizer stated that it was committed to producing promotional materials of a high standard that

conformed to the letter and the spirit of the Code. Pfizer's continuous review of promotional materials ensured an accurate reflection of up-to-date clinical data in a manner that encouraged transparency and gave the reader a comprehensive view of all the available evidence. Through rigorous internal processes Pfizer strove to ensure that it truthfully portrayed its clinical evidence to health professionals.

Pfizer submitted that it had maintained high standards relating to its promotion of Toviaz, and therefore denied a breach of Clause 9.1.

COMMENTS FROM THE COMPLAINANT

The complainant alleged that the main claim comparing the comparative efficacy of Toviaz 8mg vs tolterodine ER could not be substantiated or supported by the cited reference or the footnotes adopted for the very clear and salient reasons described by the Panel in its ruling; the complainant entirely agreed with these rulings.

Indeed, Pfizer's response clearly demonstrated that the original study never intended to produce robust and statically valid comparative data, which was normally what one expected to support a promotional claim of superior efficacy of one medicine versus another as this particular claim did. Indeed, the statistical analysis plan that Pfizer referred to explicitly stated that the comparison was primarily planned to be between Toviaz treatment groups and placebo. The only valid comparison involving tolterodine ER was with respect to placebo and even this was only undertaken to check assay sensitivity in an exploratory manner; hardly a clear and definitive basis upon which to make commercial claims of superior efficacy of Toviaz 8mg over tolterodine ER! Indeed where the statistical analysis plan mentioned a comparison of Toviaz with tolterodine ER it specified that it was with respect to the two doses of Toviaz and that it was exploratory and no p-values would be produced (ie this comparison was not statistically valid for the purposes of making promotional claims that one would reasonably expect to be based upon data that were both statistically and clinically significant).

Notwithstanding the Panel's ruling that an exploratory analysis could not be the basis on which to invite bold commercial claims of superiority for obvious reasons one must also then ask why the comparison between Toviaz 4mg and tolterodine ER was also not used in the promotional claim; surely this would be consistent with the statistical analysis plan. The complainant alleged that this was a clear example of cherry-picking the data and arguments that suited Pfizer. The complainant would not be surprised if the efficacy of Toviaz 4mg was equivalent or worse than that of tolterodine ER; a fact that would obviously not suit Pfizer's promotional strategy of promoting a switch of tolterodine ER 4mg patients to Toviaz 8mg which was clearly likely to be more efficacious than Toviaz 4mg. In fact, in the event that the statistical analysis plan allowed a valid/robust comparison capable of supporting promotional claims without qualifications (which it did not in this case), one might even question whether the comparison of the highest dosage of Toviaz (also an extended release formulation) against tolterodine ER 4mg was fair given that mg-for-mg it did not compare equivalent dosages of the two virtually similar medicines.

The complainant was sure that all ABPI companies would like to develop promotional campaigns based on exploratory data supported by post hoc analysis conducted to explore patterns that were not specified at the time of protocol development; it was called data massaging and was certainly a lot less expensive and time consuming than undertaking robust clinical studies. Indeed if Pfizer's statement did not clearly demonstrate why breaches of the Code, including Clause 2, were not warranted, then the complainant was not sure what did.

Pfizer was obviously unabashed about its reliance on what was essentially dodgy/spurious data in support of a cynical campaign which essentially now advised all prescribers of tolterodine ER, that for the many years that Pfizer promoted tolterodine ER as the best in class and encouraged its prescription for the management of OAB it had in fact got it wrong especially now that its patent expiry was imminent. The misleading reasons Pfizer promoted as to why doctors should now prescribe Toviaz instead of tolterodine ER was that the efficacy/mode of action/route of metabolism, side-effect profile of tolterodine ER were all somehow inferior to the recently launched Toviaz where patent expiry and the bottom-line were not such an urgent concern.

Prescribers expect to be provided with data/information and promotional messages in a manner and of a quality consistent with the standards prescribed by the Code. The Toviaz promotional materials that the complainant had seen both in the UK and at various international congresses, since its launch fell well below this.

APPEAL BOARD RULING

The Appeal Board noted that Pfizer had appealed the Panel's ruling of a breach of Clause 7.4 in relation to the claim 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes'. Pfizer submitted that the claim was capable of substantiation by Chapple *et al* (2008) notwithstanding the fact that it had accepted that the claim was misleading in breach of Clause 7.2. The Appeal Board was concerned that the post hoc comparison of Toviaz 8mg with tolterodine ER 4mg was not part of the original study plan and that the original study was not powered for such a comparison. Chapple *et al* (2008) did not substantiate the claim and thus the Appeal Board

upheld the Panel's ruling of a breach of Clause 7.4 of the Code. The appeal on this point was unsuccessful.

With regard to the second advertisement (TOV162) the Appeal Board considered that the claim at issue, '… Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; …' also referenced to Chapple *et al* 2008 implied statistical significance which was not so. The Appeal Board did not accept Pfizer's submission at the appeal that it was not claiming statistically significant superiority. There was a clear claim of superiority in the advertisement and this would be read as being clinically and statistically significant. The statistical analysis plan for Chapple (2008) had stated that the comparison of the two doses of Toviaz with tolterodine ER would only be done as an exploratory analysis and no p-values would be provided. Although a footnote stated 'Analysis of Toviaz 8mg v tolterodine ER was not part of the original study plan' otherwise misleading claims could not be so qualified. The Appeal Board considered that given the data upon which it was based, the claim was misleading and had not been substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

The position was further confused by a second footnote which stated 'Starting dose 4mg titrated up to 8mg for more efficacy'. This did not apply to Chapple *et al* where patients received Toviaz at the same dose (4mg or 8mg) throughout. It appeared that the footnote gave more general information about the use of Toviaz; according to its summary of product characteristics (SPC) the recommended starting dose was 4mg once daily which could, according to individual response, be increased to 8mg once daily (the maximum daily dose).

Overall, the Appeal Board considered that high standards had not been maintained and it upheld the Panel's ruling of a breach of Clause 9.1 of the Code. The appeal on this point was unsuccessful.

During its consideration the Appeal Board noted that the Toviaz SPC stated that 'The recommended starting dose is 4mg once daily. Based upon individual response, the dose may be increased to 8mg once daily. The maximum daily dose is 8mg'. The Appeal Board noted that in Chapple *et al* (2007) patients were started on either a 4mg or 8mg dose of Toviaz. The patients started on the maximum daily dose of 8mg Toviaz had not been treated in accordance with the Toviaz SPC.

APPEAL BY THE COMPLAINANT

The complainant was disappointed regarding the Panel's decision not to rule a breach of Clause 2. This seemed particularly at odds with the decision that Pfizer had not maintained high standards. Arguably the need to maintain high standards not only compromised prescriber's confidence but also patient safety and as such any ABPI company that was censured with respect to Clause 9.1 had also brought the industry into disrepute.

An analogy in this regard was the consequences faced by health professionals who failed to maintain high standards in communicating erroneous, misleading advice/information to patients; in this event the General Medical Council Fitness to Practice Committee was very likely to impose some very stringent sanctions … not simply a monetary fine, which was probably considered to be loose change to companies such as Pfizer. A ruling of a breach of Clause 2 was appropriately punitive and should be considered by the Appeal Board.

Finally, the complainant also wanted reassurance that Pfizer would be required to address and implement the Panel's rulings across all of the Toviaz promotional materials given that the latter all contained claims which were ruled to be in breach of the Code.

COMMENTS FROM PFIZER

Pfizer submitted that a breach of Clause 9.1 did not automatically warrant a breach of Clause 2 which was a sign of particular censure and was reserved for circumstances in which a company brought discredit to, and reduced confidence in, the pharmaceutical industry. Pfizer did not believe the particulars of this case fell into that category.

Pfizer did not agree with the complainant that the promotional claims in question were detrimental to patient safety or prescriber confidence. Pfizer was committed to producing high quality promotional materials that complied to both the letter and spirit of the Code.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant confirmed that the latter aspects of his response to Pfizer's appeal also referred to why he still considered a breach of Clause 2 was warranted regardless of Pfizer's comments on his appeal regarding this particular clause.

APPEAL BOARD RULING

The Appeal Board noted that Clause 2 of the Code was reserved as a sign of particular censure. Although noting its rulings above, the Appeal Board did not consider that the circumstances warranted a ruling of a breach of that clause. The Appeal Board upheld the Panel's ruling of no breach of Clause 2.

Complaint Received **25 July 2008**

Case Completed **28 October 2008**

CASE AUTH/2151/7/08

MEDIA/DIRECTOR v LILLY

Website and associated TV campaign on erectile dysfunction

The Financial Times (FT) of 29 July criticised Lilly's 40over40 campaign. In accordance with the Constitution and Procedure this matter was taken up by the Director as a complaint under the Code.

The article, 'Sex problems campaign will test rules', alleged that US-style advertising for drugs was coming to Britain in the shape of a television campaign to raise awareness of erectile dysfunction (ED). Lilly had launched a series of television and national newspaper advertisements – the most ambitious to date about ED, accompanied by internet sites and discussion groups, which would run until September. The campaign raised the prospect of Britons for the first time being subject to the kind of widespread advertising for ED medicines that had become so common to US television, particularly during sporting events and other programming that appealed to men.

Lilly's product, Cialis, was the most recent of three prescription medicines launched in the competitive ED market. The advertisements did not directly name any of the prescription medicines available for the condition, but stressed that leading treatment options included the use of three different medicines, and Lilly used its own corporate logo prominently.

The article noted that consumer advertising of prescription medicines in the US had been criticised for disease mongering.

The UK campaign, 40over40, referred to the claim that 40 per cent of men over 40 years old suffer from ED – included a table that listed three anonymous oral tablets as the most prominent form of treatment. While not naming Cialis or its rivals Viagra and Levitra, the first entry in the table was identifiable as Cialis through a description of its unique characteristics and side-effects. Lilly also placed its own logo at the foot of the web page next to another website sponsored by the company. The advertisements marked a sharp advance in a trend for medicines marketing in the UK, at a time when pharmaceutical companies were struggling to bolster revenues.

The detailed response from Lilly is given below.

The Panel considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake provided that they were in accordance with the Code. Such activities might facilitate the market development of the sponsoring company's products but this was not necessarily in breach of the Code. Each case would need to be judged on its merits.

The Panel noted that supplementary information to the Code stated that a company might conduct a disease awareness or public health campaign provided that the purpose was to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine. The use of brand or non-proprietary names and/or restricting the range of treatments described in the campaign might be likely to lead to the use of a specific medicine. Particular care must be taken where the company's product, even though not named, was the only medicine relevant to the disease or symptoms in question.

The Panel considered that the campaign was within the scope of the Code as it could not take the benefit of the exemption for information relating to human health or diseases provided there was no reference either direct or indirect to specific medicines.

The television advertisement did not refer to medicines other than a general statement that there was a range of treatments that could help. It gave details of the website 40over40.com. The Panel did not consider that the television advertisement *per se* constituted an advertisement to the public for a prescription only medicine nor would it encourage a patient to ask their health professional to prescribe a specific medicine. No breach of the Code was ruled.

The 40over40.com website gave detailed information set out under four sections 'talk' 'test' 'treat' and 'today'. In the Panel's view the sections 'talk' 'test' and 'today' gave helpful information about ED. The 'treat' section included a chart setting out various features about the medicines and devices available. The chart was also included in the 4t Action Plan for patients to download and discuss with their doctor. Neither the treatment chart on the website nor the 4t Action Plan named any of the products. The sections were divided into oral treatments where details of products 1, 2 and 3 were given, injections or insertions which gave details of three products and vacuum pumps and constriction rings which stated that ten different types were available. The features compared for each product were 'How long does it take to work', 'Duration of effect', 'Maximum recommended dosing', 'Most common side effects (over 10%) and 'Food interactions'. Below the chart there was brief mention of hormone treatment and surgery. Information was also given about counselling which, it was stated, should be an integral part of treatment. Only the section describing injections or insertions included the advice to '… discuss all

possible side effects with your doctor/nurse'. Only the section describing surgery stated that your doctor would be the best person to advise as to whether it was a suitable option. Although not named, the first oral treatment (product 1) listed in the chart was Cialis.

The Panel considered that much information had been provided about the treatment for ED. All possible treatments were mentioned. The question was whether the information constituted an advertisement to the public for a prescription only medicine or would encourage a patient to ask their health professional to prescribe a specific medicine. The Panel did not consider that the chart on the website nor its inclusion in the 4t Action Plan constituted an advertisement to the public for a prescription only medicine and no breach of the Code was ruled.

The Panel considered that the features used to describe the products in the chart would result in patients asking their health professionals to prescribe a specific medicine. In addition the Panel was concerned as to whether the information presented was balanced, particularly with regard to the presentation of data about side effects. The chart detailed the 'Most common side effects (over 10%)' and listed 'headache and indigestion' for product 1 (Cialis). These were the side effects listed in the Cialis summary of product characteristics (SPC) as very common; others were listed as common. The Panel considered that to list only two side effects, albeit at a stated frequency of ≥1/10, would give an unbalanced view of the safety of the product to a potential patient. There was no indication that other side effects were possible. The Panel had similar concerns regarding the data given for products 2 and 3. The Panel was also concerned that there was no mention of contraindications for oral treatments. There was an implication that any of the products could be used successfully to treat ED. This was not necessarily so. In the Panel's view it was to be expected that a potential patient would read the pros and cons for each treatment choice and form an opinion as to which they wanted. Patients were encouraged to take the 4t Action Plan, which included the chart, to discuss the options and their preferences with their doctor. The Panel considered that the chart was not factual and balanced. It would encourage a member of the public to request a specific prescription only medicine. Thus the Panel ruled a breach of the Code with regard to the information on the website including the 4t Action Plan.

The Panel noted that a similar chart was also included in a leaflet, 'Bring back the spontaneity into your love life'; this chart gave the brand names and non-proprietary names for each treatment choice. The leaflet was intended to be placed in surgery waiting rooms and pharmacies for ED sufferers to take. Other materials also referred to spontaneity and the Panel considered that this together with naming Cialis and the details of its duration of effect given in the chart as 'Up to 36 hours after dosing' would lead patients to ask for a prescription for Cialis. A breach of the Code was ruled.

All the items clearly stated that they were sponsored by Lilly as required by the Code. The Panel did not accept that the campaign was disease mongering as stated in the article.

The Panel considered that by naming medicines and/or giving very specific details about their advantages and certain disadvantages, Lilly had not maintained high standards and a breach of the Code was ruled.

The Panel noted that the treatment option chart gave a clear account of the positive characteristics of each oral tablet whilst very limited information had been given about side-effects and none about possible contra-indications. Whilst patients were advised to discuss the treatment options with their doctor the website also encouraged them to decide what their preferences might be and to discuss these with their doctor. There was an implication that choosing a medicine to treat ED was straightforward which was not so. It was inappropriate to encourage patients to ask a health professional to prescribe a specific prescription only medicine. The Panel considered that on the facts of this case such action brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Financial Times (FT) of 29 July carried an article entitled 'Sex problems campaign will test rules' which criticised Eli Lilly and Company Limited's 40over40 campaign. In accordance with Paragraph 6 of the 2008 Constitution and Procedure this matter was taken up by the Director as a complaint under the Code.

Lilly's product, Cialis (tadalafil) was a PDE5 inhibitor for the treatment of erectile dysfunction (ED).

COMPLAINT

The article alleged that US-style advertising for drugs was coming to Britain in the shape of a television campaign to raise awareness of ED. Lilly had launched a series of television and national newspaper advertisements – the most ambitious to date about ED, accompanied by internet sites and discussion groups, which would run until September.

The campaign raised the prospect of Britons for the first time being subject to the kind of widespread advertising for Viagra and other ED medicines that had become so common to US television, particularly during sporting events and other programming that appealed to men.

It would be closely scrutinised by regulators and competitors for any potential breach of European rules, which forbade companies to advertise prescription medicines directly to patients.

Lilly insisted its campaign respected UK and EU rules that allowed general education about a disease so long as there was no specific promotion of its own medicines.

The company produced Cialis, the most recent of three prescription medicines launched in the competitive ED market. The advertisements, which included short broadcasts after the 9pm watershed for adults on ITV and Channel 4, did not directly name any of the prescription medicine brands available for the condition, but stressed that leading treatment options included the use of three different medicines, and Lilly used its own corporate logo prominently.

A spokeswoman for Lilly said all guidelines had been rigorously respected and the campaign stressed the risk of underlying illness behind ED.

Consumer advertising of prescription medicines had been widespread over the past decade in the US, but had been criticised for disease mongering – encouraging patients to press doctors to prescribe medicines excessively and irresponsibly. A number of pharmaceutical companies had cut back on the practice in an attempt to regain public trust.

The UK campaign, 40over40, referred to the claim that 40 per cent of men over 40 years old suffer from ED – included a table that listed three anonymous oral tablets as the most prominent form of treatment.

While not naming Cialis or its rivals Viagra and Levitra, the first entry in the treatment table was identifiable as Cialis through a description of its unique characteristics and side-effects. Lilly also placed its own logo at the foot of the web page next to another website sponsored by the company. The advertisements marked a sharp advance in a trend for medicines marketing in the UK, at a time when pharmaceutical companies were struggling to bolster revenues.

When writing to Lilly, the Authority asked it to respond in relation to Clauses 2, 9.1, 22.1 and 22.2 of the 2008 Code which were the same as in the 2006 Code, though numbered differently. The case was considered under the 2008 Constitution and Procedure.

RESPONSE

Lilly refuted any allegation reported in this article in relation to its ED disease awareness campaign. Lilly submitted that the campaign was non-promotional and in accordance with the Code and the Medicines and Healthcare products Regulatory Agency (MHRA) Guidelines for conducting Disease Awareness Campaigns.

Background and design of campaign

Lilly submitted that ED was a distressing condition for both sufferers and their partners (Fisher *et al* 2005), and one with which many men tended to suffer in silence for prolonged periods of time. In the UK, 2.3 million men suffered from ED, up to 80% of whom had an underlying illness such as diabetes or heart disease (Sullivan *et al* 2001 and Sexual Dysfunction Association 2007). ED could be a warning sign of such conditions (Feldman *et al* 1994 and Journal of Community Nursing on line). Lilly's ED disease awareness campaign was designed to raise awareness among sufferers of the condition, its prevalence, link to underlying illnesses as well as the treatment options available.

Lilly submitted that essential to the success of the campaign over previous disease awareness campaigns conducted by both it and other companies with interest in the disease area, was the need to deliver a strong and memorable consumer-orientated campaign (the name 40over40 was chosen for ease of recall and because it reflected the evidence of prevalence of the condition) designed to effectively deliver the following messages in a non-promotional manner.

- ED was common – 40% of men over 40 suffered from some degree of ED (Feldman *et al*).

  Knowing that other men suffered from this distressing and embarrassing condition was considered by Lilly to be empowering and would reduce the sense of isolation felt by sufferers.

- ED was treatable – 95% of sufferers could be treated (Journal of Community Nursing online).

  A wide array of modern treatments for ED now existed, encompassing first-line (principally oral PDE5 inhibitors), second-line (principally intra-urethral or intra-cavernosal alprostadil) and third-line treatments (penile implant surgery). Together with psychosexual counselling, few, if any patients experienced no improvement in their ED.

- ED sufferers could enjoy their love life again – once diagnosed and appropriate treatment prescribed by their GP, sufferers had the possibility of again reacting spontaneously to their partners.

Elements of campaign

Lilly submitted that the 40over40 campaign comprised non-promotional materials delivered through various form of media (including TV, internet and print) and was directed to the public and health professionals. Consistent with the Code, all the materials associated with the campaign identified Lilly as sponsor of the campaign.

- **40over40 television advertisement**

Lilly submitted that television advertising was a powerful tool in bringing messages to the public's attention and such media was considered an

important element of the 40over40 campaign to effectively deliver the campaign to the widest audience of sufferers and raise awareness of the disease. The television advertisement, which was subject to pre-vetting and approval of Clearcast (the broadcast industry's pre-transmission clearance body) was therefore scheduled to be broadcast during programmes that were of most interest to men and, in light of the subject matter, and with agreement of Clearcast, was given a post-9pm broadcast restriction.

Lilly submitted that television advertisements for disease awareness campaigns, which it and other pharmaceutical companies had conducted in the past, for a variety of diseases and conditions, such as ED itself, were not prohibited by the Code or the MHRA. Lilly did not accept the suggestion that the 40over40 television advertisement amounted to a US style advertisement for medicines. The campaign as a whole, including the television advertisement, had been conceived and developed entirely by Lilly's UK company and the television advertisement, as well as all other materials of the campaign, certified in accordance with the requirements of the Code.

Lilly submitted that the television advertisement was non-promotional and in accordance with the Code and the MHRA Guidelines for conducting Disease Awareness Campaigns. Indeed, the FT article conceded that the advertisement did not name any of the ED prescription brands. Contrary to the assertion that the television advertisement stressed that leading treatment options included the use of three different medicines, the advertisement invited the viewer to consider that there existed a 'range of treatments that could help you' – with no greater level of specificity than that. Further, consistent with the Code, the advertisement also identified Lilly as sponsor of the campaign.

- **40over40.com**

Lilly submitted that the ED disease awareness campaign website, www.40over40.com, contained a comprehensive overview of the disease. There were four sections directed at ED sufferers: Talk; Test; Treat; Today; these comprised the 4T Action Plan (see below). A section to be directed to health professionals was currently under construction (see 'Health professionals materials' below). Contrary to the FT article, the campaign did not include any discussion groups or forums connected to the website or otherwise.

Talk: This section outlined the basics of ED, its prevalence, the importance of sufferers to be able to talk to their GP and their partner, as well as helpful tips on how to raise this sensitive topic.

Test: This section contained the International Index of Erectile Function (IIEF) questionnaire for sufferers to rate their severity of ED. It also contained information about the tests that a GP might carry out to determine any underlying conditions as well as a section on ED and diabetes as ED could be associated with diabetes.

Treat: This section contained a thorough, fair and balanced list of all of the treatment options available for ED, including oral PDE5 inhibitors, injections, pumps, counselling, hormone treatment and surgery.

Today: This section contained a series of links to advocacy group websites related to ED. There was also a series of videos of a media GP with an expert interest in ED, talking to viewers on similar topics that were covered throughout the website.

Lilly refuted any implication that the website constituted the advertising of prescription only medicines to the public. The table of treatments referred to comprised a fair and balanced list of the whole range of options available for the management of ED. Within the table oral treatments were listed first because they were generally the first-line treatment option for ED; hence their logical place was first in the list rather than as suggested by the article as the most prominent form of treatment. The information contained in this website was designed to be used by sufferers in discussion with their doctor and any consideration of the relative merits of the treatment options mentioned remained the responsibility of the health professional.

Lilly submitted that again, consistent with the Code, the 40over40.com website identified Lilly as the campaign sponsor. Amongst six other websites offering advice and support in this and other related areas, it also correctly identified www.lovelifematters.co.uk, a website directed to the partners of those suffering from ED, as sponsored by Lilly.

- **Consumer print materials**

Lilly submitted that the most effective way of raising ED disease awareness was through a variety of media channels. Therefore, in addition to the television advertisement and the 40over40 website, the campaign comprised printed materials directed to ED sufferers (a full list was provided). Such non-promotional materials were available in the healthcare setting, such as surgeries and pharmacies, and provided ED sufferers with information on the condition in order to enable them to discuss their problems with their GP and obtain appropriate advice.

- **Health professional materials**

Lilly submitted that the role of the health professional was an important one, as they would discuss, diagnose and decide, with the ED sufferer, appropriate management of their problems. The objective of the campaign materials for health

professionals was to inform them that Lilly was raising awareness of ED through a disease awareness campaign and to remind them of the critical role they played in talking about the condition, testing for any underlying conditions which might be causing ED and appropriately treating where necessary.

Lilly planned to launch a health professional section within the www.40over40.com website shortly. A copy of this site was provided. This particular aspect of the Lilly ED disease awareness campaign, whilst certified, was not currently live as it was under construction. Therefore the current homepage did not contain any links to a health professionals section.

- **Public relations**

To coincide with the launch of its campaign Lilly had commissioned a survey of 1,000 men aged over 40; the results highlighted a variance between men's health expectations and reality.

Lilly's public/media relations media releases highlighted the survey data plus the launch of the campaign. The media releases were tailored to audiences comprising men with ED, GPs, nurses, pharmacists and media correspondents. A full list of the media releases and other PR materials was provided.

In addition, as part of the public relations campaign associated with the launch of the disease awareness campaign, a media Doctor conducted interviews with regional and local radio stations. The approved radio script and cue sheet were provided.

FT article entitled 'Sex problems campaign will test rules'

With regard to the allegations reported in the FT article, in addition to its comments above, Lilly specifically addressed the following comments:

Allegation of advertising prescription medicines directly to the public

- The 40over40 campaign sought to educate sufferers that ED could be managed effectively. The campaign materials provided a balance of information with respect to ED as a disease, how its management could be broached and discussed with health professionals and the broad range of treatments available. Raising awareness of ED was responsible and the campaign was consistent with the Code. Lilly categorically refuted the allegation that the campaign was aimed at advertising prescription medicines directly to the public.

