NUMBER 65 AUGUST 2009

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.

CERTIFICATES

Following discussion with the Code of Practice Appeal Board, the PMCPA will be asking respondent companies to include in their responses copies of the certificates approving the materials/activities relevant to the complaint. The Authority will start requesting certificates in relation to complaints received from 1 October onwards. Clauses 14.1, 14.2 and 14.3 of the Code and their supplementary information set out which materials/activities need to be certified.

MHRA CONSULTATION

The PMCPA has responded to the MHRA consultation on European Commission proposals on information to patients about prescription only medicines (MLX358). The quality of information and not the source of that information should be the prime consideration. There are concerns that the proposed directive would mean that pharmaceutical companies in the UK would not be able to provide as much information as is currently allowed. The PMCPA view is that the current UK position should continue.

SIGNATORIES

Companies are reminded that in accordance with Clause 14.4 they are required to provide names and qualifications of their nominated signatories to the PMCPA (and also to the Medicines and Healthcare products Regulatory Agency (MHRA)). When notifying the PMCPA of any changes it would be helpful to provide in addition an updated current list of signatories.

Companies are also reminded that signatories need to be sufficiently experienced to discharge their duties as set out in the supplementary information to Clause 14.1.

HELLO VICKY!

The Authority is delighted to welcome Vicky Edgecombe to the team as the new head of communications.

Vicky joined the PMCPA in May from Freshwater Healthcare where she had been working with a range of healthcare and public sector clients. Vicky has also worked for the General Medical Council and in the NHS.

Vicky is planning for a busy twelve months which will include Code Awareness activities, the consultation and launch of the next version of the Code and some new projects to increase engagement within the NHS and help support joint working initiatives.

Vicky can be contacted via vedgecombe@pmcpa.org.uk or 020 7747 8884.

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:
Monday, 21 September
Monday, 16 November

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

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

HOW TO CONTACT THE AUTHORITY

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

www.pmcpa.org.uk

Telephone:	020 7747 8880
Facsimile:	020 7747 8881

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

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

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

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

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

CASE AUTH/2205/2/09

PUBLIC HEALTH REGISTRAR v RECKITT BENCKISER

Insert on Gaviscon Advance

A public health registrar, complained about a booklet entitled 'Reflux Disease – What Lies Beneath the Surface?' distributed with the BMJ. A sub-heading explained that the content was perspectives from a consensus meeting. The front cover stated that the booklet had been supported by an educational grant from Reckitt Benckiser and incorporated the company logo; the reader was directed to prescribing information for Gaviscon Advance on the back cover.

The complainant alleged that, for all intents and purposes, the material was an advertisement for Gaviscon Advance, which was why the prescribing information for it was included. Gaviscon Advance was presented favourably throughout. The supplement consisted of seven pages of advertising, not including the page of prescribing information. This was greater than the two pages of advertising allowed for a particular product in an issue of a journal. No details of the date and location were given for the 'consensus meeting' which this supplement purportedly described. Did this 'consensus meeting' truly take place? Or was it simply the editorial meeting for this advertisement? The listed faculty consisted of a gastroenterologist, a respiratory physician, a speech and language therapist, an ear nose and throat (ENT) surgeon and two GPs. The complainant alleged that if these individuals had met for a 'consensus meeting' it was, in effect, a ruse to obtain exemption from the Code.

The complainant alleged that there was no single generally accepted viewpoint on the issues covered in the supplement and that it was unbalanced in favour of Gaviscon Advance.

The complainant alleged that the supplement represented an extreme of format (because it used a font, colour scheme, page size and page layout that was almost identical to the BMJ with which it was circulated), an extreme of size (8 pages of A4 in sturdy card was excessive for one advertisement); and extreme of cost (the cost of distributing this number of full-colour pages amongst the tens of thousands of BMJ readers would have been extremely high).

The complainant alleged that the words, 'Supported by an educational grant from Reckitt Benckiser' were not sufficiently prominent; they appeared only once and were written in a relatively small and light font. Furthermore, the complainant alleged that this statement did not accurately reflect the nature of the company's involvement.

The complainant noted that given the similarity of the layout, font and style of the supplement to the BMJ, the words 'Advertising Feature' should have been printed prominently on every page in order to avoid misleading readers. The material was a disguised promotional material.

The Panel noted that the booklet essentially reported the output of a Reckitt Benckiser advisory board. The advisory board meeting and the resultant booklet had been facilitated by third parties. In the Panel's view, however, each of those parties was acting on behalf of Reckitt Benckiser and so the company was responsible, under the Code, for their actions.

The Panel considered that Reckitt Benckiser was wholly responsible for the advisory board meeting and thus for any output from that meeting. There was no strictly arm's length arrangement. Reckitt Benckiser had acknowledged that reference to Gaviscon Advance had rendered the document at issue promotional in nature. The document contained three main sections: 'The Spectrum of Reflux Disease'; 'Differential Diagnoses of LPR [laryngopharyngeal reflux] and GORD [gastro-oesophageal reflux disease]' and 'Evidence for the role of an alginate reflux suppressant in the treatment of LPR'. The third section detailed two clinical studies which had assessed the efficacy of Gaviscon Advance and also gave three case histories of patients who had benefitted from such therapy. The Panel noted Reckitt Benckiser's submission that the artworked document had been approved by its regulatory and medical team.

The Panel considered that the material at issue was not a supplement 'Supported by an educational grant from Reckitt Benckiser' (as stated on the front cover) but an advertisement for Gaviscon Advance. The Panel noted the supplementary information to the Code referred to inserts that might be regarded as promotional material for example reports of conference proceedings not being subject to the restrictions of the Code. The Panel did not consider that this applied in this case given that the material was, in effect, produced by Reckitt Benckiser following its advisory board meeting and the company had editorial control. The supplementary information did not give detailed guidance on the distinction between an advertisement and promotional material. Taking all the circumstances into account, the Panel decided that the material was, in effect, an eight page advertisement for Gaviscon Advance. It thus exceeded the two page limit allowed in any issue of a journal and a breach of the Code was ruled.

The Panel did not consider that the statement

'Supported by an educational grant from Reckitt Benckiser' accurately reflected the nature of the company's involvement. A breach of the Code was ruled.

The Panel did not consider that the format and style of the insert was such that it would be confused with that of the BMJ. Nonetheless, the statement 'Supported by an educational grant …' disguised the promotional nature of the material. The sub-heading on the front cover 'Perspectives from a consensus meeting …' added to the misleading impression of an independent educational supplement as it was not stated that the meeting was a Reckitt Benckiser advisory board. The Panel considered that the insert was disguised promotion and a breach of the Code was ruled.

The Panel did not consider that the insert was extreme in either its format or size. It was the same size as the BMJ page size and the copy provided by Reckitt Benckiser was not on sturdy card as submitted by the complainant. No breach of the Code was ruled which was upheld on appeal by the complainant.

The Panel noted that given its title, 'Reflux Disease – What Lies Beneath the Surface?', sub-heading 'Perspectives from a consensus meeting …' and list on the inside front cover of the faculty, the insert appeared to be an independent review of the therapy area. The introduction stated that the document would explain the difference between gastro-oesophageal reflux disease and laryngopharyngeal reflux and provide help to recognise their individual symptoms and advice on managing the two very different but related entities. There was, however, no advice on managing gastro-oesophageal reflux disease although detailed advice was given about the management of laryngopharyngeal reflux. The insert was promotional material for Gaviscon Advance. The Panel considered that the insert was misleading in this regard and a breach of the Code was ruled.