Implication of disease mongering

- Lilly refuted any suggestions, implied or otherwise, that the 40over40 campaign could be considered to be disease mongering. As stated above, ED was recognised as a serious condition with considerable implications to both the sufferer and their partner. Indeed, research had shown that ED was an indicator of other serious health issues, such as diabetes and cardiovascular disease; in one report the majority of men seeking ED treatment were newly diagnosed with hypertension, diabetes, dyslipidemia (high cholesterol) or angina (Sadovsky, 2007).

Specific identification of Cialis

- Lilly submitted that with specific regard to the treatment table that appeared in the 40over40 website, the article stated that whilst Cialis was not named, the first entry was identifiable as Cialis through a description of its unique characteristics and side-effects. Lilly did not accept that there was any basis for the assertion that a member of the public would be able to identify any particular PDE5 inhibitor (including Cialis) by reference to the characteristics of Product 1, 2 or 3 as set out in this website treatment table. Therefore, Lilly did not accept the suggestion that this treatment table constituted the promotion of Cialis to the general public or was likely to bias either the ED sufferer or their doctor towards consideration of Cialis. The treatment table presented all treatment options available for ED in a fair and balanced manner, and such presentation would not in any event restrict the naming of such treatment options, as long as such a treatment table was fair and balanced. The fact that treatments, named or anonymised, might have unique characteristics and/or side effects did not in itself preclude presentation of treatment options in the context of a fair and balanced discussion. Lilly therefore refuted any allegation that the treatment table promoted Cialis. Lilly was aware of its responsibilities with respect to the Code and had ensured that all aspects of the 40over40 campaign were consistent with this and of the highest standards and quality.

PANEL RULING

The Panel considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake provided that such programmes were in accordance with the Code. Such activities might facilitate the market development of the sponsoring company's products but this was not necessarily in breach of the Code. Each case would need to be judged on its merits.

The Panel noted that the supplementary information to Clause 22.2 stated that a company might conduct a disease awareness or public health campaign provided that the purpose was to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine. The use of brand or non-proprietary names and/or restricting the range of

treatments described in the campaign might be likely to lead to the use of a specific medicine. Particular care must be taken where the company's product, even though not named, was the only medicine relevant to the disease or symptoms in question.

The Panel considered that the campaign was within the scope of the Code as it could not take the benefit of the exemption for information relating to human health or diseases provided there was no reference either direct or indirect to specific medicines (Clause 1.2).

The Panel examined the material in question. The television advertisement did not refer to medicines other than a general statement that there was a range of treatments that could help. The television advertisement gave details of the website 40over40.com. The Panel did not consider that the television advertisement *per se* constituted an advertisement to the public for a prescription only medicine nor would it encourage a patient to ask their health professional to prescribe a specific medicine. No breach of Clauses 22.1 and 22.2 was ruled.

The 40over40.com website gave detailed information set out under four sections 'talk' 'test' 'treat' and 'today'. In the Panel's view the sections 'talk' 'test' and 'today' gave helpful information about ED including possible causes and advice about talking to a health professional. The 'treat' section included a chart setting out various features about the medicines and devices available to treat ED. The chart was also included in the 4t Action Plan for patients to download and discuss with their doctor. Neither the treatment chart on the website nor the 4t Action Plan named any of the products. The sections were divided into oral treatments where details of products 1, 2 and 3 were given, injections or insertions which gave details of three products and vacuum pumps and constriction rings which stated that ten different types were available. The features compared for each product were 'How long does it take to work', 'Duration of effect', 'Maximum recommended dosing', 'Most common side effects (over 10%) and 'Food interactions'. Below the chart there was brief mention of hormone treatment and surgery. Information was also given about counselling which, it was stated, should be an integral part of treatment. Only the section describing injections or insertions included the advice to '… discuss all possible side effects with your doctor/nurse'. Only the section describing surgery stated that your doctor would be the best person to advise as to whether it was a suitable option. Although not named the first oral treatment (product 1) listed in the chart was Cialis.

The Panel considered that much information had been provided about the treatment for ED. All possible treatments were mentioned. The question was whether the information constituted an advertisement to the public for a prescription only medicine or would encourage a patient to ask their health professional to prescribe a specific medicine. The Panel did not consider that the chart on the website nor its inclusion in the 4t Action Plan constituted an advertisement to the public for a prescription only medicine and no breach of Clause 22.1 was ruled.

The Panel considered that the features used to describe the products in the chart would result in patients asking their health professionals to prescribe a specific medicine. In addition the Panel was concerned as to whether the information presented was balanced, particularly with regard to the presentation of data about side effects. The chart detailed the 'Most common side effects (over 10%)' and listed 'headache and indigestion' for product 1 (Cialis). These were the side effects listed in the Cialis summary of product characteristics (SPC) as very common. The SPC, however, also listed the following common (≥1/100 to <1/10) side effects: dizziness, palpitations, flushing, nasal congestion, abdominal pain, gastro-oesophageal reflux, back pain and myalgia. The Panel considered that to list only two side effects, albeit at a stated frequency of ≥1/10, would give an unbalanced view of the safety of the product to a potential patient. There was no indication that other side effects were possible. The Panel had similar concerns regarding the data given for products 2 and 3. The Panel was also concerned that there was no mention of contraindications for oral treatments. There was an implication that any of the products could be used successfully to treat ED. This was not necessarily so. In the Panel's view it was to be expected that a potential patient would read the pros and cons for each treatment choice and form an opinion as to which they wanted. Patients were encouraged to take the 4t Action Plan, which included the chart to discuss the options and their preferences with their doctor. The Panel considered that the chart was not factual and balanced. It would encourage a member of the public to request a specific prescription only medicine. Thus the Panel ruled a breach of Clause 22.2 with regard to the information on the website including the 4t Action Plan.

The Panel noted that a similar chart was also included in a leaflet (ref CI1534), 'Bring back the spontaneity into your love life'; this chart gave the brand names and non-proprietary names for each treatment choice. The leaflet was intended to be placed in surgery waiting rooms and pharmacies for ED sufferers to take. Many of the other materials referred to spontaneity; for example the web banner advertisements (CI 1540), one of which started 'Go back to loving spontaneously' followed by '95% of erectile dysfunction can be treated' and 'Go to **www.40over40.com** and Talk-Test-Treat-Today'. The consumer print advertisement (CI 1536) included the statement 'Bring back spontaneity into your love life' as did the surgery poster (CI 1533) and the leaflet card dispenser (CI 1539). The Panel considered that the call to bring back spontaneity together with naming Cialis and the details of its duration of effect given in the chart as 'Up to 36 hours after dosing' would lead patients to ask for a

prescription for Cialis. A breach of Clause 22.2 was ruled.

All the items clearly stated that they were sponsored by Lilly as required by the Code. The Panel did not accept that the campaign was disease mongering as stated in the article.

The Panel considered that by naming medicines and/or giving very specific details about their advantages and certain disadvantages, Lilly had not maintained high standards and a breach of Clause 9.1 was ruled.

The Panel noted that the treatment option chart gave a clear account of the positive characteristics of each oral tablet whilst very limited information had been given about side-effects and none about possible contra-indications. Whilst patients were advised to discuss the treatment options with their doctor the website also encouraged them to decide what their preferences might be and to discuss these with their doctor. There was an implication that choosing a medicine to treat ED was straightforward which was not so. It was inappropriate to encourage patients to ask a health professional to prescribe a specific prescription only medicine. The Panel considered that on the facts of this case such action brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Proceedings commenced	**30 July 2008**
Case completed	**10 October 2008**

CASE AUTH/2152/8/08

NOVO NORDISK v SANOFI-AVENTIS

Promotion of Lantus

Novo Nordisk complained about a mailer and two leavepieces produced by Sanofi-Aventis that promoted Lantus (insulin glargine). Novo Nordisk marketed Levemir (insulin detemir).

The detailed response from Sanofi-Aventis is given below.

The claim '24-hour efficacy' appeared as a heading to a section in the mailer as did the claim 'Once daily'. The section headed 'Once daily' featured a table headed '12 month comparison of Lantus vs insulin detemir (n=582)' referenced to Rosenstock *et al* (2008). The table compared Lantus and Levemir with regard to reduction in HbA1c, percentage of patients treated once daily and the total daily insulin dose.

Whilst Novo Nordisk acknowledged that the claim 'Once daily' was substantiated by the Lantus summary of product characteristics (SPC), it had major concerns regarding the data in the table from a trial where Levemir and Lantus were compared as part of an initial basal-oral insulin regimen in insulin-naïve type 2 diabetics (Rosenstock *et al*). By the end of the trial 55% of patients randomized to Levemir used twice daily injections (45% remained on once daily injection) whilst all of the Lantus patients used the preparation once daily. The table highlighted the proportion of once daily Levemir users 45% by the end of the trial and quoted the proportion of twice daily users in brackets below (55% twice daily). All patients had taken Lantus once daily.

With regard to total daily insulin dose, it was stated in the table that the final Levemir dose for the combined (once and twice daily users) arm was 0.78U/kg*. The footnote gave the separate figures ie once daily 0.52U/kg, twice daily 1U/kg. The figure for Lantus was 0.44U/kg. Sanofi-Aventis had deliberately used the higher dose for the combined group to mislead readers that there was a massive dose difference between Lantus and Levemir when both were used once daily. The footnote provided important facts in order to fairly compare the doses and should have been placed in the table in the same manner as that for the percentage of patients using once or twice daily Levemir. Sanofi-Aventis had noted that all the data regarding doses could be found in the material. However, Novo Nordisk's major concern was about the way these data were presented.

Novo Nordisk alleged that the presentation of the information in the mailer strongly suggested Sanofi-Aventis' deliberate intention to disparage Levemir. Novo Nordisk alleged that the claims '24-hour efficacy' and 'Once daily' implied that Levemir predominantly needed to be taken twice daily which was misleading and disparaging; Sanofi-Aventis had disregarded other data which supported the once daily use of Levemir. The only direct comparison of these two insulin preparations, a clamp investigation in type 2 diabetes (Klein *et al* 2007), showed no difference in terms of duration of action. This indicated a similar use of these preparations in a clinical setting in terms of the number of daily injections. This was further confirmed in an analysis of all of the available Lantus or Levemir clamp trials (Heise *et al* 2007). The authors concluded that both preparations were suitable for once daily routine use in type 2 diabetes and could often be used once daily in type 1 diabetics. Furthermore clinical trials also suggested that Levemir could be used once daily in type 2 diabetes. In a randomized clinical trial, Philis-Tsimikas *et al* (2006), patients using exclusively once daily Levemir in combination with oral antidiabetic medicines achieved a significant improvement of 1.5% in HbA1c, a similar reduction to that observed in Rosenstock *et al*.

Novo Nordisk alleged that the claims '24 hour efficacy' and 'Once daily' implied that Sanofi-Aventis could provide substantiation from experimental and clinical studies. The substantiation was also misleading since the experimental data came from type 1 diabetes, whilst the clinical data came from type 2 diabetes. Sanofi-Aventis had not considered the only clamp trial which directly compared the two products (Klein *et al*). This promotional material had a picture of people with type 2 diabetes phenotype on the front and provided results from a clinical trial comparing Lantus and Levemir in type 2 diabetes. Therefore the only possible reason why Sanofi-Aventis had chosen to show the results from a clamp trial conducted in type 1 diabetes, instead of using available type 2 data, was to 'cherry-pick' the only clamp trial with favourable results.

Novo Nordisk alleged that the careful selection of trials and studies with favourable results for Lantus compared with Levemir, whilst disregarding other evidence, was unfair and misleading and disparaged Levemir.

The Panel noted that the table at issue detailed Rosenstock *et al* which had compared Lantus and Levemir over 12 months in insulin-naïve type 2 diabetics. It was not a comparison of only once daily usage of the two insulin preparations. At the end of the study 100% of Lantus patients were on once daily injections whereas 45% of Levemir patients were so treated with 55% being on twice

daily injections. The mean daily insulin dose for the Lantus group (n=248) was 0.44U/kg whilst for the Levemir group (n=227) it was 0.78U/kg (0.52U/kg on once daily (n=102) and 1U/kg on the twice daily dosing (n=125)). The Panel considered that it was important for prescribers to know that when treating insulin-naïve type 2 diabetics, a significant proportion were likely to need Levemir twice daily and that overall insulin use might be increased with Levemir compared with Lantus. Nonetheless the Panel considered that the presentation of the data in the table was misleading; it was unclear that the figure of 0.78U/kg given for Levemir related to the whole of that patient group given that the row of data immediately above specifically referred to once daily injections. Readers had to refer to the asterisked footnote to be able to understand the data fully. The Panel considered that in that regard the table was misleading and a breach of the Code was ruled.

The Panel did not consider that the information in the table disparaged Levemir as alleged.

Novo Nordisk further complained about a leavepiece entitled 'Why choose Lantus to complement OADs [oral antidiabetics]?'. The two centrefold pages were at issue. The left-hand page was headed 'Lantus can help patients who are uncontrolled on OADs' followed by a patient profile and details of a study by Yki-Järvinen *et al* (2007). The page concluded 'Lantus + OADs can give patients up to a 2% reduction in HbA1c in 24 weeks (p<0.001 vs baseline)'.

The right-hand page was headed 'Simple self titration with Lantus' which included a recommendation from Monnier and Colette (2006) to titrate '… up to 0.5U/kg of basal insulin; after that consider adding a rapid-acting insulin to avoid weight gain'.

The leavepiece had been voluntarily withdrawn by Sanofi-Aventis following inter-company dialogue in relation to Case AUTH/2141/7/08.

Novo Nordisk noted that the leavepiece promoted the initiation of Lantus in patients with type 2 diabetes uncontrolled on oral antidiabetic medicines. The leavepiece included a table that contained a patient profile from the INITIATE study (Yki-Järvinen *et al*) and beneath the table the claim 'Lantus + OADs can give patients up to a 2% reduction in HbA1c in 24 weeks (p<0.001 vs baseline)'. The INITIATE study showed that the final Lantus dose for the two arms was 0.60 and 0.64U/kg. In contradiction with this finding the facing page suggested that Lantus be titrated up to a 0.5U/kg dose and after that the addition of rapid-acting insulin to avoid weight gain should be considered. Clearly the INITIATE study was chosen to create the patient profile because the improvement of Hb1Ac was the greatest from all the trials conducted on the basal-oral use of Lantus. Novo Nordisk alleged that using these two claims together in the same leavepiece misled health professionals to believe that by using a dose of 0.5U/kg a 2% reduction in Hb1Ac could be achieved. In fact, the 2% reduction achieved in the INITIATE study was at the larger dose as mentioned above.

The Director noted that the leavepiece had been withdrawn due to different allegations. It was not clear that Sanofi-Aventis would not use the claims now at issue again. Thus the Director considered that inter-company dialogue had not been completely successful and the matter was referred to the Panel.

The Panel noted the title of the leavepiece 'Why choose Lantus to complement OADs' was followed on the inside page by 'Lantus can help patients who are uncontrolled on OADs' beneath which information was given about initiating treatment of type 2 diabetes with Lantus. The next page was headed 'Simple self titration with Lantus'. The Panel considered that many readers would assume that the leavepiece set out a normal course of events following initiation of Lantus. The context of claims was an important consideration.

The Panel considered that, without any statement to the contrary, readers would assume that the data regarding a 2% reduction in HbA1c was linked to the statements regarding dose titration which was not so. The Panel did not consider that readers would see the pages as distinct and separate in their own right as submitted by Sanofi-Aventis. Although the dose of Lantus (62 units) used to achieve a 2% reduction in HbA1c was stated it was impossible for the reader to know how this compared to the maximum titrated dose (0.5U/kg) recommended by Monnier and Colette. From the published study (Yki-Järvinen *et al*) it appeared that the Lantus dose which resulted in a 2% reduction in HbA1c in U/kg was 0.66U/kg (given that the mean weight at baseline had been 93.8kg and the mean dose of insulin was 62 units). (Novo Nordisk had calculated a dose of 0.64U/kg). The Panel considered that viewed together the pages gave a misleading impression and a breach of the Code was ruled.

Novo Nordisk further complained about a page in a leavepiece headed '… but what about weight gain?' which set out data for weight gain in type 1 and type 2 diabetes. The section about type 2 diabetes included a bar chart comparing of the mean weight change after 1 year with Lantus once daily (3.9kg) and twice daily Levemir (3.7kg) (p=NS). The bar chart was referenced, *inter alia*, to Rosenstock *et al*.

The leavepiece had been voluntarily withdrawn by Sanofi-Aventis following inter-company dialogue in relation to Case AUTH/2141/7/08.

Novo Nordisk was concerned about a claim about the weight gain in type 2 diabetes. Although the weight gain was significantly lower after insulin initiation with Levemir in Rosenstock *et al*, Sanofi-

Aventis had deliberately implied that there was no difference in this regard between the two products. The prominent bar chart was proof of this intention. Novo Nordisk noted that the Levemir SPC stated 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrated that glycaemic control (HbA1c) with Levemir is comparable with NPH insulin and insulin glargine and associated with less weight gain …'.

Sanofi-Aventis had repeatedly tried to suggest that Lantus resulted in the same weight gain, after insulin initiation as part of a basal-oral regimen, as Levemir and referred to a previous case (Case AUTH/2038/8/07) in that regard.

Therefore Novo Nordisk alleged that the presentation of the weight gain data in type 2 diabetes, which tried to imply the same message as had been ruled in breach earlier, was misleading. Furthermore Sanofi-Aventis highlighted itself that it compared weight results with once-daily Lantus and twice-daily Levemir. Although twice-daily use was permitted by the Levemir SPC, it was not the usual and recommended way in insulin initiation. The Levemir SPC suggested starting with once daily in combination with OADs in type 2 diabetics. The only reason to use the twice daily subgroup from Rosenstock *et al* (instead of the more relevant once daily users or the combined cohort of the once daily and twice daily users) was to find the only piece of information in the medical literature which could substantiate the weight comparison claim at issue.

The Panel noted that the page headed '… but what about weight gain?' was divided into two sections – one related to type 1 diabetes whilst the other referred to type 2 diabetes. The type 2 diabetes section featured a visually prominent bar chart showing the weight change after one year with once daily Lantus (+3.9kg) and twice daily Levemir (+3.7kg) (p=NS). Although it was also stated that weight gain over one year with Lantus plus OADs was only 0.9kg more than that seen with Levemir plus OADs (p=0.01) thus acknowledging a greater weight gain in the Lantus group, this written claim was much less obvious to the reader than the bar chart.

The bar chart detailed the results from Rosenstock *et al* in which insulin-naïve type 2 diabetes had been treated with Lantus or Levemir. Although all Lantus patients had remained on once daily injections, 55% of Levemir patients had progressed to twice daily injections. The weight gain seen with the two Levemir dosing regimens varied and in the Panel's view it was important that prescribers knew all of the facts. The bar chart had detailed once daily Lantus vs twice daily Levemir where the difference in weight gain between the two was in favour of Levemir and stated as being non-significant (the statistical significance was not stated in Rosenstock *et al* but appeared to have been taken from a Novo Nordisk review of Levemir therapy and effect on body weight). The results for once daily Lantus vs once daily Levemir, as reported by Rosenstock *et al* and applicable to 45% of patients, were not stated in the leavepiece. This would have shown a statistically significant advantage for Levemir (+2.3kg vs +3.9kg, p<0.001). The Panel considered that by reporting only some of the Rosenstock *et al* data the leavepiece was incomplete and misleading in that regard. Prescribers had not been given all of the information upon which to make a fully informed prescribing choice. A breach of the Code was ruled.

The Panel did not consider that the weight gain data in type 2 diabetes was not capable of substantiation as alleged and no breach of the Code was ruled.

The Panel did not consider that Sanofi-Aventis had failed to maintain high standards. No breach of the Code was ruled including no breach of Clause 2.

Novo Nordisk Limited complained about a mailer (LAN08/1041) and two leavepieces (LAN08/1038 and LAN08/1039) produced by Sanofi-Aventis that promoted Lantus (insulin glargine). Novo Nordisk marketed Levemir (insulin detemir).

Novo Nordisk stated that inter-company dialogue had failed to resolve matters.

This case was considered under the 2008 Constitution and Procedure. The clauses cited, 2, 7.2, 7.4, 8.1 and 9.1, were the same in the 2006 Code as in the 2008 Code. Thus the Panel used the 2008 Code.

1 Mailer – 'Why choose Lantus?' (ref LAN08/1041)

This was used once in early 2008.

The claim '24-hour efficacy' appeared as a heading to a section as did the claim 'Once daily'. The section headed 'Once daily' featured a table headed '12 month comparison of Lantus vs insulin detemir (n=582)' referenced to Rosenstock *et al* (2008). The table compared Lantus and Levemir with regard to reduction in HbA1c, percentage of patients treated once daily and the total daily insulin dose.

COMPLAINT

Novo Nordisk noted that there was an ongoing case (Case AUTH/2141/7/08) regarding the '24-hour efficacy' claim, thus it did not address this issue. However its complaint about the claim 'Once daily' (see below) would partially deal with the '24-hour efficacy' claim in order to put it into a different context and show how Sanofi-Aventis manipulated the data from different trial settings in order to imply that Lantus had trial results to substantiate the '24-hour efficacy' and 'Once daily' claims from experimental and clinical perspectives.

Whilst Novo Nordisk acknowledged that the claim

'Once daily' was substantiated by the Lantus summary of product characteristics (SPC), it had major concerns regarding the data in the table which came from a randomized clinical trial where Levemir and Lantus were compared as part of an initial basal-oral insulin regimen in insulin-naïve type 2 diabetics (Rosenstock *et al*). By the end of the trial 55% of patients randomized to Levemir used twice daily injections (45% remained on once daily injection) whilst all of the Lantus patients used the preparation once daily.

With regard to the percentage of patients treated with a once daily injection, the table highlighted the proportion of once daily Levemir users (45%) by the end of the trial and quoted the proportion of twice daily users in brackets below (55%). All patients had taken Lantus once daily.

With regard to total daily insulin dose, it was stated in the table that the final Levemir dose for the combined (once and twice daily users) arm was 0.78U/kg*. The footnote gave the separate figures ie once daily 0.52U/kg, twice daily 1U/kg. The figure for Lantus was 0.44U/kg. Sanofi-Aventis had deliberately used the higher dose for the combined group to mislead readers that there was a massive dose difference between Lantus and Levemir when both were used once daily. The additional information in the footnote provided important facts in order to fairly compare the doses and should have been placed in the table in the same manner as that for the percentage of patients using once or twice daily Levemir. Sanofi-Aventis had noted that all the data regarding doses could be found in the material. However, Novo Nordisk's major concern was not related to using only selective results from a dose perspective but the way these data were presented in the mailer. Sanofi-Aventis' argument about the use of clamp study data was completely irrelevant from a dose perspective.

Novo Nordisk alleged that the presentation of the information in the mailer strongly suggested Sanofi-Aventis' deliberate intention to disparage Levemir. Novo Nordisk alleged that the claims '24-hour efficacy' and 'Once daily' implied that Levemir predominantly needed to be taken twice daily which was misleading and disparaging; Sanofi-Aventis had disregarded other data which supported the once daily use of Levemir. In the only head-to-head comparison of these two insulin preparations, a clamp investigation in type 2 diabetes (Klein *et al* 2007), there was no difference in terms of duration of action. This indicated a similar use of these preparations in a clinical setting in terms of the number of daily injections. This was further confirmed in an analysis of the results from all the available clamp trials investigating either Lantus or Levemir (Heise *et al* 2007). The authors concluded that both preparations were suitable for once daily routine use in type 2 diabetes and could often be used once daily in type 1 diabetics. Furthermore clinical trials also suggested that Levemir could be used once daily in type 2 diabetes. In a randomized clinical trial, Philis-Tsimikas *et al* (2006), patients using exclusively once daily Levemir in combination with oral antidiabetic medicines achieved a significant improvement of 1.5% in HbA1c, a similar reduction to that observed in Rosenstock *et al*.

Novo Nordisk alleged that the claims '24 hour efficacy' and 'Once daily' implied that Sanofi-Aventis could provide substantiation from both experimental (clamp) trials and clinical studies (randomized clinical trials). In fact the substantiation used was also misleading since the experimental data came from type 1 diabetes, whilst the clinical data came from type 2 diabetes. Sanofi-Aventis had not considered the only clamp trial which compared the two products head-to-head (Klein *et al*). This promotional material had a picture of people with type 2 diabetes phenotype on the front and provided results from a clinical trial comparing Lantus and Levemir in type 2 diabetes. Therefore the only possible reason why Sanofi-Aventis had chosen to show the results from a clamp trial conducted in type 1 diabetes, instead of using available type 2 data, was to 'cherry-pick' the only clamp trial with favourable results.

Novo Nordisk alleged that the selection of trials and studies with favourable results for Lantus compared with Levemir, whilst disregarding other available evidence, was an unfair and misleading and disparaged Levemir in breach of Clauses 7.2, 8.1 and 9.1 of the Code.

RESPONSE

Sanofi-Aventis noted that Novo Nordisk was concerned about the following table which appeared beneath the claim 'Once daily':

12-month comparison of Lantus vs insulin detemir (n=582)

	Lantus (insulin glargine)	Insulin detemir
Reduction in HbA1c	**1.5% reduction**	1.4% reduction (p=NS between treatments)
Once-daily injection (% of patients)	**100%**	45% (55% twice-daily)
Total daily insulin dose	**0.44U/kg**	0.78 U/kg*

Therapies were add-ins to oral treatments in patients with type 2 diabetes.
*Once-daily 0.52U/kg; twice-daily 1U/kg.