A public health registrar, complained about a supplement (ref G-NHS-UK-01-09) that was distributed with the BMJ, 7 February 2009. The supplement was entitled 'Reflux Disease – What Lies Beneath the Surface?'. A sub-heading explained that the supplement was perspectives from a consensus meeting representing gastroenterology, otolaryngology, respiratory medicine, speech and language therapy and primary care. The front cover stated that the supplement had been supported by an educational grant from Reckitt Benckiser and incorporated the company logo; the reader was directed to prescribing information for Gaviscon Advance on the back cover.

COMPLAINT

The complainant submitted that a reasonable person would conclude that the supplement was, for all intents and purposes, an advertisement for Gaviscon Advance, which was why the prescribing information for this product, and only this product, was included. The supplement, which presented Gaviscon Advance in a light that was unquestioningly favourable throughout, consisted of seven pages of advertising, not including the page of prescribing information. This was greater than the two pages of advertising allowed for a particular product in an issue of a journal in breach of Clause 6. The complainant did not consider that the exemption to Clause 6.3 applied in this case: 'Inserts and supplements which are not advertisements as such, though they may be regarded as promotional material, for example reports of conference proceedings, are not subject to the restrictions of Clauses 6.2 and 6.3'. This was undeniably an advertisement for one product and was therefore not simply promotional material. Hence the words 'as such' did not apply in this case. No details of the date and location were given for the 'consensus meeting' which this supplement purportedly described. Did the 'consensus meeting' truly take place or was it simply the editorial meeting for this advertisement? The meeting was supposedly of those listed as the 'faculty' ie a gastroenterologist, a respiratory physician, a speech and language therapist, an ear nose and throat (ENT) surgeon and two GPs. The complainant alleged that the 'consensus meeting' between these individuals, if it did take place, was in effect a ruse to obtain exemption from Clause 6.3 in breach of the spirit of the Code.

Clause 7.2 stated that 'Where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material'. The complainant alleged that there was no single generally accepted viewpoint on the issues covered in the supplement and that it was unbalanced in favour of Gaviscon Advance.

With regard to Clause 9.7 the complainant alleged that the supplement represented an extreme of format (because it used a font, colour scheme, page size and page layout that was almost identical to the BMJ with which it was circulated), an extreme of size (8 pages of A4 in sturdy card was excessive for one advertisement); and extreme of cost (the cost of distributing this number of full-colour pages amongst the tens of thousands of BMJ readers would have been extremely high).

The complainant alleged that the words, 'Supported by an educational grant from Reckitt Benckiser' were not sufficiently prominent; they appeared only once and were written in a relatively small and light font. Furthermore, the complainant alleged that this statement did not accurately reflect the nature of the company's involvement in this supplement in breach of Clause 9.10.

The complainant noted that given the similarity of the layout, font and style of the supplement to the

BMJ, the words 'Advertising Feature' should have been printed prominently on every page in order to avoid misleading readers. The omission of the words 'Advertising Feature' constituted a disguise of promotional material in breach of Clause 12.1.

RESPONSE

Reckitt Benckiser submitted that it consulted the editorial committee of the BMJ before the supplement was distributed with the journal. This was specifically to ensure that the committee did not believe that the supplement could constitute any kind of advertising, that its readership would not be confused as to the origin of the supplement and that it did not breach the BMJ's own editorial standards. Reckitt Benckiser provided a copy of a letter from the BMJ which confirmed that the editors were satisfied that the supplement was suitable for distribution as an educational supplement. The BMJ stated that, if there had been any scope for confusion between the supplement and the journal, it would have refused to publish it. The BMJ applied the highest standards and most stringent criteria in order to protect its reputation.

With regard to the alleged breach of Clause 6.3 Reckitt Benckiser submitted that the meeting reported in the supplement took place in Leeds in May 2008. An agenda, list of participants and participant biographies were provided. The meeting was an advisory board of leading experts in the field of extra-oesophageal reflux and it was clear from the participant biographies that this was genuinely a multidisciplinary group of world class experts.