Sanofi-Aventis noted that Novo Nordisk was concerned that the total daily insulin dose for Levemir (in comparison with Lantus) was for the combined group of Levemir patients (both once daily and twice daily dosing together). Novo Nordisk alleged that this disparaged Levemir through 'using the higher dose for the combined group' to 'highlight that there was a massive dose

difference between Lantus and Levemir when used once daily', and that the additional information presented in the footnote should have been included in the table. Sanofi-Aventis disagreed.

Firstly, presenting the combined mean daily dose was the only scientific way to compare the two products. The study was designed to compare patients using Lantus (n=291) with all patients using Levemir (n=291), irrespective of frequency of dosing. The primary endpoints were described in terms of the total patient cohort for Levemir (once daily and twice daily dosing combined); Sanofi-Aventis had therefore made the most appropriate comparison by including the combined Levemir cohort data as the primary data cohort within the table.

Secondly, contrary to the allegation above, the dose in the combined Levemir group (0.78U/kg) was not the largest dose observed in the study, 1U/kg for patients receiving Levemir twice daily. Had Sanofi-Aventis included that figure in the table then that would have inappropriately drawn attention to 'a massive dose difference between Lantus and Levemir'. As this was not reflected in the item, Sanofi-Aventis disagreed with the allegation that the table was misleading and disparaged Levemir.

In summary, with the exception of the error already admitted and dealt with by inter-company dialogue, Sanofi-Aventis submitted that it did not consider that the table misled nor disparaged, and through these considerations and the manner in which the identified error had been dealt with high standards had been maintained.

Sanofi-Aventis noted that following these allegations, Novo Nordisk asserted that Sanofi-Aventis had aimed to disparage Levemir, stating that the use of 'Once daily' and '24-hour efficacy' in relation to Lantus suggested that this was not the case for Levemir. Sanofi-Aventis did not consider that any disparagement had occurred, either directly or implied. The two claims were only about Lantus, had been demonstrated in peer reviewed, published clinical trials and were substantiable as such and consistent with the SPC. Further information about Levemir was similarly derived from peer reviewed, published clinical trials, and was entirely consistent with its marketing authorization.

The SPC recommended that Levemir, in combination with oral antidiabetic agents, be initiated once daily. This implied that although once daily dosing was appropriate when starting insulin, as the dose was increased to achieve control of the condition twice daily therapy might be necessary. This was in keeping with Rosenstock *et al*, which had been incorporated into Levemir's SPC – although once daily initiation occurred in all patients, 55% subsequently required an increase to twice daily dosing to achieve adequate glycaemic control. The SPC similarly stated that as part of a basal-bolus regimen Levemir 'should be administered once or twice daily depending on patients' needs'.

Sanofi-Aventis noted that Novo Nordisk then suggested that in using 'Once daily' and '24-hour efficacy' claims Sanofi-Aventis implied that these could be substantiated from clamp studies and randomised clinical studies. It was not clear how such an implication was made. Regardless, Sanofi-Aventis disagreed with this suggestion as isoglycaemic clamp studies were widely considered the best and most appropriate way to assess duration of action of insulin, measuring specifically the period of time over which insulin exerted a pharmacological action; they were therefore the most appropriate data source to substantiate a claim of '24-hour efficacy'. This opinion was clearly made in Heise *et al* cited by Novo Nordisk and was an argument that had even been successfully proposed by Novo Nordisk in Case AUTH/1622/8/04.

In addition to the clamp studies, a number of randomised clinical trials supported the claim of once daily Lantus dosing in type 2 diabetics. Sanofi-Aventis provided a summary of these studies which showed that, following effective titration, excellent glycaemic control (ie HbA1c values of approximately 7%), was achieved using Lantus once daily. The clinical evidence therefore also supported the 'Once daily' claim.

Finally, with respect to the observation that the selection of clamp studies related to patients with type 1 diabetes but not type 2 diabetes, Sanofi-Aventis submitted that this was the approach adopted in the academic community as type 1 diabetes was best suited to demonstrate the action of an insulin in the absence of any confounding factors (such as endogenous insulin or insulin resistance, both of which might be present in patients with type 2 diabetes). Again, Novo Nordisk had previously successfully argued that clamp studies in patients with type 1 diabetes were appropriate to support such claims on the basis that it was important to examine 'the properties of insulin and not the type of diabetes' (Case AUTH/1622/8/04).

That said evidence from two published clamp studies in patients with type 2 diabetes Lantus maintained a 24-hour duration of action. In both studies, and at all doses, a single injection of Lantus was effective at preventing hyperglycaemia throughout the 24-hour duration of each study.

In summary, Sanofi-Aventis submitted that the claims '24-hour efficacy' and 'Once daily' were substantiated by the available scientific literature, reflecting an up-to-date evaluation of all applicable evidence, were consistent with the SPC, and that no breach of the Code had occurred.

PANEL RULING

The Panel noted that the table at issue detailed the results from Rosenstock *et al* which had compared Lantus and Levemir over 12 months in insulin-naïve type 2 diabetics. It was not a comparison of only

once daily usage of the two insulin preparations. At the end of the study 100% of Lantus patients were on once daily injections whereas 45% of Levemir patients were so treated with 55% being on twice daily injections. The mean daily insulin dose for the Lantus group (n=248) was 0.44U/kg whilst for the Levemir group (n=227) it was 0.78U/kg (0.52U/kg on once daily (n=102) and 1U/kg on the twice daily dosing (n=125)). The Panel considered that it was important for prescribers to know that when treating their insulin-naïve type 2 diabetics, a significant proportion of them were likely to need Levemir twice daily and that overall insulin use might be increased with Levemir compared with Lantus. Nonetheless the Panel considered that the presentation of the data in the table was misleading; it was unclear that the figure of 0.78U/kg given for Levemir related to the whole of that patient group given that the row of data immediately above specifically referred to once daily injections. Readers had to refer to the asterisked footnote to be able to understand the data fully. The Panel considered that in that regard the table of data was misleading and a breach of Clause 7.2 was ruled.

The Panel did not consider that the information in the table disparaged Levemir as alleged. Thus no breach of Clause 8.1 was ruled. The Panel noted its rulings and did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled.

2 Leavepiece – 'Why choose Lantus to complement OADs [oral antidiabetics]?' (ref LAN08/1038)

This leavepiece had been voluntarily withdrawn by Sanofi-Aventis following inter-company dialogue in relation to Case AUTH/2141/7/08.

The two centrefold pages of the leavepiece were at issue. The left-hand page was headed 'Lantus can help patients who are uncontrolled on OADs' followed by a patient profile and details of a study by Yki-Järvinen *et al* (2007). The page concluded 'Lantus + OADs can give patients up to a 2% reduction in HbA1c in 24 weeks (p<0.001 vs baseline)'.

The right-hand page was headed 'Simple self titration with Lantus' which included a recommendation from Monnier and Colette (2006) to titrate '… up to 0.5U/kg of basal insulin; after that consider adding a rapid-acting insulin to avoid weight gain'.

COMPLAINT

Novo Nordisk noted that the leavepiece promoted the initiation of Lantus in patients with type 2 diabetes uncontrolled on oral antidiabetic medicines. The leavepiece included a table that contained a patient profile from the INITIATE study (Yki-Järvinen *et al*) and beneath the table the claim 'Lantus + OADs can give patients up to a 2% reduction in HbA1c in 24 weeks (p<0.001 vs baseline)'. The INITIATE study showed that the final Lantus dose for the two arms was 0.60 and 0.64U/kg. In contradiction with this finding on the facing page of the leavepiece it was suggested that Lantus be titrated up to a 0.5U/kg dose and after that the addition of rapid-acting insulin to avoid weight gain should be considered. Clearly the INITIATE study was chosen to create the patient profile because the improvement of Hb1Ac was the greatest from all the trials conducted on the basal-oral use of Lantus. Novo Nordisk alleged that using these two claims together in the same leavepiece misled health professionals to believe that by using a dose of 0.5U/kg a 2% reduction in Hb1Ac could be achieved. In fact, the 2% reduction achieved in the INITIATE study was at the larger dose as mentioned above. Novo Nordisk alleged a breach of Clause 7.2. In inter-company dialogue Sanofi-Aventis replied that the information it provided to health professionals from the two trials could be found on separate, stand-alone pages. The page related to INITIATE contained data about HbA1c improvement and the applied insulin dose in the trial, whilst the other page referred to the titration guide from the AT.LANTUS trial.

Novo Nordisk alleged that any promotional material should be considered as one piece; it should not provide data and suggestions which contradicted each other.

Although the page about the INITIATE trial provided information about the final insulin dose which was related with the relevant HbA1c improvement in the study, but it showed the final total dose [sic].

Novo Nordisk alleged that in this way readers did not have the information about the final U/kg dose, although this information could be found in the full publication. Since the U/kg dose from the INITIATE trial was in contradiction with the suggestion on the opposite page (adding rapid-acting insulin when the dose of basal insulin exceeded 0.5U/kg) Novo Nordisk alleged that readers might be misled into assuming that with the suggested maximum basal dose (ie 0.5U/kg) HbA1c could be improved by 2% (as it was seen in the INITIATE trial with the final dose of 0.64U/kg).

RESPONSE

Sanofi-Aventis stated that the leavepiece was designed to tell clinicians about the benefits of Lantus in patients with type 2 diabetes inadequately controlled on oral hypoglycaemic agents, and how patients could be advised to adjust their own dose so as to improve their diabetes control. The leavepiece had been withdrawn as a result of inter-company discussions with respect to Case AUTH/2141/7/08.

Sanofi-Aventis submitted that the leavepiece provided important information on the optimal use of Lantus in a responsible and appropriate manner.

The two pages, although facing, were distinct and separate in their own right and were separate in both nature and content. The left-hand page had a clear and discreet title 'Lantus can help patients who are uncontrolled on OADs'. The page described the results of a clinical trial (Yki-Järvinen *et al*) in terms of the improvement in glycaemic control achieved by adding Lantus to existing oral antidiabetic agents. The page provided information of the results of this study, and the dose used to achieve these results was clearly stated (in units). The right-hand page, also discreet, covered an entirely separate and discreet topic of 'Simple self titration with Lantus'. This described a suitable regimen from another study of Lantus in type 2 diabetes (Davies *et al* 2005). Here the measure of success quoted was the final dose achieved by the patient, not the level of glycaemic control achieved. Again, this final dose was clearly stated. In addition, a second recommendation was provided for clinicians to provide advice on an upper limit for Lantus titration above which they could consider adding a meal-time insulin for additional glycaemic control. Both pages made a very clear reference to the doses utilised in each study – 62 units on the left-hand page, 45 units on the right-hand page, and were provided in this format so as to enable the reader to compare the two pieces of evidence. The intended audience would readily identify that the two doses were different and that results on the left-facing page would not be replicated by following the advice on the right-facing page.

Sanofi-Aventis therefore submitted that the leavepiece provided important information to help inform clinicians and optimise the treatment of their patients and, rather than seeking to mislead, it met high standards and no breach of the Code had occurred.

PANEL RULING

The Director noted that the leavepiece had been withdrawn due to different allegations. It was not clear that Sanofi-Aventis would not use the claims now at issue again. Thus the Director considered that inter-company dialogue had not been completely successful and the matter was referred to the Panel for it to consider.

The Panel noted the title of the leavepiece 'Why choose Lantus to complement OADs' was followed on the inside page by 'Lantus can help patients who are uncontrolled on OADs' beneath which information was given about initiating treatment of type 2 diabetes with Lantus. The next page was headed 'Simple self titration with Lantus'. The Panel considered that many readers would assume that the leavepiece set out a normal course of events following initiation of Lantus. The context of claims was an important consideration.

The Panel considered that, without any statement to the contrary, readers would assume that the data regarding a 2% reduction in HbA1c was linked to the statements regarding dose titration which was not so. The Panel did not consider that readers would see the pages as distinct and separate in their own right as submitted by Sanofi-Aventis. Although the dose of Lantus (62 units) used to achieve a 2% reduction in HbA1c was stated it was impossible for the reader to know how this compared to the maximum titrated dose (0.5U/kg) recommended by Monnier and Colette. From the published study (Yki-Järvinen *et al*) it appeared that the Lantus dose which resulted in a 2% reduction in HbA1c in U/kg was 0.66U/kg (given that the mean weight at baseline had been 93.8kg and the mean dose of insulin was 62 units). (Novo Nordisk had calculated a dose of 0.64U/kg). The Panel considered that viewed together the pages gave a misleading impression and a breach of Clause 7.2 was ruled.

3 Leavepiece – 'Lantus – getting the balance right for your diabetes patients' (ref LAN08/1039)

This leavepiece had been voluntarily withdrawn by Sanofi-Aventis following inter-company dialogue in relation to Case AUTH/2141/7/08.

The complaint concerned a page headed '… but what about weight gain?' which set out data for weight gain in type 1 and type 2 diabetes. The section about type 2 diabetes included a bar chart comparing of the mean weight change after 1 year with Lantus once daily (3.9kg) and twice daily Levemir (3.7kg) (p=NS). The bar chart was referenced, *inter alia*, to Rosenstock *et al*.

COMPLAINT

Novo Nordisk was concerned about a claim about the weight gain in type 2 diabetes. Although the weight gain was significantly lower after insulin initiation with Levemir in Rosenstock *et al*, Sanofi-Aventis had deliberately implied that there was no difference in this regard between the two products. The prominent bar chart was proof of this intention. Novo Nordisk noted that the Levemir SPC stated 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrated that glycaemic control (HbA1c) with Levemir is comparable with NPH insulin and insulin glargine and associated with less weight gain …'. A table of data in the SPC showed, *inter alia*, that at 52 weeks weight gain with Lantus was 4kg, with Levemir twice daily it was 3.7kg and with Levemir once daily it was 2.3kg.

Sanofi-Aventis had repeatedly tried to suggest to health professionals that Lantus resulted in the same weight gain, after insulin initiation as part of a basal-oral regimen, as Levemir. Novo Nordisk highlighted the previous ruling by the Appeal Board (Case AUTH/2038/8/07) that 'The Appeal Board considered that the claims at issue* [asterisk added by Novo Nordisk] were misleading as they did not reflect the totality of the data regarding the weight gain typically seen with Lantus and Levemir. The

Appeal Board upheld the Panel's ruling of a breach of Clause 7.2'.

Therefore Novo Nordisk alleged that the presentation of the weight gain data in type 2 diabetes, which tried to imply the same message as had been ruled in breach of Clause 7.2 earlier, misled health professionals and was in breach of Clause 2, 7.2 , 7.4 and 9.1. Furthermore Sanofi-Aventis highlighted itself that it compared weight results with once daily Lantus and twice daily Levemir. Although twice daily use was permitted by the Levemir SPC, it was not the usual and recommended way in insulin initiation. The Levemir SPC suggested starting with once daily in combination with OADs in type 2 diabetics. The only reason to use the twice daily subgroup from Rosenstock *et al* (instead of the more relevant once daily users or the combined cohort of the once daily and twice daily users) was to find the only piece of information in the medical literature which could substantiate the weight comparison claim at issue.

RESPONSE

Sanofi-Aventis noted that there were two comparisons made in the item with respect to type 2 diabetes and weight change:

Sanofi-Aventis submitted that the claim 'Weight gain over one year with Lantus + OADs was only 0.9kg more than the weight gain seen with Levemir + OADs (p=0.01)' was a direct comparison of the difference in weight gain in all patients using Levemir compared with all patients using Lantus in Rosenstock *et al*. The leavepiece clearly stated that weight gain was significantly greater in the Lantus group than the Levemir group, and provided both the difference (0.9kg) and level of significance (p=0.01), which was consistent with the published data. Therefore this information was accurate and substantiable, and met all the requirements of the Code.

Sanofi-Aventis noted that the claim 'In the 55% of patients taking Levemir twice daily there was no significant difference in weight gain compared with patients taking Lantus (3.7kg vs 3.9kg, p=NS)' was a direct comparison, from Rosenstock *et al*, of the weight gain seen in patients using Levemir twice daily, (which was the majority of patients, 55%), with patients using Lantus. The item clearly stated the levels of weight gain recorded in the study (3.7kg vs 3.9kg respectively), and the fact that there was no significant difference between these two groups. Sanofi-Aventis understood that it was this statement that was the origin of the complaint, through the fact that no significant difference in weight gain was reported in this statement.

Sanofi-Aventis noted that the Levemir SPC referred to the same study (although the figures were slightly different in the SPC than in the published report), and which stated that there was less weight gain for patients using Levemir twice daily (3.7kg) compared with Lantus (4kg). Although the SPC stated that there was less weight gain demonstrated in patients taking Levemir than other insulins, there were no significance levels provided in either the text or table to confirm whether the differences observed were significant.

Sanofi-Aventis noted that despite the absence of such confirmation in the SPC, it could substantiate the claim of no significant difference in weight gain between these two patient groups. Although the published paper, like the SPC, failed to provide the level of significance for this comparison, the quoted reference, a Novo Nordisk Drug Information Document, clearly indicated that the difference in weight gain was non-significant (stated as -0.55lbs, 95% CI -2.44, +1.36lbs, equivalent to -0.25kg, 95% CI -1.1, +0.62kg). In view of this, Sanofi-Aventis considered that this information was accurate and substantiable and met all the requirements of the Code.

Finally Sanofi-Aventis noted that Novo Nordisk referred to the previous case where weight gain was considered (AUTH2038/8/07), and to the Appeal Board's ruling at that time that a (different) claim made by Sanofi-Aventis of no significant difference in weight gain between patients using Lantus and Levemir did not reflect the totality of the evidence available. Novo Nordisk alleged that the leavepiece now at issue was contrary to findings of this case.

Sanofi-Aventis submitted that when this case was considered Novo Nordisk did not disclose its own drug information document confirming no significant difference in weight gain between these two groups of patients. In light of the information now known to exist, Sanofi-Aventis considered that the claim at issue was accurate, substantiable, met the requirements of the Code and was not in breach of the ruling in Case AUTH2038/8/07. The question remained as to whether the outcome in that case might have been different had Novo Nordisk disclosed this information (which was clearly relevant to the case) and had Sanofi-Aventis been able to refer to these facts and place them before the Panel and the Appeal Board when this was considered.

In conclusion, contrary to the allegation that this item was in breach of the Code and in breach of a previous ruling, Sanofi-Aventis submitted that the claims at issue could be substantiated and that high standards had been maintained throughout.

PANEL RULING

The Panel noted that the page headed '… but what about weight gain?' was divided into two sections – one related to type 1 diabetes whilst the other referred to type 2 diabetes. The type 2 diabetes section featured a visually prominent bar chart showing the weight change after one year with once daily Lantus (+3.9kg) and twice daily Levemir (+3.7kg) (p=NS). Although it was also stated that

weight gain over one year with Lantus plus OADs was only 0.9kg more than that seen with Levemir plus OADs (p=0.01) thus acknowledging a greater weight gain in the Lantus group, this written claim was much less obvious to the reader than the bar chart.

The bar chart detailed the results from Rosenstock *et al* in which insulin-naïve type 2 diabetes had been treated with Lantus or Levemir. Although all Lantus patients had remained on once daily injections, 55% of Levemir patients had progressed to twice daily injections. The weight gain seen with the two Levemir dosing regimens varied and in the Panel's view it was important that prescribers knew all of the facts so that they could advise their patients accordingly. The bar chart had detailed once daily Lantus vs twice daily Levemir where the difference in weight gain between the two was in favour of Levemir and stated as being non-significant (the statistical significance was not stated in Rosenstock *et al* but appeared to have been taken from a Novo Nordisk review of Levemir therapy and effect on body weight). The results for once daily Lantus vs once daily Levemir, as reported by Rosenstock *et al* and applicable to 45% of patients, were not stated in the leavepiece. This would have shown a statistically significant advantage for Levemir (+2.3kg vs +3.9kg, p<0.001).

The Panel considered that by reporting only some of the Rosenstock *et al* data the leavepiece was incomplete and misleading in that regard. Prescribers had not been given all of the information upon which to make a fully informed prescribing choice. A breach of Clause 7.2 was ruled.

The Panel did not consider that the weight gain data in type 2 diabetes was not capable of substantiation as alleged thus no breach of Clause 7.4 was ruled.

The Panel did not consider that Sanofi-Aventis had failed to maintain high standards and no breach of Clause 9.1 was ruled. Clause 2 was used as a sign of particular censure and reserved for such use. In the Panel's view the circumstances did not warrant a ruling of that clause.

Complaint received **5 August 2008**

Case completed **5 November 2008**

CASE AUTH/2153/8/08

PRESCRIBING SUPPORT PHARMACIST v PROCTER & GAMBLE

Actonel leavepiece

A prescribing support pharmacist complained about an Actonel (risedronate) leavepiece issued by Procter & Gamble. Procter & Gamble also marketed Didronel PMO (etidronate). Both Actonel and Didronel were for use in the treatment or prevention of postmenopausal osteoporosis.

The leavepiece entitled 'Latest NICE [National Institute for Health and Clinical Excellence] information included (July 2008) for Primary and Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women' was referenced to the relevant NICE final appraisal determinations, July 2008. The complainant telephoned NICE and was told that the guidelines were still in draft form and had not been finalised. Quotations from the guidelines were included in the leavepiece. The complainant alleged that the first quotation was misleading as it appeared to recommend risedronate above etidronate when this was not the case. The second quotation, under the heading 'Should patients be switched?' appeared to be taken out of context to suit the purpose of the company. The complainant could not actually find this quotation in the draft document.

The detailed response from Procter & Gamble is given below.

The Panel noted that running along the bottom edge of the front page of the leavepiece was a dark blue band with the following text in white 'Prescribing information appears on the back page' and then, in slightly less bold print, 'The recommendations made are preliminary and may change after consultation. Readers should consult the [final appraisal document] for full details'. The Panel noted Procter & Gamble's reliance on this statement to set the information given in the leavepiece in context. There was, however, nothing to link the title of the leavepiece to the footnote, although in general claims should not be qualified by the use of footnotes and the like. The Panel considered that the title of the leavepiece was misleading as readers would be unaware, at the outset, that the information was from recommendations that were yet to be finalised. A breach of the Code was ruled.

The Panel noted that page 2 of the leavepiece was headed 'NICE Final Appraisal Determination for Primary and Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women'. In boxed text the first bullet point read 'Risedronate is recommended as the first alternative treatment option alongside etidronate'. This claim stemmed from a discussion in the NICE document as to what therapy patients should be offered if they were unable to take alendronate – it was concluded that risedronate could be recommended for such women. With regard to etidronate, it was decided that even though it had a better cost effectiveness profile than risedronate there were concerns surrounding the clinical evidence base for the medicine and so it should not be recommended in preference to risedronate. However, etidronate could be offered to women unable to take alendronate and in deciding between risedronate and etidronate, clinicians and patients needed to balance the overall effectiveness profile of the medicines against their tolerability and adverse effects in individual patients.

The Panel did not consider that the first bullet point was a fair and balanced reflection of the NICE final appraisal document. Use of the word 'the' and the underlining of first alternative treatment option implied that risedronate should be chosen first and it was the only second line treatment for patients unable to take alendronate. There was a greater emphasis on risedronate than etidronate and an implication that NICE recommended risedronate in preference to etidronate. The Panel considered that the claim was misleading. A breach of the Code was ruled.

A second box of text contained the bullet point 'Should patients be switched?' followed by the statement 'NICE says "Women who are currently receiving treatment with one of the drugs covered by this guidance should have the option to continue treatment until they and their clinicians consider it appropriate to stop"'. The Panel noted Procter & Gamble's submission that this quotation had been taken from section 1.9 of the NICE final appraisal document. Section 1.9 of the document, however, did not include any underlining and stated 'Women who are currently receiving treatment with one of the drugs covered by this guidance, but for whom treatment should not have been recommended according to sections 1.1 to 1.4, should have the option to continue treatment until they and their clinicians consider it appropriate to stop'. The Panel thus noted that the statement in the NICE document was about patients, who according to the guidance should not have started therapy, being allowed to continue with therapy. The statement was not about switching patients from one therapy to another as implied in the leavepiece. The Panel considered that the quotation as it appeared in the leavepiece under a heading of 'Should patients be switched' was not in its correct context. The quotation was misleading in this regard; a breach of the Code was ruled. The Panel considered that the quotation, as it appeared

in the leavepiece, was not an accurate quotation nor did it reflect the meaning of the relevant sections of the NICE final appraisal document. A further breach of the Code was ruled.

A prescribing support pharmacist complained about an Actonel (risedronate) leavepiece (ref ACT3987) issued by Procter & Gamble Pharmaceuticals UK, Limited. Procter & Gamble also marketed Didronel PMO (etidronate). Both Actonel and Didronel were for use in the treatment or prevention of postmenopausal osteoporosis.

The complainant sent the Authority a copy of the complaint she had sent to the Medicines and Healthcare products Regulatory Agency (MHRA).

COMPLAINT

The complainant noted that the leavepiece stated 'Latest NICE [National Institute for Health and Clinical Excellence] information included (July 2008) for Primary and Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women'. The reference for this was the relevant NICE final appraisal determinations, July 2008. When the complainant telephoned NICE about this she was told that the guidelines were still in draft form and had not been finalised. Quotations from the guidelines were included in the leavepiece. The complainant alleged that the first quotation was misleading as it appeared to recommend risedronate above etidronate when this was not the case. The second quotation was under the heading 'Should patients be switched?' and appeared to be taken out of context to suit the purpose of the company. The complainant could not actually find this quotation in the draft document.

When writing to Procter & Gamble, the Authority asked it to respond in relation to Clauses 7.2 and 10.2 of the 2008 Code which were the same as under the 2006 Code apart from the numbering (Clause 11 in the 2006 Code was Clause 10 in the 2008 Code).

RESPONSE

Procter & Gamble did not consider that the leavepiece was in breach of the Code, in particular Clauses 7.2 or 10.2.

Procter & Gamble explained that as guidance for osteoporosis had been in development by NICE for over 6 years, during which time there had been an evolution in the NICE position, the company believed it was important to keep health professionals aware of the current thinking. Specifically, guidance on the secondary prevention of osteoporotic fractures in postmenopausal women was published in January 2005; however a new consultation was started in August 2004 and was still ongoing. Guidance for the primary prevention of osteoporotic fractures in postmenopausal women was started in March 2002 and was still ongoing.

NICE had published appraisal consultation documents and lately final appraisal determinations. These were readily available public documents. In the leavepiece at issue, Procter & Gamble endeavoured to make it abundantly clear that these guidelines were preliminary. The heading of the first page of the leavepiece stated, 'Latest NICE information…' which did not imply a final recommendation.

Additionally, a bold banner at the bottom of the first page stated, 'The recommendations made are preliminary and may change after consultation. Readers should consult the [final appraisal document] for full details'. Finally, page 2 was headed 'NICE Final Appraisal Determination…'.

It was only to be expected that health professionals would want to be informed of the latest NICE position on a particular topic. As a company with an interest in osteoporosis, Procter & Gamble developed this leavepiece to provide information on the latest NICE position.

Procter & Gamble considered that the leavepiece made it very clear that it was based on the final appraisal determination and that this might change after consultation and thus did not consider that this was a breach of Clause 7.2 .

As noted above, health professionals were interested in how Procter & Gamble's products were assessed in the latest final appraisal documents from NICE. Thus, the leavepiece stated, 'Risedronate is recommended as the first alternative treatment option alongside etidronate'. The text of the whole statement was in the same typeface and size that gave equal emphasis to etidronate.

This was consistent with the draft NICE guidelines and deliberately used the word 'option' that by definition implied there was more than one. It was well known, however, that clinically etidronate was a less preferred option when treating osteoporosis. The statement in the leavepiece was not misleading and as Procter & Gamble marketed both products it considered that the statement showed equal emphasis to both and it thus did not consider it to be in breach of Clause 7.2.

With regard to the claim on whether patients should be switched, Procter & Gamble submitted that as shown in the NICE final appraisal documents, the majority of patients eligible for osteoporosis treatment would be prescribed generic alendronate, based mainly on its acquisition cost. It followed, therefore, that health professionals questioned whether patients should be switched from their existing treatment to generic alendronate. The leavepiece shared NICE's latest thinking on this.

The guidance given in the final appraisal documents was shown on page 2 of the leavepiece. This statement was made in section 1.9 of both documents for the primary or secondary prevention of osteoporotic fractures. NICE clearly considered it

necessary to make this statement to guide health professionals in the appropriate management of patients. The text had been accurately reflected in the leavepiece and, therefore, Procter & Gamble did not consider this to be a breach of Clause 10.2.

In summary Procter & Gamble considered that it was clear that the leavepiece was based on the final appraisal documents from NICE and that these '…are preliminary and may change after consultation'. As stated above, these were publicly available documents.

The statement made on risedronate and etidronate was consistent with the latest NICE positioning and did not place undue emphasis on risedronate.

Finally, the text that the complainant was unable to find in the final appraisal documents was shown in section 1.9.

Procter & Gamble was convinced that the leavepiece conveyed information of relevance and interest to health professionals in a manner clearly reflective of the source documents and that was not in breach of Clauses 7.2 or 10.2.

PANEL RULING

The Panel noted that the leavepiece was entitled 'Latest NICE information included (July 2008) for Primary and Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women'. Running along the bottom edge of the front page was a dark blue band with the following text in white 'Prescribing information appears on the back page' and then, in slightly less bold print, 'The recommendations made are preliminary and may change after consultation. Readers should consult the [final appraisal document] for full details'. The Panel noted Procter & Gamble's reliance on this statement to set the information given in the leavepiece in context. There was, however, nothing to link the title of the leavepiece to the footnote. In any event the supplementary information to Clause 7.2 stated 'It should be borne in mind that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like'. The Panel considered that the title of the leavepiece was misleading as readers would be unaware, at the outset, that the information contained within came from recommendations that were yet to be finalised. A breach of Clause 7.2 was ruled.

The Panel noted that page 2 of the leavepiece was headed 'NICE Final Appraisal Determination for Primary and Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women'. In boxed text the first bullet point read 'Risedronate is recommended as the first alternative treatment option alongside etidronate'. This claim stemmed from a discussion in the NICE document as to what therapy patients should be offered if they were unable to take alendronate – it was concluded that risedronate could be recommended for such women. With regard to etidronate, it was decided that even though it had a better cost effectiveness profile than risedronate there were concerns surrounding the clinical evidence base for the medicine and so it should not be recommended in preference to risedronate. However, etidronate could be offered to women unable to take alendronate and in deciding between risedronate and etidronate, clinicians and patients needed to balance the overall effectiveness profile of the medicines against their tolerability and adverse effects in individual patients.

The Panel did not consider that the first bullet point was a fair and balanced reflection of the NICE final appraisal document. Use of the word 'the' and the underlining of first alternative treatment option implied that risedronate should be chosen first and it was the only second line treatment for patients unable to take alendronate. There was a greater emphasis on risedronate than etidronate and an implication that NICE recommended risedronate in preference to etidronate. The Panel considered that the claim was misleading. A breach of Clause 7.2 was ruled.

A second box of text contained the bullet point 'Should patients be switched?' followed by the statement 'NICE says "Women who are currently receiving treatment with one of the drugs covered by this guidance should have the option to continue treatment until they and their clinicians consider it appropriate to stop"'. The Panel noted Procter & Gamble's submission that this quotation had been taken from section 1.9 of the NICE final appraisal document. Section 1.9 of the document, however, did not include any underlining and stated 'Women who are currently receiving treatment with one of the drugs covered by this guidance, but for whom treatment should not have been recommended according to sections 1.1 to 1.4, should have the option to continue treatment until they and their clinicians consider it appropriate to stop'. The Panel thus noted that the statement in the NICE document was about patients who, according to the guidance should not have started therapy, being allowed to continue with therapy. The statement was not about switching patients from one therapy to another as implied in the leavepiece. The Panel considered that the quotation as it appeared in the leavepiece under a heading of 'Should patients be switched' was not in its correct context. The quotation was misleading in this regard; a breach of Clause 7.2 was ruled. The Panel considered that the quotation, as it appeared in the leavepiece, was not an accurate quotation nor did it reflect the meaning of the relevant sections of the NICE final appraisal document. A breach of Clause 10.2 was ruled.

Complaint received **5 August 2008**

Case completed **15 September 2008**

VOLUNTARY ADMISSION BY ROCHE and CHUGAI

Tocilizumab media release

Roche and Chugai Pharma made a joint voluntary admission about a media release which they had issued on 13 June 2008. The media release related to the presentation of new clinical data on tocilizumab, a biologic therapy currently under consideration for marketing authorization by the US and European regulatory authorities for the management of rheumatoid arthritis. These data were presented at the recent European League Against Rheumatism (EULAR) meeting.

Following discussions with Wyeth it had become apparent that the headline claims 'New data reveals tocilizumab is the first and only biologic drug to show superiority over current standard of care in rheumatoid arthritis' and 'This new data, presented today at the European League Against Rheumatism (EULAR) meeting in Paris, makes tocilizumab the first and only biologic therapy to have achieved superiority over MTX [methotrexate]' within the media release might be considered factually incorrect when read alone and therefore might be in breach of the Code.

During inter-company dialogue Wyeth had asked for a corrective statement to be published in scientific journals. However, as tocilizumab was currently unlicensed Roche and Chugai considered that such a statement would potentially be in breach of the Code. Therefore inter-company dialogue had been unsuccessful and thus Roche and Chugai had decided that a voluntary submission to the Authority was the only appropriate course of action.

The Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. Issuing a potentially misleading press release was a serious matter and the admission was accordingly treated as a complaint.

The detailed response from Roche and Chugai is given below.

The Panel considered that the heading, 'New data reveals tocilizumab is the first and only biologic drug to show superiority over current standard of care in rheumatoid arthritis' was a strong unqualified claim. The first paragraph explained that the current standard of care was methotrexate. The Panel noted the companies' submission that other biologic therapies had shown superiority but unlike tocilizumab not across all American College of Rheumatology (ACR) measures. Superiority had not been uniformly shown in this regard at 6 months and it was this point that was intended to be conveyed in the media release. The Panel was concerned about the general claims for superiority. The media release also contained the claim 'No previous biologic therapy has demonstrated superiority compared to MTX' which was not so. The Panel noted that the media release had been sent to UK national and medical media. The product was not authorized in the UK and the media release was extremely positive; it used 'novel', 'innovative' and 'most exciting' to describe the product. The Panel considered that the media release was not factual and that the results of a clinical study had not been presented in a balanced way. The media release would raise unfounded hopes of successful treatment. Thus the Panel ruled a breach of the Code.

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

Roche Products Ltd and Chugai Pharma UK Ltd made a joint voluntary admission about a media release (ref PRX3158) concerning tocilizumab issued on 13 June.

Claims 'New data reveals tocilizumab is the first and only biologic drug to show superiority over current standard of care in rheumatoid arthritis' and **'This new data, presented today at the European League Against Rheumatism (EULAR) meeting in Paris, makes tocilizumab the first and only biologic therapy to have achieved superiority over MTX [methotrexate]'**

The first claim was the headline to the media release and the second claim appeared within the media release.

COMPLAINT

The companies brought the Authority's attention to a media release they had issued on 13 June 2008. This media release related to the presentation of new clinical data on tocilizumab, a biologic therapy currently under consideration for marketing authorization by the US and European regulatory authorities for the management of rheumatoid arthritis. These data were presented at the European League Against Rheumatism (EULAR) meeting in Paris.

Roche and Chugai stated that following discussions with Wyeth Pharmaceuticals it had become apparent that the claims at issue might be considered factually incorrect when read alone and therefore might be in breach of the Code, in particular Clause 7.

Inter-company dialogue had been ongoing, with a

request by Wyeth for a corrective statement to be published in scientific journals. This was considered; however, as tocilizumab was currently unlicensed the issuing of such a statement had been deemed by Roche and Chugai to be unachievable without potentially being in breach of the Code. Therefore inter-company dialogue had been unsuccessful and thus Roche and Chugai had decided that a voluntary admission was the only appropriate course of action.

Paragraph 5.4 of the 2008 Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. Issuing a potentially misleading press release was a serious matter and the admission was accordingly treated as a complaint.

When writing to Roche and Chugai, the Authority asked them to respond in relation to Clauses 2, 9.1 and 20.2 of the 2006 Code which were the same in the 2008 Code though numbered differently Clause 20.2 being Clause 22.2 in the 2008 Code. This case was considered under the 2008 Constitution and Procedure.

RESPONSE

Roche and Chugai submitted a joint response and explained that tocilizumab was currently being reviewed by the EU and US regulators. Market authorization in the EU was anticipated in 2009. Tocilizumab was the first anti-interleukin 6 (IL-6) receptor antagonist to be developed.

The media statement for tocilizumab 'New data reveals tocilizumab is the first and only biologic drug to show superiority over current standard of care in rheumatoid arthritis' was issued on 13 June following the presentation of new data at the EULAR annual meeting in Paris. This media release was adapted from the global press release and was issued from the UK to the UK national and medical media. It was signed off in accordance with the approval and certification and public relations standard operating procedures (SOPs) of both Roche and Chugai.

The media release covered two phase III trials. The claims at issue related to the presentation of a phase III trial on the use of tocilizumab monotherapy compared with MTX monotherapy in patients with active rheumatoid arthritis who had not been treated with MTX within 6 months prior to randomization, the AMBITION trial (Tocilizum**A**b versus **M**ethotrexate double-**B**lind **I**nvestigative **T**rial In m**ON**therapy).

Patients were randomized in the 24 weeks, double-blind, double-dummy parallel group, phase III study to either 8mg/kg tocilizumab every 4 weeks or to an escalating MTX dose of 7.5-20mg weekly. The primary analysis for non-inferiority used the per protocol population (n=524), and the secondary analysis for superiority used the intention to treat (ITT) population (n=570). The demonstration of superiority was based on the regulatory authority required efficacy measures of the ACR20, 50 and 70 scores. The American College of Rheumatology (ACR) scoring system was a composite measure and represented percentage improvement from baseline at defined time points. Because rheumatoid arthritis was a chronic systemic disease, that was probably best described as a syndrome, efficacy needed to be assessed beyond just the improvement in a patient's joints or inflammatory markers and must account for both the physical and psychological effects of the disease. As such the ACR scoring system was made up of the following parameters, tender joint count, swollen joint count, patient's assessment of pain, patient's and physician's global assessments of disease activity, patient's assessment of physical function, and laboratory evaluation of one acute-phase reactant eg C-reactive protein.

In defining a patient's ACR20 improvement following the initiation of treatment a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR core set measures (patient and physician global assessments, pain, disability, and an acute-phase reactant) was needed. For an ACR50 a 50% improvement would be needed and so forth.

The ACR measures sampled the broad range of improvement in rheumatoid arthritis, and all were at least moderately sensitive to change. Many of them predicted other important long-term outcomes, including physical disability, radiographic damage, and death.

When looking at the results of the AMBITION study the mean baseline characteristics were similar between groups. Non-inferiority was demonstrated for the primary endpoint ACR20 response at week 24 (71% tocilizumab/52% MTX). This led on to show that tocilizumab was superior to MTX treatment, with a higher proportion of ACR20/50/70 responders at week 24 (table below).

Results at Week 24 (ITT population)	Tocilizumab 8mg/kg (n=286)	MTX (n=284)	p value
ACR20 response (%)	70	53	p<0.0001
ACR50 response (%)	44	34	p=0.0023
ACR70 response (%)	28	15	p=0.0002
Pts with DAS28<2.6(%)	34	12	-
Mean change in DAS28	-3.3	-2.2	-
Mean change in HAQ-DI	-0.7	-0.6	-

To further support the superiority of tocilizumab over MTX a higher proportion of patients achieved a good/moderate EULAR response as early as week 2 (64% tocilizumab/19% MTX), with rates reaching 82% vs 65%, respectively, at week 24.

These results were very significant as this was the first time any biologic therapy had demonstrated superiority across all ACR measures as well as DAS remission rates. This was achieved at 6 months. These results formed the basis of the media release and the two claims at issue.

The relevant section of the media statement stated:

> 'New data reveals tocilizumab is the first and only biologic drug to show superiority over current standard of care in rheumatoid arthritis
>
> Two new international studies also show high remission rates in patients treated with this novel therapy
>
> Welwyn Garden City 13 June 2008: The innovative rheumatoid arthritis drug tocilizumab has shown superiority over current standard of care, methotrexate (MTX), by achieving a greater reduction of signs and symptoms at 6 months in patients suffering from rheumatoid arthritis (RA). This new data, presented today the European League Against Rheumatism (EULAR) meeting in Paris, makes tocilizumab the first and only biologic therapy to have achieved superiority over MTX.'

At this point of sign off Roche and Chugai believed that the context in which these claims were made was sufficiently clear to allow a distinction to be made between what was seen in the AMBITION trial compared with what had been shown with other biologic agents in similar populations. However Roche and Chugai had now raised this matter with the Authority as it recognised that the claims, when read alone, could potentially misrepresent the overall evidence base. Roche and Chugai also recognised that superiority of one therapy over another could be demonstrated in many different ways and therefore careful explanation for the basis of such a claim was needed.

Roche and Chugai noted when approving the media release that, on systematic review other biologic therapies had shown superiority, but either using other patient assessments, such as the DAS28 score or only part of the ACR scoring system eg ACR20 and 50 but not 70. Alternatively X-ray changes had been reported. However, superiority had not been uniformly shown at 6 months as with tocilizumab, and it was this point that was intended to be conveyed in the media release.

Two other studies reported the efficacy and safety of biologic monotherapy vs MTX monotherapy in the management of early rheumatoid arthritis. Bathon *et al* (2000) compared etanercept (ETN) and MTX in patients with early rheumatoid arthritis. This study's primary end point looked at the ACR-N of ETN 10mg twice weekly subcutaneous (sc), ETN 25mg twice weekly sc (licensed dose) and MTX. The ACR-N gave the overall response of each patient by calculating the smallest degree of improvement from baseline in the number of tender joints, the number of swollen joints and the median of the five remaining ACR criteria described above. Therefore the ACR-N represented the cumulative effect over time. When the ACR20, 50 and 70 were observed the ETN 25mg group showed significant improvement over MTX at six months for ACR70 only ($p<0.05$), the ACR20 and 50 were non significant. Significance at 4 months was shown at ACR20, 50 and 70. At no point beyond 6 months was there a significant difference between groups for ACR20, 50 and 70.

The ACR-N over 6 months was significant over time demonstrating rapid improvement in the patient's condition but this measure alone could not demonstrate that ETN was superior to MTX at 6 months. This study also looked at radiographic changes over time. Radiographic measures were used to determine the disease modifying effect of one treatment against another. Bathon *et al* showed significant improvement in the ETN group over the MTX group at 6 months in two of the three scoring criteria, ie erosion and total Sharp score ($p=0.001$). Joint-space-narrowing score however was non significant.

Genovese *et al* (2002) compared ETN and MTX in early rheumatoid patients and looked at radiographic changes at two years as a primary endpoint. ACR20, 50 and 70 were also recorded as a secondary endpoint. Statistical significance between the 25mg licensed dose and MTX for ACR20, 50 and 70 at 6 months was not formally reported. ACR20 at 24 months was significant between 25mg ETN and MTX groups, ACR50 and 70 were however non significant. Reviewing the radiographic endpoints significant improvement in the 25mg ETN group over MTX was seen at 24 months but no other time points were reported. Other endpoints within the study also showed significance over MTX at 24 months including the Health Assessment Questionnaire that measured improvement in function and disability. The authors concluded that 'the benefits of 25mg etanercept as monotherapy were shown to be superior to those of MTX at 2 years'.

When these data sets were compared with the tocilizumab trial results it could be seen that in terms of showing superiority there might be multiple differing opinions on what constituted clinical superiority. Roche and Chugai considered that as tocilizumab had demonstrated superiority across the entire ACR core set at 6 months, which was the clinical utility measure and time point employed by both the EU and US regulatory authorities in evaluating treatments for rheumatoid arthritis, they had the evidence to make the claims at issue. Roche and Chugai accepted that other therapies demonstrated superiority in some

respect of the data and this should have been made clearer.

In considering Clause 20.2 (2006 Code) Roche and Chugai contested that the media release would bring unfounded hopes of successful treatment as tocilizumab was the first therapy to demonstrate superiority across the ACR core criteria which had not been achieved before. Within the media statement the safety profile of tocilizumab was clearly described. However, whilst the media release was factual, Roche and Chugai accepted that the superiority claims should be placed more clearly into context. However, although they accepted that the media release might have been better constructed, they strongly refuted that it had brought discredit to or reduced confidence in, the industry (Clause 2) or failed to maintain high standards (Clause 9.1).

This media release was legitimately issued as the information released at the EULAR meeting represented a significant development in the management of rheumatoid arthritis and was thus newsworthy. There was a high level of interest in terms of finding new treatments in this area as there was a significant unmet need. The media release reflected the specific results of the two trials within it in an accurate and objective manner. It was released in line with Roche and Chugai internal SOPs. The media release did not constitute promotion and was reviewed and signed off in good faith and with competent care. Roche and Chugai considered that high standards had been maintained throughout. They accepted that it needed to be clearer regarding the superiority claim; however in the companies' opinion the media release did not represent the profile of tocilizumab in an unbalanced fashion compared with existing therapies.

Roche and Chugai therefore accepted that the media release might breach Clause 20.2 of the 2006 Code but refuted strongly that the material was in breach of Clauses 2 or 9.1.

PANEL RULING

The Panel considered that the heading to the media release, 'New data reveals tocilizumab is the first and only biologic drug to show superiority over current standard of care in rheumatoid arthritis' was a strong unqualified claim. The first paragraph of the media release explained that the current standard of care was methotrexate. The Panel noted the companies' submission that other biologic therapies had shown superiority but unlike tocilizumab not across all ACR measures. Superiority had not been uniformly shown in this regard at 6 months and it was this point that was intended to be conveyed in the media release. The Panel was concerned about the general claims for superiority. The media release also contained the claim 'No previous biologic therapy has demonstrated superiority compared to MTX' which was not so. The Panel noted that the media release had been sent to UK national and medical media. The product was not authorized in the UK and the media release was extremely positive; it used 'novel', 'innovative' and 'most exciting' to describe the product. The Panel considered that the media release was not factual and that the results of the AMBITION study had not been presented in a balanced way. The media release would raise unfounded hopes of successful treatment. Thus the Panel ruled a breach of Clause 20.2 of the 2006 Code.

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

Although noting its rulings above, the Panel did not consider that the media release warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Proceedings commenced	**7 August 2008**	
Cases completed	**AUTH/2154/8/08**	**7 October 2008**
	AUTH/2155/8/08	**9 October 2008**

CASE AUTH/2156/8/08

GLAXOSMITHKLINE v SANOFI PASTEUR MSD

Gardasil letter to health professionals

GlaxoSmithKline complained about a letter sent to health professionals on 18 June by Sanofi Pasteur MSD.

GlaxoSmithKline noted that it had already complained (Case AUTH/2147/7/08) in relation to Sanofi Pasteur MSD's activities after the Department of Health (DoH) granted the contract to supply the human papillomavirus (HPV) vaccine for the national immunisation programme to Cervarix (GlaxoSmithKline's vaccine). Sanofi Pasteur MSD marketed Gardasil and had also competed for the contract.

GlaxoSmithKline stated that its concerns about the letter now at issue were similar to its previous concerns and provided further evidence of non-compliant activity by Sanofi Pasteur MSD in the immediate aftermath of the government's decision.

GlaxoSmithKline stated that anonymous health professionals sent it copies of the letter in question, concerned that it appeared to imply that the DoH had chosen the wrong vaccine; one that the rest of the world had not chosen. The health professionals were concerned that it was an attempt to undermine confidence in the choice of vaccine for the national HPV immunisation programme.

GlaxoSmithKline stated that Sanofi Pasteur MSD had asserted that the letter was sent to a limited number of experts with whom it had worked closely and came under the Code's exclusion of 'factual, accurate and informative announcements and reference material', but for this to apply, then the letter must 'include no product claims'. GlaxoSmithKline noted that the letter contained a number of claims, and provided examples.

GlaxoSmithKline contended that had Sanofi Pasteur MSD simply wished to inform these health professionals of the DoH's decision as a matter of courtesy, then the first and last paragraphs would have been adequate. However, the letter also included a further three paragraphs which promoted Gardasil. Consequently, GlaxoSmithKline considered that the letter was promotional and subject to the requirements of the Code including the requirements for prescribing information and an adverse event statement.

The claim '… Gardasil has recently received a positive opinion from the CHMP for protection against pre-malignant lesions of the vagina as a licence extension' constituted promotion of indications not covered by the marketing authorization. Readers were unlikely to know the nuances of the regulatory processes and would not be clear that a positive opinion did not equate to a licence granted, but was one of the final steps on the ladder towards it. As such, readers were left with the impression that the licence had already been extended.

GlaxoSmithKline stated that during inter-company correspondence Sanofi Pasteur MSD claimed the inclusion of the positive opinion announcement was a legitimate exchange of medical and scientific information with a number of experts, but the letter could not be both a factual informative announcement as claimed initially and also a bona fide exchange of scientific or medical views.

GlaxoSmithKline alleged that as part of a concerted campaign to undermine confidence in the DoH's decision to use Cervarix as the vaccine of choice, the letter had not maintained high standards.

The detailed response from Sanofi Pasteur MSD is given below.

The Panel noted Sanofi Pasteur MSD's submission that the letter had been sent to a group of clinicians with whom the company had worked closely as part of an ongoing legitimate scientific dialogue. According to information supplied by Sanofi Pasteur MSD the letter had been sent to just over 50 health professionals, the majority being hospital consultants. Sanofi Pasteur MSD had given details of its relationship with each health professional; many had spoken at Sanofi Pasteur MSD meetings. It appeared that for some of the health professionals, however, their only relationship with Sanofi Pasteur MSD was that the company had sponsored them to attend a European meeting on gynaecological oncology.

The Panel considered that the letter was promotional for Gardasil. Details of its indications were included and Gardasil was referred to as the 'world's leading HPV vaccine'. The Panel noted Sanofi Pasteur MSD's submission that the letter was not promotional and was part of an ongoing legitimate scientific dialogue with selected clinicians. In the Panel's view, however, each clinician would have a slightly different relationship with the company and so an identical letter to all of them could not be seen as part of that relationship. Further, the letter was purely product related and did not put any of that information into context with regard to the relationship between the recipient and the company. The Panel considered that the inclusion of product claims made the letter promotional and in that regard it could not benefit from the exemption to promotion given to factual, accurate, informative announcements. It was not

relevant whether Gardasil could or could not be used outside the national immunisation programme. The Panel considered that the letter should have included prescribing information and a statement about adverse event reporting and as both were absent breaches of the Code were ruled.