The meeting was facilitated and documented by a communications agency that specialised in consumer healthcare public relations campaigns and medical education programmes, and not by Reckitt Benckiser. The meeting objective was to gather evidence of the experiences of the participants in managing patients with extra-oesophageal reflux and to agree a treatment algorithm of best practice for the diagnosis and treatment of patients presenting with symptoms of extra-oesophageal reflux in primary care. The need for the meeting had been established by research which suggested that extra-oesophageal reflux as a disease area was not fully understood by health professionals and that successful treatment protocols were lacking. A summary of the research was provided.

Following the meeting the advisory group considered that an algorithm would be prescriptive in broader practice and that the publication of shared experiences via case studies would be of more educational value. The output of the meeting was therefore amended in line with this view. Reckitt Benckiser noted that all those who attended not only agreed the format of the output, an educational booklet with case studies, but could also view, edit and approve the output.

In essence, this was a recognised multidisciplinary meeting with an educational focus within the group but also with the primary purpose of educating health professionals about extra-oesophageal reflux by means of producing an educational booklet, reviewed and supported by leading experts in the form of an advisory board.

Reckitt Benckiser noted that the supplement was written by an independent, qualified medical writer, procured by the communications agency, not by Reckitt Benckiser. The Gaviscon Advance prescribing information was included for information because the product was mentioned rendering the piece promotional in nature, not because it was an advertisement.

Reckitt Benckiser strongly refuted the allegations that the meeting merely comprised some 'editorial' gathering or that the meeting report was merely disguised advertising. Consequently, the two page maximum page limit for journal advertising did not apply as stated in the supplementary information for Clause 6.3 and Reckitt Benckiser submitted that in its length the supplement did not breach the Code.

With regard to Clause 7.2, Reckitt Benckiser submitted that within the supplement Gaviscon Advance was mentioned in details of a clinical study and in a number of case reports. The reported findings of a study using Gaviscon Advance in patients suffering symptoms of laryngopharyngeal reflux was a genuine study report that had been published in a peer reviewed journal and could not therefore be considered to be biased of itself (McGlashan *et al* 2008). Nor could it be argued that there was a bias in not describing other products that could be taken for laryngopharyngeal reflux as no other products were currently licensed for that indication. Furthermore, proton pump inhibitors, which despite not being licensed for laryngopharyngeal reflux were commonly prescribed for it, had been reported to be no more effective than placebo in a recent meta analysis (Gatta *et al* 2007).

Reckitt Benckiser submitted that, in line with the discussion at the meeting, Gaviscon Advance was referred to in the case studies cited. The case studies were provided by the meeting participants who were independent health professionals. There was no encouragement or inducement by Reckitt Benckiser to include any named product in the case studies that they supplied.

With regard to Clause 9.7 Reckitt Benckiser submitted that the design of the supplement was not intended to mislead readers in any way into believing it to be part of the BMJ. Crucially the BMJ would not distribute material that it believed to be misleading in style or content. Indeed the complainant was clearly aware that the supplement was not part of the BMJ and was supported by Reckitt Benckiser. The BMJ understood its readership better than Reckitt Benckiser and so to

take advice from the journal itself in order to ensure the company did not mislead or create confusion amongst the journal's readership was sufficient.

Nevertheless, in response to the complainant's allegation of an extreme of style Reckitt Benckiser compared the print from the BMJ with that of the supplement and demonstrated that they were not the same in style, colour or layout.

The complainant's assertion of extremes of both size and cost were also unfounded. There was no restriction on the number of pages of an educational supplement even if it might be considered promotional material, indeed reports of some meetings ran to many more than eight pages. The supplement was produced to fit within the BMJ, being only A4 in size, which could not be considered extreme. To suggest that this was an extreme of cost because of the large circulation of the BMJ would be to suggest that supplements, advertorials and advertising could not be placed in any respected publication that had succeeded in attracting a large readership as this would be extreme, which was clearly unreasonable.

With regard to Clause 9.10 Reckitt Benckiser submitted that there was no attempt to disguise the support that it had provided. The sponsorship declaration only featured once, however there was no requirement for it to appear multiple times and it was quite unreasonable to suggest that the declaration was not sufficiently prominent. It was clearly noted on the front cover of the supplement which featured very little other text, making it clearly noticeable on a plain white background.

Reckitt Benckiser submitted that the company logo next to the sponsorship declaration drew the reader's eye and ensured due prominence; the logo was also featured on the back cover. Viewed from either side the company name was included on the supplement and therefore there was no attempt to hide the company's support. Furthermore, the BMJ had raised no concern with the prominence of the sponsorship statement, which it required to be included.

Reckitt Benckiser submitted that in terms of the wording of the declaration, the nature of the meeting, that it was facilitated by a third party and documented by an external medical writer, had been described and it had also been clarified that this supplement was not an advertisement. To this end it was thought quite reasonable to note in the declaration that the supplement had been supported by Reckitt Benckiser by way of an educational grant; again no attempt had been made to disguise the company's involvement.

Reckitt Benckiser noted the complainant's suggestion that the copy should have been marked 'Advertisement Feature'. Reckitt Benckiser submitted that this would not have been appropriate as this supplement was not an advertisement, but the report of a legitimate multidisciplinary educational meeting – facilitated by a third party – sponsored by Reckitt Benckiser.

In response to a request for further information, Reckitt Benckiser submitted that faculty members were chosen and invited by its communications agency; some based on their peer recommendations. They were invited based on the requirements for the project, which was to assemble a multidisciplinary advisory group of specialists within the specific fields considered relevant for the discussion and output. All contact with the faculty including arrangements for the meeting and subsequent interactions to coordinate the output from the meeting were carried out by the agency. Reckitt Benckiser had no influence in this decision.

Whilst some of the faculty members had had previous involvement with the communications agency on projects undertaken by Reckitt Benckiser, the company did not have an association with any of the chosen faculty members.

Each member of the faculty was paid an honoraria for their time commitment which included attending and contributing at the meeting and for review and comment on the output, as well as reimbursement of their travel expenses which had been paid on actual receipts submitted. All payments were made by the communications agency. Details of the honoraria paid to each faculty member were provided.

Reckitt Benckiser provided copies of invitations sent to two of the faculty members. These were based either on peer recommendation or directly from the agency. This was the standard format for all faculty members except two who Reckitt Benckiser understood had been contacted by telephone.

Reckitt Benckiser submitted that the idea for the supplement came from the faculty. Reckitt Benckiser had initially expected that there would have been discussions around the need to educate health professionals. The primary objective should have focused on an output of a treatment algorithm which captured how GPs could diagnose laryngopharyngeal reflux correctly and enabled a successful treatment pathway to be decided without unnecessary referrals. However, based on the discussion at the advisory board meeting, the faculty considered and decided that it was premature to suggest a treatment algorithm for this condition with primary care physicians, and hence a more educational output based on case studies (anonymous actual experiences of the faculty) would be more appropriate. This changed the whole scope of the meeting. The faculty's advice was wholly accepted by Reckitt Benckiser. This clearly demonstrated independence from the faculty which had made the necessary decision based on its clinical experience and judgement, rather than any requirement from Reckitt Benckiser or that of its communications agency.

Placement of the supplement in the BMJ was also

based on advice from the faculty, due to the need for widespread educational dissemination. The BMJ was contacted by Reckitt Benckiser's media agency.

Reckitt Benckiser did not provide any material for inclusion within the body of the educational supplement. The clinical evidence pertaining to Gaviscon Advance Aniseed Suspension and that of certain proton pump inhibitors (specifically omeprazole and esomeprazole) were independently discussed by experts within the group. Reckitt Benckiser only suggested that prescribing information should be included as its product was mentioned in the supplement.

The deadline for receipt of inserts at the printers was Thursday, 29 January, ie 9 days prior to publication on 7 February. Owing to the number of members involved at the meeting, all changes by the faculty members were incorporated and agreement reached at the end of November 2008. The deadline from the BMJ was established only following the review and agreement of the supplement by all members of the faculty.