The claim 'In addition Gardasil has recently received a positive opinion for protection against pre-malignant lesions of the vagina as a licence extension' in a press release had been considered in Case AUTH/2147/7/08 and ruled to be misleading in breach of the Code by the Panel. The material now at issue was promotional material aimed at health professionals. The Panel considered that by referring to the positive CHMP opinion and licence extension the letter promoted Gardasil for an as yet unauthorized indication. This was inconsistent with the marketing authorization and thus a breach of the Code was ruled.

The Panel noted that GlaxoSmithKline stated that as part of a concerted campaign to undermine confidence in the DoH decision to use Cervarix as the vaccine of choice the letter failed to maintain high standards. The Panel noted that the letter had been sent to a limited audience all of whom had had some specific interaction with Sanofi Pasteur MSD and interest in the UK HPV vaccination programme. Nonetheless, the Panel considered that Sanofi Pasteur MSD's failure to regard the letter as promotional material demonstrated a poor knowledge of the requirements of the Code. High standards had not been maintained. A breach of the Code was ruled.

GlaxoSmithKline UK Ltd complained about a letter (ref 0608 UK11970) sent to health professionals on 18 June by Sanofi Pasteur MSD Ltd.

GlaxoSmithKline noted that it had already complained to the Authority (Case AUTH/2147/7/08) in relation to Sanofi Pasteur MSD's activities after the Department of Health (DoH) granted the contract to supply the human papillomavirus (HPV) vaccine for the national immunisation programme to Cervarix (GlaxoSmithKline's vaccine). Sanofi Pasteur MSD marketed Gardasil and had also competed for the contract.

GlaxoSmithKline stated that its concerns about the letter now at issue were similar to its previous concerns and provided further evidence of non-compliant activity by Sanofi Pasteur MSD in the immediate aftermath of the government's decision. Inter-company dialogue had been unsuccessful. The clauses referred to were in relation to the 2006 Code as the letter in question was dated before 1 July 2008. The case was considered using the 2008 Constitution and Procedure.

COMPLAINT

GlaxoSmithKline stated that anonymous health professionals sent it copies of the letter which they had received from Sanofi Pasteur MSD, concerned that it appeared to imply that the DoH had chosen the wrong vaccine; one that the rest of the world had not chosen. The health professionals were concerned that it was an attempt to undermine confidence in the choice of vaccine made for the national HPV immunisation programme.

GlaxoSmithKline stated that in inter-company correspondence Sanofi Pasteur MSD had asserted that the letter was sent to a limited number of experts with whom it had worked closely and came under the exclusions of Clause 1.2, 'factual, accurate and informative announcements and reference material', but for this to apply, then the letter must 'include no product claims'. GlaxoSmithKline noted that the letter contained a number of claims, from 'In addition to protection from cervical cancer…', '… world's leading HPV vaccine…', '… more than 26 millions doses of Gardasil having been distributed…', '… Gardasil provides early health and economic benefits…' to '… good safety profile'.

GlaxoSmithKline contended that had Sanofi Pasteur MSD simply wished to inform these health professionals of the DoH's decision as a matter of courtesy, then the first and last paragraphs would have been adequate. However, the letter also included a further three paragraphs which promoted Gardasil. Consequently, GlaxoSmithKline considered that the letter was promotional and subject to the requirements of the Code. There was no stipulation in the Code that only blanket mailings were promotional, and campaigns targeted to a particular group of health professionals were often used as a marketing tool. As such the letter required prescribing information and an adverse event statement. Lack of these breached Clauses 4.1 and 4.10.

As the letter was promotional, the inclusion of the claim '… Gardasil has recently received a positive opinion from the CHMP for protection against pre-malignant lesions of the vagina as a licence extension' constituted promotion of indications not covered by the marketing authorization. A similar claim was included in the Sanofi Pasteur MSD press release considered in Case AUTH/2141/7/08 ie 'In addition to protection from cervical cancer, Gardasil provides protection from precancerous cervical, vulval and vaginal lesions (an extension to the licence following a recent CHMP positive opinion) and genital warts caused by virus types targeted by the vaccine'. Readers were unlikely to know the nuances of the regulatory authority processes and would not be clear that a positive opinion did not equate to a licence granted, but was one of the final steps on the ladder towards it. As such, readers were left with the impression that the licence had already been extended. GlaxoSmithKline alleged that this was in breach of Clause 3.2.

GlaxoSmithKline stated that during inter-company correspondence Sanofi Pasteur MSD claimed the inclusion of the positive opinion announcement was a legitimate exchange of medical and scientific

information with a number of experts, but the letter could not be both a factual informative announcement as claimed initially and also a bona fide exchange of scientific or medical views.

GlaxoSmithKline noted that Sanofi Pasteur MSD had stated that the second paragraph outlined information on the indication of Gardasil which any of the limited number of experts with whom it had worked closely would have known. The language used did not suggest an audience with whom Sanofi Pasteur MSD had worked closely, or it would not need to be told that Gardasil was 'the four type (6, 11, 16 and 18) HPV vaccine', or what its indication was.

GlaxoSmithKline noted that one paragraph was dedicated to noting how many doses had been distributed worldwide, which on its own did not constitute scientific or medical exchange. The bland nature of the clinical information 'good safety profile and generally well tolerated' also indicated that this was not a personal letter to individual experts, but a targeted promotional mailing to a number of health professionals.

GlaxoSmithKline alleged that as part of a concerted campaign to undermine confidence in the DoH's decision to use Cervarix as the vaccine of choice, the letter had not maintained high standards and as such breached Clause 9.1.

RESPONSE

Sanofi Pasteur MSD noted that GlaxoSmithKline had alleged that its letter to health professionals was promotional. Sanofi Pasteur MSD refuted this for several reasons. The letter was sent by its medical director as part of an ongoing, legitimate scientific dialogue with a selected group of clinicians with whom it had worked closely over time. Throughout this dialogue, no clinician had complained or asked it to stop sending them information. The distribution list and details of the relationship with Sanofi Pasteur MSD was provided in confidence. This long-term relationship with the clinicians was clear from the final paragraph of the letter which concluded: 'We would like to thank you for your continued support and look forward to the opportunity to work with you again on future vaccine initiatives'.

There were many stakeholders that had an interest in the national HPV immunisation programme yet, out of these, only a selected number were sent the letter. Sanofi Pasteur MSD had chosen to maintain close contact with these individuals as they represented a broad range of specialties eg out of approximately 550 senior genito-urinary medicine clinicians in the country, only 11 were sent the letter.

Furthermore, Sanofi Pasteur MSD did not believe that the letter contained promotional claims. The DoH's book - Immunisation Against Infectious Disease (The 'Green Book') stated that the HPV vaccine was not routinely recommended for those outside the national immunisation programme and there was no mention in the letter that the vaccine could be prescribed on a case-by-case basis. Consequently Sanofi Pasteur MSD believed that the letter actually deterred clinicians from prescribing Gardasil. It therefore rebutted the allegation that the letter was promotional and as such it would not have been appropriate to include prescribing information or an adverse event statement. On the basis of this Sanofi Pasteur MSD refuted the allegations of a breach of Clauses 4.1 and 4.10.

Sanofi Pasteur MSD had responded to GlaxoSmithKline's allegation of a breach of Clause 3.2 in Case AUTH/2147/7/08 in relation to the press release (UK12004) with reference to a positive CHMP opinion. It restated that whilst GlaxoSmithKline correctly pointed out that a positive CHMP opinion did not equate to a licence extension, it was nonetheless the step before the licence extension was granted. The second paragraph of the letter did not state that this was the indication of Gardasil, therefore Sanofi Pasteur MSD refuted this allegation of a breach of Clause 3.2.

Sanofi Pasteur MSD disagreed with GlaxoSmithKline that the letter could not be both a factual informative announcement as well as a bona fide exchange of scientific or medical views. Whilst a letter to an individual in itself could not be considered an exchange, since the information was only flowing in one direction, this must be taken in the broader context of an ongoing dialogue which was two way, components of which might include telephone calls, emails, as well as face to face meetings, as was the case with the letter's recipients and thus forming a legitimate exchange of scientific or medical views.

Sanofi Pasteur MSD had certainly not undertaken a concerted campaign to undermine confidence in the DoH's decision to choose GlaxoSmithKline's HPV vaccine instead of Gardasil. In fact the opposite was true. Sanofi Pasteur MSD had continued to be supportive of the DoH's HPV vaccination programme even though it was not successful in the tender process as evidenced by a range of initiatives which had included the following:

- A series of meetings run in conjunction with the Royal Society of Medicine focused on the prevention of cervical cancer.
- Sanofi Pasteur MSD had sponsored the Royal Society for the Promotion of Health's Human Papillomavirus Education programme including an education pack for schools to support Personal, Social and Health Education as well as a leaflet written and evaluated by a professor. The latter had been distributed on request to the primary care sector and had also been requested by schools.
- Sanofi Pasteur MSD had undertaken a disease awareness campaign entitled 'tell her' which provided educational information about HPV and cervical cancer.

- Sanofi Pasteur MSD provided a series of workshops for primary care organisations to support the implementation of the national HPV immunisation programme.

Sanofi Pasteur MSD did not believe that the letter was misleading, inaccurate or damaging. On the contrary it believed that the letter appropriately conveyed the outcome of the tender decision and gave the recipients of the letter the necessary context to help them understand its position. Sanofi Pasteur MSD had conformed to the highest standards and consequently it refuted the allegation of a breach of Clause 9.1.

In summary, Sanofi Pasteur MSD believed that it had acted appropriately in light of the DoH's decision to select GlaxoSmithKline's HPV vaccine for the national HPV immunisation programme. It strongly refuted the allegations of breaches of Clauses 3.2, 4.1 and 4.10. It was a responsible company, dedicated to vaccines and public health, and believed that it had maintained high standards and consequently denied breaching Clause 9.1.

PANEL RULING

The Panel noted Sanofi Pasteur MSD's submission that the letter had been sent to a group of clinicians with whom the company had worked closely as part of an ongoing legitimate scientific dialogue. According to information supplied by Sanofi Pasteur MSD the letter had been sent to just over 50 health professionals, the majority being hospital consultants. Sanofi Pasteur MSD had given details of its relationship with each health professional; many had spoken at Sanofi Pasteur MSD meetings. It appeared that for some of the health professionals, however, their only relationship with Sanofi Pasteur MSD was that the company had sponsored them to attend a European meeting on gynaecological oncology.

The Panel examined the letter at issue. It considered that it was promotional for Gardasil. Details of its indications were included and Gardasil was referred to as the 'world's leading HPV vaccine'. The Panel noted Sanofi Pasteur MSD's submission that the letter was not promotional and was part of an ongoing legitimate scientific dialogue with selected clinicians. In the Panel's view, however, each clinician would have a slightly different relationship with the company and so an identical letter to all of them could not be seen as part of that relationship. Further, the letter was purely product related and did not put any of that information into context with regard to the relationship between the recipient and the company. The Panel considered that the inclusion of product claims made the letter promotional and in that regard it could not benefit from the exemption to promotion given to factual, accurate, informative announcements in Clause 1.2 of the Code. It was not relevant whether Gardasil could or could not be used outside the national immunisation programme. The Panel considered that the letter should have included prescribing information and a statement about adverse event reporting; as both were absent breaches of Clauses 4.1 and 4.10 were ruled respectively.

The claim 'In addition Gardasil has recently received a positive opinion for protection against pre-malignant lesions of the vagina as a licence extension' in a press release had been considered in Case AUTH/2147/7/08 and ruled to be misleading in breach of the Code by the Panel. The material now at issue was promotional material aimed at health professionals. The Panel considered that by referring to the positive CHMP opinion and licence extension the letter promoted Gardasil for an as yet unauthorized indication. This was inconsistent with the marketing authorization and thus a breach of Clause 3.2 was ruled.

The Panel noted that GlaxoSmithKline alleged that as part of a concerted campaign to undermine confidence in the DoH decision to use Cervarix as the vaccine of choice the letter failed to maintain high standards. The Panel noted that the letter had been sent to a limited audience all of whom had had some specific interaction with Sanofi Pasteur MSD and interest in the UK HPV vaccination programme. Nonetheless, the Panel considered that Sanofi Pasteur MSD's failure to regard the letter as promotional material demonstrated a poor knowledge of the requirements of the Code. High standards had not been maintained. A breach of Clause 9.1 was ruled.

Complaint received **6 August 2008**

Case completed **13 October 2008**

CASE AUTH/2157/8/08

PRACTICE PHARMACIST v SANOFI-AVENTIS

Acomplia leavepiece

A practice pharmacist complained about a four page leavepiece 'Nice news for Norman' promoting Acomplia (rimonabant) left by a Sanofi-Aventis representative.

The complainant alleged that the front and back covers of the leavepiece implied that Acomplia was the treatment recommended by the National Institute for Health and Clinical Excellence (NICE) for overweight type 2 diabetics. Inside, the leavepiece stated its use for those unable to take orlistat or sibutramine but not on the outside. However NICE only recommended it for patients intolerant to, or who had inadequately responded to, orlistat or sibutramine ie third line.

The leavepiece also stated NICE 'recommends patients should continue beyond 2 years only after clinical review' whereas NICE guidance stated 'rimonabant should not be continued for longer than 2 years without a formal clinical assessment and discussion of the individual risks and benefits with the person receiving the treatment'. The leavepiece implied its virtues as an antidiabetic medicine in that it would reduce HbA1c.

The complainant alleged that the leavepiece was misleading as the bottom line appeared to be that Acomplia was first line for overweight type 2 diabetics as well as being antidiabetic.

The detailed response from Sanofi-Aventis is given below.

The Panel noted that the front and back pages stated 'NICE approves Acomplia for overweight patients (BMI>27kg/m²) with type 2 diabetes. The NICE guidance stated '[Acomplia], within its licensed indications, is recommended as an adjunct to diet and exercise for adults who are obese [BMI>30kg/m²] or overweight [BMI>27kg/m²] and who have had an inadequate response to, are intolerant of or are contraindicated to orlistat and sibutramine'. The Panel thus considered that the claim summarising the NICE guidance was misleading; it implied that NICE had approved the use of Acomplia in any type 2 diabetic who had a BMI of more than 27kg/m² which was not so. A breach of the Code was ruled.

The Panel noted that after accurately reflecting NICE guidance regarding Acomplia treatment at 6 months page 2 of the leavepiece stated 'NICE recommends that patients should continue beyond 2 years only after clinical review'. The NICE guidance stated '[Acomplia] treatment should not be continued for longer than 2 years without a formal clinical assessment and discussion of the individual risks and benefits with the person receiving treatment'. In the Panel's view, the subtle change of wording changed the meaning and emphasis of the original guidance. The Panel considered that this was not an accurate reflection of the NICE guidance. A breach of the Code was ruled.

The Panel noted that Acomplia was indicated 'As an adjunct to diet and exercise for the treatment of obese patients (BMI≥ 30kg/m²), or overweight patients (BMI≥ 27kg/m²) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia'. Section 5.1 of the summary of product characteristics (SPC) referred to Acomplia's beneficial effects in lowering HbA1c stating that it was estimated that approximately half of the mean improvement in HbA1c was beyond that expected from weight loss alone.

The Panel considered that it was not necessarily unacceptable to promote the benefits of treatment as long as these were clearly expressed within the context of the product's licensed indication. The Panel noted that claims for Acomplia and its effect on HbA1c appeared on page 3 of the leavepiece beneath the heading 'Weight loss, with glycaemic control'. In that regard the Panel considered that equal emphasis had been given to weight loss, the licensed indication, and glycaemic control, the benefit of therapy. The Panel considered that glycaemic control had not been placed sufficiently within the context of weight loss and thus the leavepiece was misleading in that regard. A breach of the Code was ruled.

A practice pharmacist complained about a four page leavepiece 'Nice news for Norman' promoting Acomplia (rimonabant) left by a representative of Sanofi-Aventis.

COMPLAINT

The complainant alleged that both the front and back cover of the leavepiece implied that Acomplia was the treatment recommended by the National Institute for Health and Clinical Excellence (NICE) for overweight type 2 diabetics. Inside, the leavepiece stated its use for those unable to take orlistat or sibutramine but not on the outside. However NICE only recommended it as a treatment for those intolerant to, or who had had an inadequate response to orlistat or sibutramine ie third line.

The complainant alleged that the leavepiece also stated NICE 'recommends patients should continue beyond 2 years only after clinical review'. NICE

guidance stated 'rimonabant should not be continued for longer than 2 years without a formal clinical assessment and discussion of the individual risks and benefits with the person receiving the treatment'. The leavepiece implied its virtues as an antidiabetic medicine in that it would reduce HbA1c.

The complainant alleged that the leavepiece was misleading as the bottom line appeared to be that Acomplia was first line for overweight type 2 diabetics as well as being antidiabetic.

When writing to Sanofi-Aventis, the Authority asked it to respond in relation to Clause 7.2 of the Code. This was the same in the 2006 Code as in the 2008 Code. The case was considered under the 2008 Constitution and Procedure.

RESPONSE

Sanofi-Aventis stated that the leavepiece was designed to inform health professionals of important information following the approval of Acomplia by NICE on 25 June 2008.

Sanofi-Aventis believed that the claim on the front and back covers and the claims within the leavepiece were an accurate introductory summary of the NICE guidance for Acomplia and consistent with the Acomplia summary of product characteristic (SPC). Further clarification regarding the guidance and the reference for the full guidance were then contained within the leavepiece.

NICE guidance for Acomplia stated: 'Rimonabant, within its licensed indications, is recommended as an adjunct to diet and exercise for adults who are obese or overweight and who have had an inadequate response to, are intolerant of or are contraindicated to orlistat and sibutramine'.

The licensed indication for Acomplia was: 'As an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30kg/m²), or overweight patients (BMI ≥ 27kg/m²) with associated risk factor(s) such as type 2 diabetes or dyslipidaemia (see Section 5.1)'. It was clear from this that NICE guidance therefore recommended the use of Acomplia in overweight (BMI ≥ 27) patients with type 2 diabetes, as it recommended the use of Acomplia within its licensed indications and the group of overweight (BMI ≥ 27) type 2 diabetics were within that licence, as above. Whilst the claim on the leavepiece did not describe every patient type covered by the licence that NICE had approved the use of Acomplia for, there was no requirement within Clause 7.2 for the entirety of a licensed indication to be promoted. Sanofi-Aventis believed that the claim on the leavepiece therefore complied with this clause.

The complainant also noted correctly that the leavepiece stated that Acomplia was approved by NICE only to be used in patients who were 'unable to take orlistat and sibutramine'. Again, NICE guidance stated: 'Rimonabant, within its licensed indications, is recommended as an adjunct to diet and exercise for adults who are obese or overweight and who have had an inadequate response to, are intolerant of or are contraindicated to orlistat and sibutramine'. This sentence clearly described that Acomplia should only be used when the patient could not take the other two weight loss products because of lack of efficacy, poor tolerability or a contraindication.

Sanofi-Aventis believed therefore that the claim in the leavepiece accurately reflected NICE guidance and clearly described what NICE had stated, that Acomplia should only be used when the other two products could not be taken by the patient.

Sanofi-Aventis believed that the phrase on the leavepiece that 'patients should continue beyond 2 years only after clinical review' adequately reflected NICE guidance, in that it would be unreasonable and outside the terms of good medical practice for a clinician to carry out a 'clinical review' of a chronic therapy that did not include a discussion of the risks and benefits with the patient, as recommended by NICE in its guidance. The leavepiece also clearly invited the reader to review the full guidance on the NICE website under this statement.

The final assertion in the complaint was that the leavepiece implied the virtues of Acomplia as an antidiabetic drug in that it would reduce HbA1c. The emphasis of the leavepiece however was on the overweight patient (BMI ≥ 27) and the phrases 'weight loss' and 'significantly reduce weight' were used first, ahead of any additional mention of beneficial change in HbA1c. The leavepiece did not describe Acomplia as an antidiabetic medicine.

It was however justifiable and not misleading to describe the additional beneficial effects of Acomplia on HbA1c as well as on weight loss. Acomplia had been shown to reduce weight and in addition HbA1c and improvements in HbA1c were also recognised in the SPC. The licence statement (see above) further recognised the beneficial changes in HbA1c in addition to weight loss, as it referred the reader to Section 5.1 of the SPC, which described this effect:

> 'In the trial in type 2 diabetic patients (RIO-diabetes) who were overweight or obese treated with metformin or sulfonylurea improvements in HbA1c and body weight were observed. The absolute change in HbA1c at one year was -0.6 for rimonabant 20mg (baseline 7.3%) and +0.1 on placebo (baseline 7.2%). Differences were statistically significant (Difference – 0.7%, CI95%; -0.5, p<0.001).'

Overall within the leavepiece, however, the beneficial improvements in HbA1c were presented only as an addition to the main beneficial changes of weight loss. This fact was particularly emphasised by the phrase 'Acomplia is proven to significantly reduce weight and, in addition, HbA1c

levels compared with placebo', which was consistent with the licensed indication and SPC.

Sanofi-Aventis did not consider that the leavepiece promoted Acomplia as first line, or as an antidiabetic medicine, and was not misleading as alleged and therefore not in breach of Clause 7.2.

PANEL RULING

The Panel noted that the front page of the four page leavepiece featured the claim 'NICE approves Acomplia for overweight patients (BMI>27kg/m²) with type 2 diabetes. This claim was repeated on the back page. In full, however, point 1.1 of the NICE guidance stated '[Acomplia], within its licensed indications, is recommended as an adjunct to diet and exercise for adults who are obese [BMI>30kg/m²] or overweight [BMI>27kg/m²] and who have had an inadequate response to, are intolerant of or are contraindicated to orlistat and sibutramine'. The Panel thus considered that the claim summarising the NICE guidance, printed on the front and back of the leavepiece, was misleading; it implied that NICE had approved the use of Acomplia in any type 2 diabetic who had a BMI of more than 27kg/m² which was not so. The claim was misleading in that regard and a breach of Clause 7.2 was ruled.

The Panel noted that the leavepiece, after accurately reflecting NICE guidance regarding Acomplia treatment at 6 months stated 'NICE recommends that patients should continue beyond 2 years only after clinical review'. Point 1.4 of the NICE guidance stated '[Acomplia] treatment should not be continued for longer than 2 years without a formal clinical assessment and discussion of the individual risks and benefits with the person receiving treatment'. In the Panel's view, the subtle change of wording was enough to change the meaning and emphasis of the original guidance – NICE had stated '[Acomplia] treatment should not be continued …' whereas the leavepiece stated 'NICE recommends that patients should continue …'. The Panel considered that when reporting the guidance of third parties, pharmaceutical companies must avoid any change of emphasis. The Panel considered that the claim in the leavepiece was not an accurate reflection of the NICE guidance. A breach of Clause 7.2 was ruled. During its consideration of this matter the Panel noted that the Acomplia SPC stated 'The safety and efficacy of rimonabant have not been evaluated beyond 2 years'.

The Panel noted that Acomplia was indicated 'As an adjunct to diet and exercise for the treatment of obese patients (BMI≥ 30kg/m²), or overweight patients (BMI≥ 27kg/m²) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia'. Section 5.1 of the SPC (Pharmacodynamic properties) referred to Acomplia's beneficial effects in lowering HbA1c. It was stated that it was estimated that approximately half of the mean improvement in HbA1c in patients receiving Acomplia 20mg was beyond that expected from weight loss alone.

The Panel considered that it was not necessarily unacceptable to promote the benefits of treatment as long as such benefits were clearly expressed within the context of the product's licensed indication. The Panel noted that claims for Acomplia and its effect on HbA1c appeared on page 3 of the leavepiece beneath the heading 'Weight loss, with glycaemic control'. In that regard the Panel considered that equal emphasis had been given to weight loss, the licensed indication, and glycaemic control, the benefit of therapy. The Panel considered that glycaemic control had not been placed sufficiently within the context of weight loss and thus the leavepiece was misleading in that regard. A breach of Clause 7.2 was ruled.

Complaint received **6 August 2008**

Case completed **22 September 2008**

ANONYMOUS v BRISTOL-MYERS SQUIBB and OTSUKA

Alleged inappropriate hospitality

Anonymous complainants alleged that Bristol-Myers Squibb had provided inappropriate hospitality at a meeting for psychiatrists; delegates had enjoyed the food, hotels and cultural programme. It was alleged that the meeting did not have a scientific committee, abstracts were not invited or selected as was recognised at scientific conferences. The complainants questioned whether there was a special relationship between these doctors and Bristol-Myers Squibb.

The complaint was originally only taken up with Bristol-Myers Squibb but the company submitted a joint response with Otsuka as the meeting in question had been sponsored by both companies.

The detailed response from Bristol-Myers Squibb and Otsuka is given below.

The Panel noted that the two day meeting started mid-morning on a Friday and, with a break for lunch, and one in the afternoon for tea, the scientific programme continued until early evening. Saturday's scientific programme started at 9.30am and, again with breaks for meals and refreshments, continued until 4.30pm. The programme stated that the presentations given by two international speakers had been sponsored by Bristol-Myers Squibb and Otsuka. The programme further stated that the hotel accommodation and hospitality for the meeting had been paid for by the companies.

The Panel considered that according to the programme, the scientific/educational content was not unreasonable for sponsorship by a pharmaceutical company. There was no cultural programme as alleged by the complainants. The prime purpose of the meeting was scientific/educational. The costs involved had not exceeded those which the delegates might normally adopt when paying for themselves. No breach of the Code was ruled.

Anonymous and uncontactable complainants complained about a meeting for psychiatrists sponsored by Bristol-Myers Squibb Pharmaceuticals Limited. The complaint was originally only taken up with Bristol-Myers Squibb but the company submitted a joint response with Otsuka Pharmaceuticals (UK) Limited as the meeting in question had been sponsored by both companies.

COMPLAINT

The complainants noted that Bristol-Myers Squibb marketed aripiprazole and stated that it was not very well prescribed compared with other antipsychotics. It appeared that in order to improve the market share Bristol-Myers Squibb sponsored a two day meeting for about 150 psychiatrists the majority of whom enjoyed hospitality at the hotel in Birmingham. The meeting was organised by 'West Midland Psychiatric Research Group'. It needed to be investigated as to whether this meeting/conference of Asian psychiatrists was approved by the ABPI or not. The speakers' lectures were not approved by the ABPI. Bristol-Myers Squibb had invested a huge amount of money in this meeting. Delegates enjoyed the food, hotels and cultural programme. The meeting did not have a scientific committee, abstracts were not invited or selected as was recognised in scientific conferences. This was strong evidence to suggest this company had breached the Code with regard to hospitality provided to doctors and a huge amount of money was paid to the organisers. The complainants requested full thorough investigations.

- How much did Bristol-Myers Squibb pay the organiser of the meeting? There should be bank to bank record. Had the company also paid cash?
- Why did only Bristol-Myers Squibb sponsor and not others?
- Was there a special relationship between this group of doctors and Bristol-Myers Squibb?

When writing to Bristol-Myers Squibb, the Authority asked it to respond in relation to Clauses 2, 9.1 and 19.1 of the 2006 Code.

RESPONSE

Bristol-Myers Squibb and Otsuka submitted that the allegations were untrue. Both had taken all necessary steps to ensure that they had adhered to the Code and internal (Standard operating procedures (SOPs). From their review they did not believe that they had breached the Code, specifically in relation to Clauses 2, 9.1 and 19.1.

The companies agreed with the Midlands Psychiatric Research Group to be sole sponsors (at its request) of its two day International Seminar on Psychiatry. The sponsorship included provision of two international speakers for the meeting (honoraria, travel and accommodation) – recruited and managed by the companies. Speaker agreements (provided) were signed by these two speakers and they received the same hospitality and stayed at the same hotel as all other delegates.

A further £5,500 was given to the Midlands Psychiatric Research Group to cover the travel cost for four other international speakers (£3,000) and travel cost for three international chairpersons (£1,500) – these individuals were all recruited and managed directly by the

Midlands Psychiatric Research Group. The cost for all other speakers and chairpersons was paid for by the Midlands Psychiatric Research Group. The remaining £1,000 was provided for administration costs (secretariat service, postage, printing, registration, local logistics and follow up). Meeting room and equipment hire, meals, beverages and overnight accommodation (one night for delegates, three for international speakers) as required were provided at a cost of £37,883.50.

The meeting had 10 hours 30 minutes of scientific content; 4 hours 30 minutes on the Friday and 6 hours on the Saturday. This meeting was only open to health professionals and the invitation and registration of delegates was managed independently by the Midlands Psychiatric Research Group. Delegates were predominantly from the Midlands but some also came from other parts of the UK. Delegates were invited to attend both days of the meeting. There were 175 health professional attendees including the various speakers and chairpersons.

Sponsorship of the meeting was clearly declared on the front of the approved draft invitation by Bristol-Myers Squibb and Otsuka. An additional declaration of sponsorship for the Bristol-Myers Squibb/Otsuka presentations was added to that particular section of the programme.

A draft invitation and agenda were created by the chairperson in collaboration with the companies for planning purposes only. The final approved version was provided. A copy of the registration form and attached programme that was sent out to delegates was provided. The scientific programme was of a very high quality and included a number of eminent speakers and chairmen.

The hospitality was provided at a level appropriate for such a scientific meeting. No partners were invited and although the venue was selected by the Midlands Psychiatric Research Group it was not deemed to be unsuitable by the companies (a four star hotel with excellent conference facilities near Birmingham airport).

The meals and beverages provided for delegates on the Friday evening after the academic session were modest in terms of costs and quantity. The overall cost per head for the two day meeting was £202.50 – this excluded equipment hire. The total hotel cost (including all equipment hire) was £37,883.50. Lunch and coffee breaks were provided on the Saturday as part of a day delegate rate (£55 per person). The overnight rate (£120 per person) included breakfast, lunch, dinner and all coffee breaks as well as the overnight stay.

As this was planned as a two day meeting and since many delegates came from across the Midlands and other parts of the UK, optional accommodation was provided. For unknown reasons thirteen rooms that were booked and paid for were not used by the clinicians. Of the 175 delegates, 148 stayed over on the Friday night. On the Thursday night 19 of the international speakers and chairpersons (coming from as far afield as Australia, Canada, USA, Malaysia and Pakistan) stayed overnight (at £99 per person) and on the Saturday night 18 of this group stayed overnight. No entertainment was provided at any time during the meeting and the total beverage bill was £958.50 on the Friday evening which if divided by the attendees at the meal (148) approximated to an average of £6.48 per person.

In summary, Bristol-Myers Squibb and Otsuka believed they complied fully with the Code and that the allegations were unfounded. They therefore did not believe they had breached Clauses 2, 9.1 or 19.1.

PANEL RULING

The Panel noted that the two day meeting started on a Friday at 10.15am; with a break for lunch, and one in the afternoon for tea, the scientific programme continued until 7pm. Saturday's programme started at 9.30am and, again with breaks for meals and refreshments, the scientific sessions continued until 4.30pm. The programme stated that the presentations given by two international speakers had been sponsored by Bristol-Myers Squibb and Otsuka Pharmaceuticals. The programme further stated that the hotel accommodation and hospitality for the meeting had been paid by the companies.

The Panel considered that according to the programme, the scientific/educational content was not unreasonable for sponsorship by a pharmaceutical company. There was no cultural programme as alleged by the complainants. The prime purpose of the meeting was scientific/educational.

As noted on the programme, Bristol-Myers Squibb and Otsuka had sponsored presentations by two international speakers. The companies had submitted that such sponsorship had included honoraria, travel and accommodation. The two speakers had been recruited by the companies. The companies had also covered the travel costs of four other international speakers and three chairpersons chosen by the Midlands Psychiatric Research Group.

The total hotel cost for the 175 attendees, speakers and chairman was £37,883.50 which gave a cost per head of £216.48. The beverage bill on the Friday night was £958.50 which, divided by the number of people at the meal (148) was approximately £6.48 per head.

The Panel did not consider Bristol-Myers Squibb's and Otsuka's sponsorship of the meeting was unreasonable. The main purpose of the meeting was scientific/educational and the costs involved had not exceeded those which the delegates might normally adopt when paying for themselves. No breach of Clauses 2, 9.1 and 19.1 was ruled.

Complaint received **8 August 2008**

Case completed **9 September 2008**

WYETH v ROCHE and CHUGAI

Press statements regarding Actemra

Wyeth complained about Roche and its media activities regarding its unlicensed medicine Actemra (tocilizumab). Actemra was being developed jointly by Roche and Chugai Pharma Europe for the treatment of rheumatoid arthritis (RA). Wyeth's product Enbrel (etanercept) was indicated for the treatment of moderate to severe active rheumatoid arthritis in adults in certain circumstances.

Inter-company dialogue had been unsuccessful and while Wyeth understood that Roche had made a voluntary admission to the Authority about a media release (Cases AUTH/2154/8/08 and AUTH/2155/8/08) it had no option but to submit a formal complaint.

The claims 'New Data Reveals Tocilizumab Is The First And Only Biologic Drug To Show Superiority Over Current Standard Of Care In Rheumatoid Arthritis' and 'No previous biologic therapy has demonstrated superiority compared to [methotrexate] MTX' appeared in a Roche media statement dated 13 June. Wyeth alleged that these claims were inaccurate, misleading and did not reflect up-to-date evidence. The press release referred to tocilizumab being the only biologic agent to show superiority to methotrexate (MTX). This was incorrect as there was a wealth of evidence supporting the superiority over MTX of other biologic agents with existing marketing authorizations (Bathon *et al*, 2000).

The detailed response of Roche and Chugai is given below.

The Panel considered that its rulings in Cases AUTH/2154/8/08 and AUTH/2155/8/08 were relevant. In Cases AUTH/2154/8/08 and AUTH/2155/8/08 the Panel considered that the heading to the media release, 'New data reveals tocilizumab is the first and only biologic drug to show superiority over current standard of care in rheumatoid arthritis' was a strong unqualified claim. The first paragraph of the media release explained that the current standard of care was methotrexate. The Panel noted the companies' submission that other biologic therapies had shown superiority but unlike tocilizumab not across all American College of Rheumatology (ACR) measures. Superiority had not been uniformly shown in this regard at 6 months and it was this point that was intended to be conveyed in the press release. The Panel was concerned about the general claims for superiority. The media release also contained the claim 'No previous biologic therapy has demonstrated superiority compared to MTX' which was not so. The Panel noted that the media release had been sent to UK national and medical media. The product was not authorized in the UK and the media release was extremely positive; it used 'novel', innovative' and 'most exciting' to describe the product. The Panel considered that the media release was not factual and that the results of the AMBITION study had not been presented in a balanced way. The media release would raise unfounded hopes of successful treatment. Thus the Panel ruled a breach of the Code.

The Panel considered that given its comments above high standards had not been maintained. A breach of the Code was ruled. Although noting its rulings, the Panel did not consider that the media release warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Turning to Cases AUTH/2160/8/08 and AUTH/2161/8/08 the Panel noted that the alleged breaches of the Code in these cases differed from Cases AUTH/2154/8/08 and AUTH/2155/8/08 albeit that the allegations were similar ie that the claims were misleading. The Panel considered that the claims were misleading and could not be substantiated. Breaches of the Code were ruled.

The claim 'What made this result even more impressive was the fact that 12-18% of the study population had failed to respond to one or more prior anti-TNF [tumour necrosis factor] therapies, leaving them with little hope of further symptom relief from these traditional treatments' also appeared in a Roche media statement dated 13 June.

Wyeth alleged that the claim employed emotive, inappropriate language ('impressive') and did not objectively represent the findings. There was a wealth of evidence showing that patients benefited from sequential use of biological therapies. To claim that patients who had failed anti-TNF therapy would be left with little hope of further symptom relief from these traditional treatments was misleading in breach of the Code. Referring to anti-TNF agents as traditional treatment was inappropriate. The medical literature referred to classic disease modifying antirheumatic drugs (DMARDs) such as MTX as traditional, whilst anti-TNF agents were considered to be a relatively new class of medicines. In Wyeth's view, this reference therefore aimed to convey an advantage of tocilizumab over anti-TNF agents. This was factually wrong, unsubstantiated and disparaging.

The Panel noted the respondents' submission that

the statement relating to 'little hope of further symptom relief' was true if patients had failed on three anti-TNFs. To state that the same was true when patients had failed to respond to one or more prior anti-TNF therapies was thus misleading, unsubstantiable and exaggerated. Breaches of the Code were ruled. The Panel further considered that the statement disparaged anti-TNF therapies. A breach of the Code was ruled.

The claim 'Tocilizumab (to be called Actemra) is the first humanised interleukin-6 (IL-6) receptor inhibiting monoclonal antibody and represents a novel mechanism of action to treat RA, a disease with a high unmet medical need. This treatment is not yet licensed in Europe and is the result of research collaboration by Roche and Chugai, it is being co-developed globally' appeared on the Roche UK Website.

Wyeth noted that 'reference information' could be provided on a company website as an up-to-date resource for the public. However, reference information must relate to prescription only medicines which had a marketing authorization. As tocilizumab was not licensed, this was a breach of the Code. As there had been a clear advertisement to the public by Roche, this had also breached the Code.

Wyeth alleged that high standards had not been maintained. This was especially important as tocilizumab did not have a UK marketing authorization.

The Panel considered that a press release was different to reference information. The Panel did not consider it was necessarily unacceptable for a press release to refer to an unlicensed medicine, it would depend what was said. The Panel noted that the press release was on the Roche UK website in an area clearly marked for the media; it was not in a section which provided reference information for the public. The Panel did not consider that the press release promoted an unlicensed medicine and thus no breach of the Code was ruled. The Panel did not consider that the press release advertised tocilizumab to the public. No breach of the Code was ruled.

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

Wyeth noted that a number of press articles in the Daily Mail, 16 June 2008, which resulted from a Roche press release, had shared the same style of promotional claims mentioned above, had been released following the European League Against Rheumatism (EULAR) meeting. Wyeth had tried unsucessfully to obtain the necessary press releases from Roche. Wyeth found this unacceptable.

With regard to the claim 'Tocilizumab is the first treatment to outperform the standard therapy methotrexate, when used in isolation', Wyeth alleged that etanercept monotherapy had shown superior efficacy in relation to MTX in clinical trials, and the summary of product characteristics (SPC) reflected this. Wyeth alleged that the claim was factually incorrect, did not reflect the up-to-date evaluation of all current evidence, could not be substantiated and raised unfounded hopes of successful treatment.

The Panel considered that its consideration of this point was covered by its rulings above. Breaches of the Code were ruled.

Wyeth alleged that a price had not been established for tocilizumab, and therefore the claim '… expensive anti-TNF drugs' was misleading as it implied that tocilizumab had a price advantage. This raised unfounded hopes of successful treatment.

The Panel noted that the press release of 13 June 2008 had not referred to the cost of anti-TNF therapies thus no breach was ruled.

With regard to the claim '[Anti-TNFs] can be effective for a while, but eventually patients build up resistance to them' Wyeth alleged that etanercept had not been shown to induce neutralising antibodies in humans, and there was a wealth of evidence to suggest that patients did not develop resistance against Enbrel therapy. The claim was factually incorrect, disparaging and raised unfounded hopes of successful treatment.

The Panel noted that the press release of 13 June 2008 had not referred to the development of resistance to anti-TNF therapies thus no breach of the Code was ruled.

Wyeth alleged that taking into account the above breaches of the Code, Roche had brought discredit upon and reduced confidence in the industry, in breach of Clause 2.

Although noting its rulings above, the Panel did not consider that these cases warranted a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such.

With regard to Wyeth's request that a corrective statement be issued, the Panel noted that it could not require a corrective statement to be published. That sanction was available to the Appeal Board.

Wyeth Pharmaceuticals complained about Roche Products Ltd and its media activities regarding its unlicensed medicine Actemra (tocilizumab). Actemra was being developed jointly by Roche and Chugai Pharma Europe Ltd for the treatment of rheumatoid arthritis. Wyeth's product Enbrel (etanercept) was indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adults in certain circumstances.

Inter-company dialogue had been unsuccessful and

while Wyeth understood that Roche had made a voluntary admission to the Authority about a media release (Cases AUTH/2154/8/08 and AUTH/2155/8/08) it nonetheless considered that its complaint to Roche had not been resolved and so it had no option but to submit a formal complaint.

This case was considered under the 2006 Code using the 2008 Constitution and Procedure.

COMPLAINT

A Medical News Today

The claims at issue in points 1 and 2 below appeared in a Roche media statement dated 13 June.

1 Claims 'New Data Reveals Tocilizumab Is The First And Only Biologic Drug To Show Superiority Over Current Standard Of Care In Rheumatoid Arthritis' and 'No previous biologic therapy has demonstrated superiority compared to MTX'

COMPLAINT

Wyeth alleged that these claims were in breach of Clauses 7.2, 7.3 and 7.4 as they were inaccurate, misleading and did not reflect up-to-date evidence. The press release referred to tocilizumab being the only biologic agent to show superiority to methotrexate (MTX). This was incorrect as there was a wealth of evidence supporting the superiority over MTX of other biologic agents with existing marketing authorizations (Bathon *et al*, 2000).

RESPONSE

Roche and Chugai provided a joint response and submitted that tocilizumab was the first anti-interleukin 6 (IL-6) receptor monoclonal antibody to be developed for the management of rheumatoid arthritis. It was the first product to be born from the Chugai and Roche development collaboration. The results from the tocilizumab development programme were not only of significance and relevance medically but also from a financial services perspective. The media release was therefore deemed newsworthy.

The media statement covered the release of two data sets presented at the European League Against Rheumatism (EULAR) meeting in Paris. The main body of the release covered the presentation of data from the AMBITION study (Tocilizum**a**b versus **M**ethotrexate Double-**B**lind **I**nvestigative **T**rial **I**n M**on**otherapy) (Jones *et al* 2008) and also referred to the RADIATE study (**R**esearch on Tocilizum**a**b **D**etermining eff**i**cacy after **A**nti-**T**NF failur**e**s) (Emery *et al* 2007).

Both studies represented an important development in the management of rheumatoid arthritis. AMBITION was the first study to categorically demonstrate superiority over MTX when using the regulatory required American College of Rheumatology (ACR) scoring system of 20, 50 and 70% improvement from baseline at 6 months. No other biologic therapy had shown this. Etanercept had shown superiority at different time points with different measuring techniques (eg X ray) (Bathon *et al*, Genovese *et al* 2002) but this media release referred to signs and symptoms across the ACR 20, 50 and 70 core set at 6 months, not partial response eg ACR 70 only at 6 months. The companies fully accepted, and had never suggested otherwise, that etanercept had shown superiority when using X ray changes (not signs and symptoms) at 2 years (Genovese *et al*).

Roche and Chugai accepted that when the media release was reviewed, if the headline statements were read independently, it would not fully explain the context in which the claims were made; this was why the companies referred the matter to the Authority (Cases AUTH/2154/8/08 and AUTH/2155/8/08). Wyeth had stated that unless Roche and Chugai issued a corrective statement Wyeth would refer the matter to the Authority. In order to guarantee such a statement to be published, the companies would have had to pay for advertising space. As tocilizumab was not licensed such an advertisement would have been in breach of the Code. Roche and Chugai therefore decided that a corrective statement would not be possible under the Code and thus referred the matter to the Authority. The companies were disappointed that Wyeth had referred this matter as the two claims, 'New data reveals Tocilizumab is the first and only biologic drug to show superiority over current standard of care in RA' and 'No previous biologic therapy has demonstrated superiority compared to MTX' were being dealt with under Cases AUTH/2154/8/08 and AUTH/2155/8/08.

PANEL RULING

The Panel considered that its rulings in Cases AUTH/2154/8/08 and AUTH/2155/8/08 were relevant.

Cases AUTH/2154/8/08 and AUTH/2155/8/08

The Panel considered that the heading to the media release, 'New data reveals tocilizumab is the first and only biologic drug to show superiority over current standard of care in rheumatoid arthritis' was a strong unqualified claim. The first paragraph of the media release explained that the current standard of care was methotrexate. The Panel noted the companies' submission that other biologic therapies had shown superiority but unlike tocilizumab not across all ACR measures. Superiority had not been uniformly shown in this regard at 6 months and it was this point that was intended to be conveyed in the press release. The Panel was concerned about the general claims for superiority. The media release also contained the

claim 'No previous biologic therapy has demonstrated superiority compared to MTX' which was not so. The Panel noted that the media release had been sent to UK national and medical media. The product was not authorized in the UK and the media release was extremely positive; it used 'novel', innovative' and 'most exciting' to describe the product. The Panel considered that the media release was not factual and that the results of the AMBITION study had not been presented in a balanced way. The media release would raise unfounded hopes of successful treatment. Thus the Panel ruled a breach of Clause 20.2 of the 2006 Code.

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

Although noting its rulings above, the Panel did not consider that the media release warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Cases AUTH/2160/8/08 and AUTH/2161/8/08

The Panel noted that the alleged breaches of the Code in these cases differed from Cases AUTH/2154/8/08 and AUTH/2155/8/08 albeit that the allegations were similar ie that the claims were misleading. The Panel considered that the claims were misleading and could not be substantiated. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

2 Claim 'What made this result even more impressive was the fact that 12-18% of the study population had failed to respond to one or more prior anti-TNF therapies, leaving them with little hope of further symptom relief from these traditional treatments'

COMPLAINT

Wyeth alleged that the claim employed emotive, inappropriate language ('impressive') and did not objectively represent the findings in breach of Clause 7.10. There was a wealth of evidence showing that patients benefited from sequential use of biological therapies. To claim that patients who had failed anti-tumour necrosis factor (anti-TNF) therapy would be left with little hope of further symptom relief from these traditional treatments was misleading in breach of Clause 7.3. Referring to anti-TNF agents as traditional treatment was inappropriate. The medical literature referred to classic disease modifying antirheumatic drugs (DMARDs) such as MTX as traditional, whilst anti-TNF agents were considered to be a relatively new class of medicines. In Wyeth's view, this reference therefore aimed to convey an advantage of tocilizumab over anti-TNF agents. This was factually wrong, unsubstantiated and disparaging in breach of Clauses 7.2, 7.4 and 8.1.

RESPONSE

Roche and Chugai noted that the claim related to the RADIATE study. Traditionally patients with rheumatoid arthritis were initially managed with DMARDs and then by the addition of anti-TNF therapy. Anti-TNFs had been available in the UK for the last 9 years and were widely accepted as standard therapy; they had been recommended by the National Institute for Health and Clinical Excellence (NICE) as an option for the treatment of moderate to severe rheumatoid arthritis following the failure to response to a least two DMARDs. To suggest that anti-TNFs were not part of standard, traditional therapy did not reflect the long standing and wide ranging use of these therapies.

Unfortunately around a third of patients would either fail to respond, lose response or not tolerate anti-TNFs (Hyrich *et al* 2007). These patients were difficult to manage. Roche's product MabThera (rituximab) was indicated in combination with MTX for adults with severe active rheumatoid arthritis who had an inadequate response or intolerance to other DMARDs including one or more TNF inhibitor therapies. NICE recommended rituximab as an option for the management of anti-TNF inadequate responders, however, again, not all patients would respond, nor was it suitable for all patients. There was, therefore, a large unmet need.

Data from the sequential use of anti-TNFs was consistent, largely observational in nature with a population with varying baseline characteristics (van Vollenhoven 2007). Currently NICE had issued a final appraisal determination (FAD) stating that, in its opinion the sequential use of anti-TNFs would not be recommended. This was currently being appealed.

The statement relating to 'little hope of further symptom relief' was factually correct when patients had failed three anti-TNFs. In the event that patients had failed three anti-TNFs there was little hope of any symptom relief from restarting patients on these therapies. Roche and Chugai, however accepted that by not specifying three anti-TNFs within the release and instead using the term one or more anti-TNFs this might not have been as clear as it could have been.

PANEL RULING

The Panel noted the respondents' submission that the statement relating to 'little hope of further symptom relief' was true if patients had failed on three anti-TNFs. To state that the same was true when patients had failed to respond to one or more prior anti-TNF therapies was thus misleading, unsubstantiable and exaggerated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled. The Panel further considered that the statement disparaged anti-TNF therapies. A breach of Clause 8.1 was ruled.

B Roche UK Website

1 'Tocilizumab (to be called Actemra) is the first humanised interleukin-6 (IL-6) receptor inhibiting monoclonal antibody and represents a novel mechanism of action to treat RA, a disease with a high unmet medical need. This treatment is not yet licensed in Europe and is the result of research collaboration by Roche and Chugai, it is being co-developed globally'

COMPLAINT

Wyeth noted that the Code allowed 'reference information' to be provided on a company website as an up-to-date resource for the public on that company's prescription only medicines (supplementary information to Clause 20.2). However, reference information must relate to prescription only medicines which had a marketing authorization. As tocilizumab was not licensed, this was a breach of Clause 3.1. As there had been a clear advertisement to the public by Roche, this had also breached Clause 20.1.

Wyeth alleged that high standards had not been maintained. This was especially important as tocilizumab did not have a UK marketing authorization. In view of this Clause 9.1 had also been breached.

RESPONSE

The companies noted that this statement was in the editor's notes at the end of a press release (dated 22 August 2007) that was about Roche's other rheumatoid arthritis treatment rituximab and was clearly placed within the press area of the Roche UK website. This area of Roche's corporate website was clearly labelled 'media'. To source the press statement, 'tocilizumab' had to be entered into the website search engine. Its visibility on the website was therefore extremely limited and reasonable care was taken to ensure that information was only accessed by the audience for which was intended.

PANEL RULING

The Panel noted that although Roche and Chugai had both responded to this point, the press release was only available on the Roche website. Its rulings would only apply to Roche.

The Panel noted that the supplementary information to Clause 20.2, Information to the Public, stated that the primary purpose of reference information was to be a library resource for the public giving information about prescription only medicines with marketing authorizations. Examples given in the supplementary information included summaries of product characteristics, the package information leaflet etc. The Panel considered that a press release was different to reference information. The Panel did not consider it was necessarily unacceptable for a press release to refer to an unlicensed medicine it would depend what was said. The Panel noted that the press release was on the Roche UK website in an area clearly marked for the media; it was not in a section which provided reference information for the public. The Panel did not consider that the press release promoted an unlicensed medicine and thus no breach of Clause 3.1 was ruled. The Panel did not consider that the press release advertised tocilizumab to the public. No breach of Clause 20.1 was ruled.