Reckitt Benckiser, nor any of its agencies, had any editorial control over the output. Discussions with the BMJ on placement dates were carried out by the media agency, and post agreement of the faculty of the written output, it was artworked prior to placement with appropriate approval requirements by Reckitt Benckiser's regulatory and medical team and the BMJ.

Reckitt Benckiser submitted that a medical information scientist and a senior brand manager from the company attended the meeting as observers only; neither made any active contribution to the discussion.

Reckitt Benckiser explained that the communications agency was a medical education specialist agency whose services were procured by Reckitt Benckiser on an *ad hoc* basis, based on medical, educational and clinical advisory needs for its brands. Reckitt Benckiser's role was to provide the agency with a brief or objective of the requirements; subsequently the agency would propose detail of the activity, budget and timings which were then discussed and agreed with Reckitt Benckiser prior to the activity being implemented. Fees were paid on a project-by-project basis by Reckitt Benckiser.

The objective on this occasion was to construct a multidisciplinary advisory panel that would discuss current understanding with regards the characteristics and clinical management of extra-oesophageal reflux or laryngopharyngeal reflux. As a result of these discussions it was hoped that an educational output would be created for use in primary care and for patients suffering from this condition. This was based on research evidence that laryngopharyngeal reflux, whilst being a common condition was relatively poorly understood by GPs. Although its symptoms were recognised within primary care, it was common to refer these patients to ENT specialists, gastroenterologist or cough specialists.

It was considered that education of the disease area would be beneficial, as it could lead to more appropriate prescribing; a reduction of unnecessary referrals to ENT, gastro and specialist clinics, whilst gaining improved patient outcomes.

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 further noted that the term 'promotion' meant any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription, supply, sale or administration of its medicines. The Panel noted Reckitt Benckiser's submissions regarding the roles of third parties in the generation of the material at issue. In the Panel's view, however, each of those parties was acting on behalf of Reckitt Benckiser and so the company was responsible, under the Code, for their actions.

The Panel noted that, through its communications agency, Reckitt Benckiser had formed an advisory board to discuss the management of symptoms of extra oesophageal reflux. Invitations to the meeting clearly stated that they were being sent on behalf of Reckitt Benckiser. Recipients were told that the morning session would be based on discussions and brainstorming around the need to educate health professionals and consumers on the condition. The afternoon session would focus on producing a treatment algorithm to capture how GPs could diagnose the condition correctly and treat patients successfully without unnecessary referrals. Some of the faculty members had previously been involved in other projects undertaken by Reckitt Benckiser.

The agenda for the meeting showed that in the morning there was a twenty minute presentation entitled 'The Role of Alginates in Treating Patients with Extra-oesophageal Reflux' which was delivered by a former global research and development manager of Reckitt Benckiser. The Panel noted that the former employee was listed

as a meeting participant in the company's response and had received an honorarium; he was not, however, listed as one of the participating experts in the material at issue.

The Panel considered that Reckitt Benckiser was wholly responsible for the advisory board meeting and thus for any output from that meeting. There was no strictly arm's length arrangement. Reckitt Benckiser had acknowledged that reference to Gaviscon Advance had rendered the document at issue promotional in nature. The document contained three main sections: 'The Spectrum of Reflux Disease'; 'Differential Diagnoses of LPR [laryngopharyngeal reflux] and GORD [gastro-oesophageal reflux disease]' and 'Evidence for the role of an alginate reflux suppressant in the treatment of LPR'. The third section detailed two clinical studies which had assessed the efficacy of Gaviscon Advance and also gave three case histories of patients who had benefitted from such therapy. The Panel noted Reckitt Benckiser's submission that the artworked document had been approved by its regulatory and medical team.