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

C Claims in the Daily Mail, 16 June 2008

Wyeth noted that the following press articles, which shared the same style of promotional claims mentioned above, had been released following the EULAR meeting. The relevant newspapers and PR companies had confirmed the source to be a Roche press release. Wyeth had tried to obtain the necessary press releases from Roche but had not been successful. Wyeth found this unacceptable.

1 Claim 'Tocilizumab is the first treatment to outperform the standard therapy methotrexate, when used in isolation'

COMPLAINT

Wyeth alleged that etanercept monotherapy had shown superior efficacy in relation to MTX in clinical trials, and the summary of product characteristics (SPC) reflected this: 'Enbrel can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate'. Wyeth alleged that the claim was factually incorrect, did not reflect the up-to-date evaluation of all current evidence and could not be substantiated in breach of Clauses 7.2 and 7.4. Wyeth further alleged that the claim raised unfounded hopes of successful treatment in breach of Clause 20.2.

RESPONSE

The companies noted that the claim 'Tocilizumab is the first treatment to outperform the standard therapy methotrexate when used in isolation' related to the claims already being considered in Cases AUTH/2154/8/08 and AUTH/2155/8/08.

PANEL RULING

The Panel considered that its consideration of this point was covered by its rulings in point A1 above. Breaches of Clauses 7.2, 7.4 and 20.2 were ruled.

2 Claim '… expensive anti-TNF drugs'

COMPLAINT

Wyeth alleged that a price had not been established for tocilizumab, and therefore it was misleading to make a comparison with anti-TNF. NICE had recommended etanercept be used in multiple indications because it was considered to be a cost-effective treatment. The claim implied that tocilizumab had a price advantage. This was misleading in breach of Clauses 7.2, 7.3, 7.4 and 8.1. Wyeth further alleged that the claim raised unfounded hopes of successful treatment in breach of Clause 20.2.

RESPONSE

Roche and Chugai submitted that this claim was the author's own; the media release did not refer to cost. The companies took no responsibility for this claim.

PANEL RULING

The Panel noted that the press release of 13 June 2008 had not referred to the cost of anti-TNF therapies thus no breach of Clauses 7.2, 7.3, 7.4, 8.1 and 20.2 were ruled.

3 Claim '[Anti-TNFs] can be effective for a while, but eventually patients build up resistance to them'

COMPLAINT

Wyeth alleged that etanercept had not been shown to induce neutralising antibodies in humans, and there was a wealth of evidence to suggest that patients did not develop resistance against Enbrel therapy. This statement was therefore factually incorrect and disparaging in breach of Clauses 7.2, 7.3, 7.4 and 8.1. Wyeth further alleged that the claim raised unfounded hopes of successful treatment in breach of Clause 20.2 of the Code.

RESPONSE

As in point C2 above, Roche and Chugai noted that this claim about developing resistance to anti-TNF therapy was the author's own. No reference to durability of response was made in the media release. The companies therefore took no responsibility for this claim.

PANEL RULING

The Panel noted that the press release of 13 June 2008 had not referred to the development of resistance to anti-TNF therapies thus no breach of Clauses 7.2, 7.3, 7.4, 8.1 and 20.2 were ruled.

4 Conclusion

COMPLAINT

Wyeth alleged that taking into account the above breaches of the Code, Roche had brought discredit upon and reduced confidence in the industry, in breach of Clause 2.

Wyeth requested corrective statements in all relevant rheumatology journals, journals relevant to UK payers and the BMJ, admitting that misleading and incorrect statements had been widely publicised. Wyeth would expect to verify all relevant corrective statements for accuracy, given the significance of the claims.

RESPONSE

Roche and Chugai did not submit a specific response to this point.

PANEL RULING

Although noting its rulings above, the Panel did not consider that these cases warranted a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such.

With regard to Wyeth's request that a corrective statement be issued, the Panel noted that it could not require a corrective statement to be published. That sanction was available to the Code of Practice Appeal Board.

Complaint received **18 August 2008**

Cases completed **29 October 2008**

Case AUTH/2162/8/08

PROSTRAKAN v GALEN

Promotion of Calceos

ProStrakan complained about a six page, gatefolded leavepiece and a letter to a hospital consultant both issued in support of Calceos (calcium/vitamin D_3) by Galen. ProStrakan supplied Adcal-D_3 (calcium/vitamin D_3).

The leavepiece at issue stated on the front page that 'Calceos is formulated with Taste in mind'. The second page stated that taste was important for patient preference and adherence. The third page gave details of how Calceos was formulated with taste in mind. The fourth page included a cost comparison of Calceos, Adcal-D_3 and Calcichew-D_3 Forte and the fifth (which was adjacent to page 2 when opening the leavepiece) referred to high adherence with calcium and vitamin D_3 supplements doubling the reduction in fracture risk.

The detailed response from Galen is given below.

The claim 'Taste is important for: – Patient preference: – Long-term patient adherence with calcium/vitamin D_3 chewable tablets' appeared on page 2 of the leavepiece; both bullet points were referenced to Reginster *et al* (2005). ProStrakan stated that the study cited measured the preference for, and acceptability of, one tablet and one effervescent powder formulation of calcium and vitamin D_3 supplement. The study did not assess taste in terms of patient preference but rather as part of a set of acceptability criteria. The preference assessment was limited to a simple choice of one formulation over the other. ProStrakan regarded preference and acceptability as fundamentally different and non-interchangeable; preference pertained to the comparison of two or more products whereas acceptability referred to the qualities or properties of a single product. This was how the study assessed the formulations and ProStrakan alleged that the first bullet point regarding taste and preference was misleading, in breach of the Code.

Regarding the second bullet point, Reginster *et al* was conducted over 28 days; this was not long enough to assess 'long-term' adherence, particularly in view of the long extent of treatment in calcium/vitamin D_3 supplementation. Additionally, the authors stated that taste might have an impact, but the leavepiece made a categorical statement. ProStrakan therefore alleged that the second bullet point was also misleading, in breach of the Code.

Reginster *et al* compared the preference and acceptability of a chewable tablet containing the same active ingredients as Calceos and an effervescent formulation. This was important when considering further claims.

The Panel considered that, upon reading the claim at issue, most readers would assume that Reginster *et al* had shown that patients preferred Calceos because of its taste and for that reason would adhere to long-term therapy. This was not so. Reginster *et al* compared Steovit D_3 (chewable tablet) and Calcit D_3 (effervescent powder). Patients completed a widely accepted (but not validated) 11 point rating scale which included 5 acceptability variables; taking the dose, time spent taking the dose, taking the dose out of the container, general convenience of taking the dose and taste. 72.5% of patients preferred the chewable tablet, 19.1% preferred the effervescent powder and 8.4% had no preference (both $p<0.001$ vs tablet). The preference for the tablet was based on consistently and significantly higher mean scores on all 5 variables of acceptability (all $p<0.001$).

The Panel noted that in the study patients had preferred Steovit D_3 to Calcit D_3. The active ingredients of Steovit D_3 were the same as Calceos ie calcium carbonate 1250mg and vitamin D_3 400IU, however it was likely that the tablet excipients, which would contribute to the taste, were not the same. There had been no assessment of the preference for, or the acceptability of Calceos. Although the claim at issue did not mention Calceos, in the context of a Calceos leavepiece, readers would assume that the study cited had included Calceos; the failure to make clear that it did not was misleading.

Reginster *et al* assessed taste as one aspect of acceptability not as the sole reason for patient preference as implied in the leavepiece. In that regard, the claim that taste was important for patient preference was misleading in breach of the Code.

The claim that taste was important for long-term patient adherence did not make clear that the study cited in support had lasted for 28 days only. The authors stated that based on the results of previous studies acceptability and preference might influence long-term compliance. They added that the long-term effects of acceptability of the two formulations were beyond the scope of their study and whether similar results could be found in long-term treatment periods should be the subject of future studies. The Panel thus considered that the claim at issue was misleading and a breach of the Code was ruled.

The claim 'The additive effect of xylitol and sorbitol enhances the lemon flavour of Calceos' appeared on page three of the leavepiece and was referenced to the Calceos summary of product characteristics

(SPC) and the Handbook of Pharmaceutical Excipients (2006). ProStrakan stated that the references cited did not support the claim. The Calceos SPC contained no information regarding the flavour-enhancing properties of either xylitol or sorbitol, The Handbook of Pharmaceutical Excipients stated '…xylitol…is highly effective in enhancing the flavour of tablets…' but had no similar information regarding sorbitol's qualities as a flavour enhancer, referring only to sorbitol's '…pleasant, sweet taste…'. Additionally, the handbook contained no information concerning any additive flavour-enhancing effect of xylitol and sorbitol when combined together in a single formulation. ProStrakan therefore alleged that the claim was misleading. Additionally, the claim that xylitol and sorbitol acted synergistically to enhance the flavour of Calceos could not be substantiated.

The Panel noted Galen's submission that the word 'additive' might be misconstrued and an alternative would be used in future. The Panel, however, remained unsure as to how the references cited supported the claim with regard to enhancing the lemon flavour *per se* of Calceos. The Panel considered that to cite the SPC and Handbook of Pharmaceutical Excipients in support of the claim was misleading and they did not substantiate the claim. No other material was provided. Breaches of the Code were ruled.

A page headed 'Taste the NEW savings with Calceos' was followed by a table comparing the cost of calcium/vitamin D_3 supplements (Calceos, Adcal-D_3 and Calcichew-D_3 Forte).

ProStrakan stated that it was important to consider the previous pages in context with this page which compared Calceos with Adcal-D_3 and Calcichew-D_3 Forte. The central theme hereto was that taste was an important determinant of success in calcium/vitamin D_3 supplementation and that Calceos had unique advantages in terms of taste.

Reginster *et al* did not compare Calceos with other chewable tablets, but rather compared a tablet with similar active ingredients to Calceos with an effervescent tablet. The previous two pages of claims, which had been constructed in a misleading fashion and were largely unsubstantiated by the references cited, would lead the reader to conclude that other calcium/vitamin D_3 supplements should be replaced by Calceos which tasted better and therefore would have better patient adherence rates. The leavepiece in fact contained no data concerning the taste, preference, acceptability or adherence of Calceos either alone or in comparison with either Adcal-D_3 or Calcichew-D_3 Forte. To refer to Adcal-D_3 and Calcichew-D_3 Forte in a leavepiece whose central theme was taste was therefore misleading.

The Panel noted that the leavepiece made a number of claims for taste advantages for Calceos. The context of the cost comparison was an important consideration. The use of the word 'Taste' in the heading to the cost comparison extended this theme and might be read as implying that Calceos had taste advantages over Adcal-D_3 and Calcichew-D_3 Forte. The Panel considered that on balance this implication was misleading and a breach of the Code was ruled.

The claim 'High adherence with calcium and vitamin D supplements *doubles* the reduction in fracture risk' was a heading to a bar chart showing the % reduction of fracture risk for ≥80% adherence (24%), 60-69% adherence (8%) and 50-59% adherence (4%). The bar chart was referenced to a meta-analysis by Tang *et al* (2007). The Calceos logo appeared beneath the bar chart.

ProStrakan noted that the Tang *et al* meta-analysis was of 29 trials of calcium, and calcium/vitamin D_3 supplementation. The claim was true. However, the leavepiece contained no data on the adherence of Calceos and it was therefore misleading to associate Calceos with the benefits of high adherence to calcium/vitamin D_3 supplementation. Moreover, in the context of this piece (which misleadingly implied that Calceos had taste and therefore adherence advantages over other products), this claim implied Calceos would deliver greater (perhaps even double) reduction in fracture risk than competitor products. ProStrakan alleged that the claim, in this context, was misleading.

Additionally, none of the eight studies in Tang *et al* used the dose of calcium and vitamin D_3 (1000mg and 800IU) that was present in Calceos. It was therefore misleading to claim increased fracture risk reduction for Calceos using this reference, in a breach of the Code.

Finally, Tang *et al* made clear recommendations about the minimum doses of calcium and vitamin D_3 (1200mg and 800IU respectively) required for best effect. Since Calceos contained only 1000mg of calcium, ProStrakan considered it misleading to refer to Tang *et al*.

The Panel noted that the statement at issue, referenced to Tang *et al*, claimed that high adherence with calcium and vitamin D_3 supplements would double the reduction in fracture risk. It also included the Calceos logo and appeared immediately on turning the front page which claimed 'Calceos is formulated with Taste in mind' and opposite page 2 which read 'Taste is important for: … Long-term patient adherence with calcium/vitamin D chewable tablets'. The claim would be read as applying to Calceos ie that high adherence with Calceos had been shown to double the reduction in fracture risk. This was not so.

None of the studies in Tang *et al* used the Calceos dose (ie a fixed combination of calcium 1000mg and vitamin D_3 800IU). Thus the Panel considered that in the context in which they appeared the bar chart from Tang *et al* and the claim were misleading; the claim had not been substantiated. Breaches of the Code were ruled.

ProStrakan stated that the letter to a hospital consultant, signed by an employee of Galen, contained information regarding Calceos and cited Tang *et al*. As discussed above, ProStrakan believed this was misleading, as Tang *et al* recommended a dose of calcium that was higher than that contained in Calceos.

The Panel noted that the letter did not refer to any published studies. The Business Case document which accompanied the letter did refer to Tang *et al* but the document did not appear to be the subject of ProStrakan's complaint. There was no reference in the letter to Tang *et al* and no mention of adherence and fracture risk. The Panel ruled no breach of the Code with regard to the allegations made about the letter to the consultant.

ProStrakan complained about the promotion of Calceos (calcium 500mg/vitamin D_3 400IU) by Galen. The materials at issue were a six page, gatefolded leavepiece and a letter to a hospital consultant. ProStrakan supplied Adcal-D_3 (calcium/vitamin D_3). ProStrakan stated that inter-company negotiation had not resolved the matter.

Galen stated that following an internal review the leavepiece was already being withdrawn; ProStrakan would have been informed of this fact had it not moved precipitately to make a formal complaint.

The leavepiece at issue stated on the front page that 'Calceos is formulated with Taste in mind'. The second page stated that taste was important for patient preference and adherence. The third page gave details of how Calceos was formulated with taste in mind. The fourth page included a cost comparison of Calceos, Adcal-D_3 and Calcichew-D_3 Forte and the fifth (which was adjacent to page 2 when opening the leavepiece) referred to high adherence with calcium and vitamin D supplements doubling the reduction in fracture risk.

A Leavepiece

1 Claim 'Taste is important for:
– Patient preference
– Long-term patient adherence with calcium/vitamin D chewable tablets'

This claim appeared on page 2 of the leavepiece; both bullet points were referenced to Reginster *et al* (2005).

COMPLAINT

ProStrakan stated that the study cited measured the preference for, and acceptability of, one tablet and one effervescent powder formulation of calcium and vitamin D_3 supplement. The study did not assess taste in terms of patient preference but rather as part of a set of acceptability criteria. The preference assessment was limited to a simple choice of one formulation over the other.

ProStrakan regarded preference and acceptability as fundamentally different and non-interchangeable in that preference pertained to the comparison of two or more products, whereas acceptability referred to the qualities or properties of a single product. This was how the study assessed the formulations and ProStrakan alleged that the first bullet point regarding taste and preference was misleading, in breach of Clause 7.2.

Regarding the second bullet point, Reginster *et al* was conducted over 28 days; this was not long enough to assess 'long-term' adherence, particularly in view of the long extent of treatment in calcium/vitamin D_3 supplementation. Additionally, the authors stated that taste might have an impact, but the leavepiece made a categorical statement. ProStrakan therefore alleged that the second bullet point was also misleading, in breach of Clause 7.2.

Reginster *et al* compared the preference and acceptability of a chewable tablet containing the same active ingredients as Calceos and an effervescent formulation. This was important when considering further claims.

RESPONSE

Galen stated that the fact that Reginster *et al* compared an oral and effervescent formulation of calcium/vitamin D_3 was not of any relevance as no claims were made regarding the potential advantages of one formulation over another.

Taste was assessed as part of the study. In the penultimate paragraph of the discussion the authors commented:

> 'Marriott and Rees and Howe found that the acceptability of taste is related to product preference and willingness to continue treatment on a long-term basis. For optimal compliance, the taste, size and administration formulation of oral preparations should be acceptable and convenient. Based on the results of the previously mentioned studies, acceptability and preference of any dietary supplement containing calcium and vitamin D_3 may influence compliance in the long term.'

Galen believed that the statements in the leavepiece were a reasonable interpretation of the available data and accordingly not misleading or in breach of Clause 7.2

PANEL RULING

The Panel considered that, upon reading the claim at issue, most readers would assume that Reginster *et al* had shown that patients preferred Calceos because of its taste and for that reason would adhere to long-term therapy. This was not so. The two products Reginster *et al* compared were Steovit

D_3 (chewable tablet) and Calcit D_3 (effervescent powder). Patients completed a widely accepted (but not validated) 11 point rating scale which included 5 acceptability variables; taking the dose, time spent taking the dose, taking the dose out of the container, general convenience of taking the dose and taste. 72.5% of patients preferred the chewable tablet, 19.1% preferred the effervescent powder and 8.4% had no preference (both $p<0.001$ vs tablet). The preference for the tablet was based on consistently and significantly higher mean scores on all 5 variables of acceptability (all $p<0.001$).

The Panel noted that in the study patients had preferred Steovit D_3 to Calcit D_3. The active ingredients of Steovit D_3 were the same as Calceos ie calcium carbonate 1250mg and vitamin D_3 400IU, however it was likely that the tablet excipients, which would contribute to the taste of the products, were not the same. There had been no assessment of the preference for, or the acceptability of Calceos. Although the claim at issue did not mention Calceos, in the context of a Calceos leavepiece, readers would assume that the study cited had included Calceos; the failure to make clear that it did not was misleading.

Reginster *et al* assessed taste as one aspect of acceptability not as the sole reason for patient preference as implied in the leavepiece. In that regard, the claim that taste was important for patient preference was misleading in breach of Clause 7.2.

The claim that taste was important for long-term patient adherence did not make clear that the study cited in support had lasted for 28 days only. The authors stated that based on the results of previous studies acceptability and preference might influence long-term compliance. They added that the long-term effects of acceptability of the two formulations were beyond the scope of their study and whether similar results could be found in long-term treatment periods should be the subject of future studies. The Panel thus considered that the claim at issue was misleading and a breach of Clause 7.2 was ruled.

2 Claim 'The additive effect of xylitol and sorbitol enhances the lemon flavour of Calceos'

This claim appeared on page three of the leavepiece and was referenced to the Calceos summary of product characteristics (SPC) and the Handbook of Pharmaceutical Excipients (2006).

COMPLAINT

ProStrakan stated that the references cited did not support the claim. The Calceos SPC contained no information regarding the flavour-enhancing properties of either xylitol or sorbitol, The Handbook of Pharmaceutical Excipients contained information on xylitol and sorbitol. It stated '…xylitol…is highly effective in enhancing the flavour of tablets…' but had no similar information regarding sorbitol's qualities as a flavour enhancer, referring only to sorbitol's '…pleasant, sweet taste…'. Additionally, the handbook contained no information concerning any additive flavour-enhancing effect of xylitol and sorbitol when combined together in a single formulation. ProStrakan therefore alleged that the claim was misleading, in breach of Clause 7.2. Additionally, ProStrakan did not believe that the claim that xylitol and sorbitol acted synergistically to enhance the flavour of Calceos could be substantiated in breach of Clause 7.4.

RESPONSE

Galen noted that with the Calceos SPC confirmed that xylitol and sorbitol were excipients in the tablet. The Handbook of Pharmaceutical Excipients provided information on the properties and applications of both agents. Xylitol was described as being '….highly effective in enhancing the flavour of tablets and syrups…' and '… can provide chewable tablets with a desirable sweet taste and cooling sensation, without the "chalky" texture experienced with some other tablet diluents'. Sorbitol was described as being '…particularly useful in chewable tablets owing to its pleasant, sweet taste and cooling sensation'.

The word 'additive' referred to the addition of these agents to the tablets rather than meaning a synergistic action of the two agents together. As the word 'additive' might be misconstrued an alternative term would be substituted in future.

However, Galen believed that the references were not misleading, supported the claim and accordingly were not a breach of Clause 7.2 or 7.4.

PANEL RULING

The Panel noted that the claim at issue was referenced to the Calceos SPC and the Handbook of Pharmaceutical Excipients. The Panel noted Galen's submission that the word 'additive' might be misconstrued and an alternative would be used in future. The Panel, however, remained unsure as to how the references cited supported the claim with regard to enhancing the lemon flavour *per se* of Calceos. The Panel considered that to cite the SPC and Handbook of Pharmaceutical Excipients in support of the claim was misleading and they did not substantiate the claim. No other material was provided. Breaches of Clauses 7.2 and 7.4 were ruled.

3 Page headed 'Taste the NEW savings with Calceos'

This was followed by a table comparing the cost of calcium/vitamin D_3 supplements (Calceos, Adcal-D_3 and Calcichew-D_3 Forte).

COMPLAINT

ProStrakan stated that it was important to consider the previous pages in context with this page which compared Calceos with Adcal-D_3 and Calcichew-D_3 Forte. The central theme hereto was that taste was an important determinant of success in calcium/vitamin D_3 supplementation and that Calceos had unique advantages in terms of taste.

Reginster *et al* did not compare Calceos with other chewable tablets, but rather compared a tablet with similar active ingredients to Calceos with an effervescent tablet. The previous two pages of claims, which had been constructed in a misleading fashion and were largely unsubstantiated by the references cited, would lead the reader to conclude that other calcium/vitamin D_3 supplements should be replaced by Calceos which tasted better and therefore would have better patient adherence rates. The leavepiece in fact contained no data concerning the taste, preference, acceptability or adherence of Calceos either alone or in comparison with either Adcal-D_3 or Calcichew-D_3 Forte. To refer to Adcal-D_3 and Calcichew-D_3 Forte in a leavepiece whose central theme was taste was therefore misleading, in breach of Clause 7.2.

RESPONSE

Galen stated that the page 'Taste the NEW savings with Calceos' was a straightforward price comparison between Calceos and the two market leaders Adcal-D_3 and Calcichew-D_3 Forte. This compared the cost of equivalent dosages of the three agents and was accurate as of the prices in January 2008 when the leavepiece was produced. It made no claims regarding any potential advantages of Calceos over the other two agents beyond that it was the cheapest on the market.

Galen believed that a robust price comparison was not misleading and accordingly not in breach of Clause 7.2.

PANEL RULING

The Panel noted that the leavepiece made a number of claims for taste advantages for Calceos. The context of the cost comparison was an important consideration. The use of the word 'Taste' in the heading to the cost comparison extended this theme and might be read as implying that Calceos had taste advantages over Adcal-D_3 and Calcichew-D_3 Forte. The Panel considered that on balance this implication was misleading and a breach of Clause 7.2 was ruled.

4 Claim 'High adherence with calcium and vitamin D supplements *doubles* the reduction in fracture risk'

This was a heading to a bar chart showing the % reduction of fracture risk for ≥80% adherence (24%), 60-69% adherence (8%) and 50-59% adherence (4%). The bar chart was referenced to a meta-analysis by Tang *et al* (2007). The Calceos logo appeared beneath the bar chart.

COMPLAINT

ProStrakan noted that the Tang *et al* meta-analysis was of 29 trials of calcium, and calcium/vitamin D_3 supplementation. The claim was true. However, the leavepiece contained no data on the adherence of Calceos and it was therefore misleading to associate Calceos with the benefits of high adherence to calcium/vitamin D_3 supplementation. Moreover, in the context of this piece (which misleadingly implied that Calceos had taste and therefore adherence advantages over other products), this claim implied Calceos would deliver greater (perhaps even double) reduction in fracture risk than competitor products. ProStrakan alleged that the claim, in this context, was misleading, in breach of Clause 7.2.

Additionally, none of the eight studies in Tang *et al* that showed high compliance with overall 24% fracture risk reduction used the combination of calcium and vitamin D_3 (1000mg and 800IU) that was the recommended Calceos dose. It was therefore misleading for Galen to make any claim regarding increased fracture risk reduction for Calceos using this reference, in a breach of Clauses 7.2 and 7.4.

Finally, Tang *et al* made clear recommendations about the minimum doses of calcium and vitamin D_3 (1200mg and 800IU respectively) required for best effect. Since Calceos contained only 1000mg of calcium, ProStrakan considered it misleading for Galen to refer to Tang *et al*. A further breach of Clause 7.2 was alleged.

RESPONSE

Galen stated that the purpose of the page was to remind physicians that adherence to calcium and vitamin D_3 supplements was an important factor in the long-term effectiveness of these agents. This was generally accepted and was as applicable to any of the other calcium and vitamin D_3 supplements as it was to Calceos. No claim was made that Calceos would improve adherence, that it had adherence advantages over other products or that it would provide a greater reduction in fracture risk than other products.

Accordingly, Galen believed the statement 'High adherence with calcium and vitamin D_3 supplements doubles the reduction in fracture risk' was not misleading and not in breach of Clause 7.2

Tang *et al* was a large meta-analysis of 29 studies in which 8 studies with compliance of 80% or more reported a significantly greater risk reduction than

those with lower compliance. These 8 studies had widely varying doses of calcium alone (750mg-1600mg) or calcium/vitamin D_3 (500mg calcium/700IU – 1200mg calcium/800IU). If any claim was made, it was that compliance rather than dosage of either calcium alone or calcium and vitamin D_3 was important and in fact the authors reported that they found no relation between compliance and an increased dose of calcium (p=0.57).

No claim was made that Calceos increased fracture risk reduction and Galen believed that the reference supported the statement and was not in breach of Clauses 7.2 or 7.4.

Tang *et al* did indeed make clear recommendations about the minimum doses of calcium alone and separately for vitamin D_3 in combination with calcium. In the discussion the authors stated that:

> 'For calcium only supplementation, a minimum dose of 1200mg is needed for best therapeutic effect. For calcium in combination of vitamin D supplementation, a minimum dose of 800IU of vitamin D is recommended' and
>
> 'On the basis of our recommended minimum dose of 1200mg of calcium or 800IU of vitamin D….'

The authors made recommendations for calcium alone and for vitamin D_3 in combination with calcium but not for a combined calcium and vitamin D_3 preparation. As Calceos contained 800IU vitamin D_3 in combination with calcium it complied with the recommendations in the paper and was not a breach of Clause 7.2 either in the leavepiece or the letter to the hospital consultant.

PANEL RULING

The Panel noted that the statement at issue, referenced to Tang *et al*, claimed that high adherence with calcium and vitamin D_3 supplements would double the reduction in fracture risk. It also included the Calceos logo and appeared immediately on turning the front page which claimed 'Calceos is formulated with Taste in mind' and opposite page 2 which read 'Taste is important for: … Long-term patient adherence with calcium/vitamin D chewable tablets'. The claim would be read as applying to Calceos ie that high adherence with Calceos had been shown to double the reduction in fracture risk. This was not so.

None of the studies in Tang *et al* meta-analysis used the Calceos dose (ie a fixed combination of calcium 1000mg and vitamin D_3 800IU). Thus the Panel considered that in the context in which they appeared the bar chart from Tang *et al* and the claim were misleading; the claim had not been substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

B Letter to a hospital consultant

COMPLAINT

ProStrakan stated that this letter, signed by an employee of Galen, contained information regarding Calceos. The letter referenced the Tang *et al* review of calcium/vitamin D_3 supplementation. As discussed above, ProStrakan believed this was misleading, in breach of Clause 7.2, as Tang *et al* recommended a dose of calcium that was higher than that contained in Calceos.

RESPONSE

Galen submitted that this allegation was covered in point A5 above.

PANEL RULING

The Panel noted that the letter to the consultant provided by Galen did not refer to any published studies. The Business Case document which accompanied the letter did refer to Tang *et al* but the document did not appear to be the subject of ProStrakan's complaint. There was no reference in the letter to Tang *et al* and no mention of adherence and fracture risk. The Panel ruled no breach of Clause 7.2 with regard to the allegations made about the letter to the consultant.

Complaint received **18 August 2008**

Case completed **5 November 2008**

CASE AUTH/2163/8/08

CONSUMERS INTERNATIONAL v LILLY

Website and associated TV campaign on erectile dysfunction

Consumers International was concerned that a website www.40over40.com and associated TV campaign about erectile dysfunction (ED), sponsored by Lilly, promoted that company's medicine Cialis (tadalafil), in breach of the Code as prescription only medicines must not be promoted to the public.

One page of the website contained a table that listed the treatment types available. 'Product 1' in the list was clearly Cialis. Any member of the public that entered 'erectile dysfunction' and 'Eli Lilly' into a search engine could make this discovery in less than 30 seconds. (The name of the company appeared in the TV campaign and on every website page).

Naming Cialis 'product 1' and placing it at the top of the table effectively promoted this treatment over other options; information relating to 'product 1' was more likely to be read compared with information about other products and the positioning was, in itself, likely to give the impression that this treatment was preferable to others. Further, the information given in the table was also likely to steer members of the public towards thinking that 'product 1' was preferable to other treatments because across three of the five criteria (time to become effective, duration of effect and food interactions) it was preferable to the other products listed (on the remaining two criteria it was equivalent).

Consumers International believed that this contravened guidance that: 'A company may conduct a disease awareness or public health campaign provided that the purpose is to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine'. The guidance 'Particular care must be taken where the company's product, even though not named, is the only product relevant to the disease or symptoms in question' was also relevant.

Even though Cialis was clearly not the only relevant product, given the information in the table it appeared to be preferable, in several respects, to the other treatments. Consumers International believed that equal 'care' should be taken in these circumstances.

Members of the public were told 'You can discuss these options and your preferences with your doctor'. Given the way in which this information was presented Consumers International believed it was highly likely that members of the public would approach doctors stating a preference for Cialis or 'product 1.' This meant that this disease awareness campaign was effectively promotion. Given the link to the TV campaign Consumers International considered that this was a high profile abuse of the Code that would reach an unusually high number of people.

The detailed response from Lilly is given below.

The Panel noted that as part of Case AUTH/2151/7/08 it had already considered an allegation that the website and TV campaign promoted a prescription only medicine to the public.

In Case AUTH/2151/7/08, the Panel considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake provided that they were in accordance with the Code. Such activities might facilitate the market development of the sponsoring company's products but this was not necessarily in breach of the Code. Each case would need to be judged on its merits.

The supplementary information to the Code stated that a company might conduct a disease awareness or public health campaign provided that the purpose was to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine. The use of brand or non-proprietary names and/or restricting the range of treatments described in the campaign might be likely to lead to the use of a specific medicine. Particular care must be taken where the company's product, even though not named, was the only medicine relevant to the disease or symptoms in question.

The Panel considered that the campaign was within the scope of the Code as it could not take the benefit of the exemption for information relating to human health or diseases provided there was no reference either direct or indirect to specific medicines.

The television advertisement did not refer to medicines other than a general statement that there was a range of treatments that could help. It gave details of the website 40over40.com. The Panel did not consider that the television advertisement *per se* constituted an advertisement to the public for a prescription only medicine nor would it encourage a patient to ask their health professional to prescribe a specific medicine. No breach of the Code was ruled.

The 40over40.com website gave detailed information set out under four sections 'talk', 'test',

'treat' and 'today'. In the Panel's view the sections 'talk', 'test' and 'today' gave helpful information about ED. The 'treat' section included a chart setting out various features about the medicines and devices available. The chart was also included in the 4t Action Plan for patients to download and discuss with their doctor. Neither the treatment chart on the website nor the 4t Action Plan named any of the products. The sections were divided into oral treatments where details of products 1, 2 and 3 were given, injections or insertions which gave details of three products and vacuum pumps and constriction rings which stated that ten different types were available. The features compared for each product were 'How long does it take to work', 'Duration of effect', 'Maximum recommended dosing', 'Most common side effects (over 10%) and 'Food interactions'. Below the chart there was brief mention of hormone treatment and surgery. Information was also given about counselling which, it was stated, should be an integral part of treatment. Only the section describing injections or insertions included the advice to '… discuss all possible side effects with your doctor/nurse'. Only the section describing surgery stated that your doctor would be the best person to advise as to whether it was a suitable option. Although not named the first oral treatment (product 1) listed in the chart was Cialis.

The Panel considered that much information had been provided about the treatment for ED. All possible treatments were mentioned. The question was whether the information constituted an advertisement to the public for a prescription only medicine or would encourage a patient to ask their health professional to prescribe a specific medicine. The Panel did not consider that the chart on the website nor its inclusion in the 4t Action Plan constituted an advertisement to the public for a prescription only medicine and no breach of the Code was ruled.

The Panel considered that the features used to describe the products in the chart would result in patients asking their health professionals to prescribe a specific medicine. In addition the Panel was concerned as to whether the information presented was balanced particularly with regard to the presentation of data about side effects. The chart detailed the 'Most common side effects (over 10%)' and listed 'headache and indigestion' for product 1 (Cialis). These were the side effects listed in the Cialis summary of product characteristics (SPC) as very common. The Panel considered that to list only two side effects, albeit at a stated frequency of ≥1/10, would give an unbalanced view of the safety of the product to a potential patient. There was no indication that other side effects were possible. The Panel had similar concerns regarding the data given for products 2 and 3. The Panel was also concerned that there was no mention of contraindications for oral treatments. There was an implication that any of the products could be used successfully to treat ED. This was not necessarily so. In the Panel's view it was to be expected that a potential patient would read the pros and cons for each treatment choice and form an opinion as to which they wanted. Patients were encouraged to take the 4t Action Plan, which included the chart to discuss the options and their preferences with their doctor. The Panel considered that the chart was not factual and balanced. It would encourage a member of the public to request a specific prescription only medicine. Thus the Panel ruled a breach of the Code with regard to the information on the website including the 4t Action Plan.

The Panel considered that by naming medicines and/or giving very specific details about their advantages and certain disadvantages, Lilly had not maintained high standards and a breach of the Code was ruled.

The Panel noted that the treatment option chart gave a clear account of the positive characteristics of each oral tablet whilst very limited information had been given about side effects and none about possible contraindications. Whilst patients were advised to discuss the treatment options with their doctor the website also encouraged them to decide what their preferences might be and to discuss these with their doctor. There was an implication that choosing a medicine to treat ED was straightforward which was not so. It was inappropriate to encourage patients to ask a health professional to prescribe a specific prescription only medicine. The Panel considered that on the facts of this case such action brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel considered that the rulings in Case AUTH/2151/7/08 as set out above applied in the case now before it, Case AUTH/2163/8/08.

The Panel did not accept that placing the information about Lilly's product Cialis as product 1 in the table was necessarily unacceptable. This did not in itself promote product 1 above other products. Thus on this narrow point no breach of the Code was ruled.

COMPLAINT

Consumers International was concerned that the website www.40over40.com and associated TV campaign about erectile dysfunction (ED), sponsored by Lilly, promoted the company's medicine Cialis (tadalafil), in breach of Clause 22 of the Code that stated that prescription only medicines must not be promoted to the public.

The website page relating to treatment http://www.40over40.com/erectile-dysfunction-drugs.html contained a table that listed the treatment types available. 'Product 1' in the list was clearly Cialis, produced by Lilly.

Any member of the public that entered 'erectile

dysfunction' and 'Eli Lilly' into a search engine could make this discovery in less than 30 seconds. (The name of the company appeared in the TV campaign and on every website page.) Naming Cialis 'product 1' and placing it at the top of the table effectively promoted this treatment over other options. This placement meant that information relating to 'product 1' was more likely to be read compared with information about other products and the positioning was, in itself, likely to give the impression that this treatment was preferable to others.

The information given in the table was also likely to steer members of the public towards thinking that 'product 1' was preferable to other treatments, because across three of the five criteria (time to become effective, duration of effect and food interactions) it was preferable to the other products listed (on the remaining two criteria it was equivalent).

Consumers International believed that this contravened guidance that: 'A company may conduct a disease awareness or public health campaign provided that the purpose is to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine'.

Consumers International stated that the following guidance was also relevant: 'Particular care must be taken where the company's product, even though not named, is the only product relevant to the disease or symptoms in question'.

Even though Cialis was clearly not the only product relevant to this condition, given the information in the table it appeared to be preferable, in several respects, to the other treatments. Consumers International believed that equal 'care' should be taken in these circumstances.

Members of the public were told 'You can discuss these options and your preferences with your doctor'. Given the way in which this information was presented Consumers International believed it was highly likely that members of the public would approach doctors stating a preference for Cialis or 'product 1.' This meant that this disease awareness campaign was effectively promotion. Given the link to the TV campaign Consumers International considered that this was a high profile abuse of the Code that would reach an unusually high number of people.

When writing to Lilly, the Authority asked it to respond in relation to Clauses 2, 9.1, 22.1 and 22.2 of the 2008 Code which were the same as in the 2006 Code though differently numbered.

RESPONSE

Lilly refuted any suggestion that it had breached Clauses 2, 9.1, 22.1 and/or 22.2 of the 2008 Code; the campaign was non-promotional and in accordance with the Code and the Medicines and Healthcare products Regulatory Agency (MHRA) Guidelines for conducting disease awareness campaigns.

Background and design of campaign

Lilly explained that erectile dysfunction was a common condition, with 40% of men over the age of 40 suffering from it to some degree. It was a distressing condition for both sufferers and their partners. Many men tended to suffer in silence for prolonged periods of time due to the taboo surrounding the condition. Moreover, ED was often an early warning sign of serious, potentially life-threatening conditions, such as diabetes or heart disease.

However, ED was treatable in 95% of all patients. With the wide array of modern treatments, encompassing first-line (principally oral PDE5 inhibitors), second-line (principally intra-urethral or intra-cavernosal alprostadil) and third-line treatments (penile implant surgery), and psychosexual counselling, few if any patients would experience no improvement in their ED.

The disease awareness campaign at issue was designed to raise awareness of the prevalence of ED, its link to underlying illness and the range of treatment options available. Knowing that others suffered from this distressing and embarrassing condition was empowering and reduced the sense of shame and isolation felt by many men with ED, which negatively impacted on their ability to seek medical attention. Knowing that the condition was treatable was also empowering for ED sufferers, as many believed that the condition was a part of ageing and could not be treated.

In addition, Lilly considered that essential to the success of the current campaign over previous disease awareness campaigns, conducted by both Lilly and others, was the need to deliver a strong and memorable consumer-orientated campaign. The name '40over40' was chosen for its ease of recall, as well as reflecting the evidence of prevalence of this condition. The various elements of the campaign were designed to effectively deliver this and the other key messages in a non-promotional manner.

Elements of the campaign

The 40over40 campaign comprised non-promotional materials delivered through various forms of media, including TV, internet and print, and was directed to both the public and to health professionals. The campaign was non-promotional and in accordance with the Code and with the MHRA Guidelines for conducting disease awareness campaigns. Consistent with the Code, all the materials associated with the campaign identified Lilly as its sponsor.

40over40 TV advertisement

Television was a powerful tool to bring messages to the public's attention and, as such, was considered an important element of the 40over40 campaign, to effectively deliver the campaign to the widest audience of sufferers. The advertisement was subject to pre-vetting and approval by Clearcast and was scheduled to be broadcast during programmes of most interest to men and, in light of the subject matter, after the 9pm watershed.

Television advertisements for disease awareness campaigns had been conducted in the past by Lilly and others, for a variety of conditions including ED, and were not prohibited by the Code or by the MHRA.

40over40.com website

The disease awareness campaign website, www.40over40.com contained four sections directed at ED sufferers: 'talk' included a comprehensive overview of the disease and helpful tips on how to raise this sensitive topic with partner and GP; 'test' included a questionnaire for sufferers to rate their severity of ED and information about tests that GPs might perform to determine any underlying conditions; 'treat' was a thorough, fair and balanced list of all of the treatment options available for ED; and 'today' linked to advocacy group websites that related to ED; these together comprised the '4t Action Plan'.

The table of treatments in the 'treat' section, http://www.40over40.com/erectile-dysfunction-drugs.html, referred to by the complainant, comprised a fair and balanced list of the whole range of options available for management of ED. Within this table 'oral tablets' were listed first, since oral treatment represented the first-line treatment option for ED, hence this was its logical place.

Although the complainant correctly deduced 'product 1' to be Cialis, Lilly refuted that placing product 1 at the top of the table 'effectively promoted this treatment over other options'. Lilly also did not accept that 'information relating to 'product 1' was more likely to be read compared with information about other products', nor that 'the positioning was, in itself, likely to give the impression that this treatment was preferable to others'. Cialis was denoted as 'product 1' simply because it was first in the alphabetical order of the products, with product 2 being Levitra and product 3 being Viagra. The treatment table presented factual information for all three oral treatments in a fair and balanced manner, consistent with the respective summaries of product characteristics (SPCs). Information regarding other, non-pharmacological treatments for ED was also presented in a similar manner. The fact that some treatments, named or anonymised, might have particular characteristics and/or side effects did not in itself preclude presentation of treatment options in the context of a fair and balanced discussion, and this was consistent with both the MHRA Guidelines and with the Code. Lilly therefore refuted any allegation that the treatment table promoted Cialis.

All materials associated with the campaign were non-promotional and provided ED sufferers with information on the condition in order to help facilitate discussions with their GP, should they wish to do so, and obtain appropriate advice. The campaign clearly indicated that all treatment decisions should be made with the ED sufferer's GP. Since the treatment options presented were all prescription only medicines, or options requiring a medical referral, treatment could only be obtained in conjunction with a consultation with a medical practitioner.

Hence, Lilly did not consider that the way in which the treatment options were presented placed any undue influence on the clinical consultation. Whilst consultations involving well-informed patients were to be welcomed, it remained the responsibility of qualified medical practitioners to decide upon the relative benefit and risks associated with any particular treatment. This involved consideration of information such as potential medicine interactions, side effects and co-morbidities, which could not be appropriately detailed in any disease awareness campaign. Lilly did not accept the assertion that qualified medical practitioners relied on consumer awareness material in order to make prescribing decisions, or allowed patient choice to over-ride the clinical decisions relating to treatment options, particularly if this was not appropriate for the patient.

Similarly, Lilly did not accept the complainant's assertion that the guidance concerning disease awareness campaigns for 'diseases or conditions where there is only one, one leading or few medicinal treatments' to be of relevance with regard to this matter, since there were a number of available treatment options, and hence did not accept that special 'care' should be applied to the current Lilly disease awareness campaign. The modern treatment for ED encompassed a wide range of effective treatments, some pharmacological, some not, as previously noted. Different treatments suited different men, with different lifestyles. Lilly considered that the complainant's assertion that Cialis, or product 1, was a treatment of such clear desirability and preference, over and above all other treatments mentioned, including other PDE5 inhibitors, was subjective and did not necessarily reflect other opinion.

In summary, Lilly was fully cogniscent of its responsibilities with respect to the Code and had ensured that all aspects of the ED disease awareness campaign were of the highest standards and quality.

Lilly categorically rejected the unfounded allegation of the complainant of an abuse of the Code and

trusted that the information provided helped in the Authority's consideration of this matter.

PANEL RULING

The Panel noted that as part of Case AUTH/2151/7/08 it had already considered an allegation that the website and TV campaign promoted a prescription only medicine to the public.

Case AUTH/2151/7/08

The Panel considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake provided that such programmes were in accordance with the Code. Such activities might facilitate the market development of the sponsoring company's products but this was not necessarily in breach of the Code. Each case would need to be judged on its merits.

The Panel noted that the supplementary information to Clause 22.2 stated that a company might conduct a disease awareness or public health campaign provided that the purpose was to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine. The use of brand or non-proprietary names and/or restricting the range of treatments described in the campaign might be likely to lead to the use of a specific medicine. Particular care must be taken where the company's product, even though not named, was the only medicine relevant to the disease or symptoms in question.

The Panel considered that the campaign was within the scope of the Code as it could not take the benefit of the exemption for information relating to human health or diseases provided there was no reference either direct or indirect to specific medicines (Clause 1.2).

The Panel examined the material in question. The television advertisement did not refer to medicines other than a general statement that there was a range of treatments that could help. The television advertisement gave details of the website 40over40.com. The Panel did not consider that the television advertisement *per se* constituted an advertisement to the public for a prescription only medicine nor would it encourage a patient to ask their health professional to prescribe a specific medicine. No breach of Clauses 22.1 and 22.2 was ruled.

The 40over40.com website gave detailed information set out under four sections 'talk', 'test', 'treat' and 'today'. In the Panel's view the sections 'talk', 'test' and 'today' gave helpful information about ED including possible causes and advice about talking to a health professional. The 'treat' section included a chart setting out various features about the medicines and devices available to treat ED. The chart was also included in the 4t Action Plan for patients to download and discuss with their doctor. Neither the treatment chart on the website nor the 4t Action Plan named any of the products. The sections were divided into oral treatments where details of products 1, 2 and 3 were given, injections or insertions which gave details of three products and vacuum pumps and constriction rings which stated that ten different types were available. The features compared for each product were 'How long does it take to work', 'Duration of effect', 'Maximum recommended dosing', 'Most common side effects (over 10%) and 'Food interactions'. Below the chart there was brief mention of hormone treatment and surgery. Information was also given about counselling which, it was stated, should be an integral part of treatment. Only the section describing injections or insertions included the advice to '… discuss all possible side effects with your doctor/nurse'. Only the section describing surgery stated that your doctor would be the best person to advise as to whether it was a suitable option. Although not named the first oral treatment (product 1) listed in the chart was Cialis.

The Panel considered that much information had been provided about the treatment for ED. All possible treatments were mentioned. The question was whether the information constituted an advertisement to the public for a prescription only medicine or would encourage a patient to ask their health professional to prescribe a specific medicine. The Panel did not consider that the chart on the website nor its inclusion in the 4t Action Plan constituted an advertisement to the public for a prescription only medicine and no breach of Clause 22.1 was ruled.

The Panel considered that the features used to describe the products in the chart would result in patients asking their health professionals to prescribe a specific medicine. In addition the Panel was concerned as to whether the information presented was balanced particularly with regard to the presentation of data about side effects. The chart detailed the 'Most common side effects (over 10%)' and listed 'headache and indigestion' for product 1 (Cialis). These were the side effects listed in the Cialis SPC as very common. The SPC, however, also listed the following common (≥1/100 to <1/10) side effects: dizziness, palpitations, flushing, nasal congestion, abdominal pain, gastro-oesophageal reflux, back pain and myalgia. The Panel considered that to list only two side effects, albeit at a stated frequency of ≥1/10, would give an unbalanced view of the safety of the product to a potential patient. There was no indication that other side effects were possible. The Panel had similar concerns regarding the data given for products 2 and 3. The Panel was also concerned that there was no mention of contraindications for oral treatments. There was an implication that any of the products could be used successfully to treat ED. This was not necessarily so. In the Panel's view it was to be expected that a potential patient would read the pros and cons for each treatment choice and form

an opinion as to which they wanted. Patients were encouraged to take the 4t Action Plan, which included the chart to discuss the options and their preferences with their doctor. The Panel considered that the chart was not factual and balanced. It would encourage a member of the public to request a specific prescription only medicine. Thus the Panel ruled a breach of Clause 22.2 with regard to the information on the website including the 4t Action Plan.

The Panel considered that by naming medicines and/or giving very specific details about their advantages and certain disadvantages, Lilly had not maintained high standards and a breach of Clause 9.1 was ruled.

The Panel noted that the treatment option chart gave a clear account of the positive characteristics of each oral tablet whilst very limited information had been given about side effects and none about possible contraindications. Whilst patients were advised to discuss the treatment options with their doctor the website also encouraged them to decide what their preferences might be and to discuss these with their doctor. There was an implication that choosing a medicine to treat ED was straightforward which was not so. It was inappropriate to encourage patients to ask a health professional to prescribe a specific prescription only medicine. The Panel considered that on the facts of this case such action brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Case AUTH/2163/8/08

The Panel considered that the rulings in Case AUTH/2151/7/08 as set out above applied in the case now before it, Case AUTH/2163/8/08.

The Panel did not accept that placing the information about Cialis as product 1 in the table was necessarily unacceptable. This did not in itself promote product 1 above other products. Thus on this narrow point no breach of Clauses 22.1 and 22.2 was ruled.

Complaint received **20 August 2008**

Case completed **13 October 2008**

CODE OF PRACTICE REVIEW – NOVEMBER 2008

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

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2125/5/08	**GlaxoSmithKline v Takeda Europe**	**Actos journal advertisement**	**Breaches Clauses 2, 3.2, 7.2, 7.9 and 7.10**	**No appeal**	**Page 18**
2126/5/08	**Procter & Gamble v Servier Laboratories**	**Misleading and damaging information about bisphosphonates**	**Three breaches Clause 7.2** **Three breaches Clause 8.1**	**Appeal by respondent**	**Page 23**
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2152/8/08	**Novo Nordisk v Sanofi-Aventis**	**Promotion of Lantus**	**Three breaches Clause 7.2**	**No appeal**	**Page 126**
2153/8/08	**Prescribing Support Pharmacist v Procter & Gamble**	**Actonel leavepiece**	**Three breaches Clause 7.2 Breach Clause 10.2**	**No appeal**	**Page 135**
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2156/8/08	**GlaxoSmithKline v Sanofi Pasteur MSD**	**Gardasil letter to health professionals**	**Breaches Clauses 3.2, 4.1, 4.10 and 9.1**	**No appeal**	**Page 142**
2157/8/08	**Practice Pharmacist v Sanofi-Aventis**	**Accomplia leavepiece**	**Three breaches Clause 7.2**	**No appeal**	**Page 146**
2159/8/08 & 2166/9/08	Anonymous v Bristol-Myers Squibb and Otsuka	Alleged inappropriate hospitality	No breach	No appeal	Page 149
2160/8/08 & 2161/8/08	**Wyeth v Roche and Chugai**	**Press statements regarding Actemra**	**Three breaches Clause 7.2 Breach Clause 7.3 Three breaches Clause 7.4 Breaches Clauses 7.10, 8.1 and 20.2**	**No appeal**	**Page 151**
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2163/8/08	**Consumers International v Lilly**	**Website and associated TV campaign on erectile dysfunction**	**Breaches Clauses 2, 9.1 and 22.2**	**No appeal**	**Page 163**

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.