The Panel considered that the material at issue was not a supplement 'Supported by an educational grant from Reckitt Benckiser' (as stated on the front cover) but an advertisement for Gaviscon Advance issued by Reckitt Benckiser. The Panel noted the supplementary information to Clause 6.3 referred to inserts that might be regarded as promotional material for example reports of conference proceedings not being subject to the restrictions of Clause 6.3. The Panel did not consider that this applied to the material before it given that the material was, in effect, produced by Reckitt Benckiser following its advisory board meeting and the company had editorial control. The supplementary information did not give detailed guidance on the distinction between an advertisement and promotional material. Taking all the circumstances into account, the Panel decided that the material was, in effect, an eight page advertisement for Gaviscon Advance. It thus exceeded the two page limit allowed in any issue of a journal and so a breach of Clause 6.3 of the Code was ruled.

The Panel considered that the declaration of sponsorship statement on the front cover ('Supported by an educational grant from Reckitt Benckiser') did not accurately reflect the nature of the company's involvement. A breach of Clause 9.10 was ruled.

The Panel did not consider that the format and style of the insert was such that it would be confused with that of the BMJ; the two were quite dissimilar. Nonetheless, the sponsorship statement 'Supported by an educational grant …' disguised the promotional nature of the material. The sub-heading on the front cover 'Perspectives from a consensus meeting …' added to the misleading impression of an independent educational supplement as it was not stated that the meeting was a Reckitt Benckiser advisory board. The Panel considered that the insert was disguised promotion and a breach of Clause 12.1 of the Code was ruled.

The Panel did not consider that the insert was extreme in either its format or size. It was the same size as the BMJ page size and the copy provided by Reckitt Benckiser was not on sturdy card as submitted by the complainant. No breach of Clause 9.7 was ruled.

The Panel noted that given its title, 'Reflux Disease – What Lies Beneath the Surface?', sub-heading 'Perspectives from a consensus meeting …' and list on the inside front cover of the faculty, the insert appeared to be an independent review of the therapy area. The introduction stated that the document would explain the difference between gastro-oesophageal reflux disease and laryngopharyngeal reflux and provide help to recognise their individual symptoms and advice on managing the two very different but related entities. There was, however, no advice on managing gastro-oesophageal reflux disease although detailed advice was given about the management of laryngopharyngeal reflux. The insert was promotional material for Gaviscon Advance. The Panel considered that the insert was misleading in this regard and a breach of Clause 7.2 was ruled.

The Panel considered that the generation of the insert demonstrated a lack of control and apparent poor knowledge of the requirements of the Code. The artworked document had been reviewed by regulatory and medical teams within Reckitt Benckiser. The Panel noted the company's comments about the role of its agents but considered that responsibility under the Code could not be delegated to third parties.

The Panel further considered that as a consequence of its rulings, the whole of the insert needed to comply with the Code. Clause 7, Information, Claims and Comparisons, was particularly relevant. The Panel had not been called upon to consider any particular claims made in the insert and its lack of comment did not mean that the content of the supplement was acceptable in that regard. The Panel requested that Reckitt Benckiser be advised of its concerns in this regard.

APPEAL BY THE COMPLAINANT

The complainant noted that he had not been told how much the advertisement cost. Without this information he assumed that an eight page advertisement in the BMJ cost an inordinately large amount of money, and therefore represented an extreme cost for promotional material. The complainant thus appealed the Panel's ruling of no breach of Clause 9.7.

COMMENTS FROM RECKIT BENKISER

Reckitt Benckiser submitted that it had paid £7,000 to distribute the supplement in the BMJ General Practice and BMJ Clinical Research editions. Standard rates for a double page spread advertisement in the BMJ Clinical Research edition cost £8,115 and in the BMJ General Practice edition cost £7,875. The total cost being £15,990.

Reckitt Benckiser submitted that the amount it had paid did not constitute an 'inordinately large amount of money' as stated by the complainant. In fact, it was much cheaper than standard double page spread advertising that would normally be paid for by advertisers in the BMJ. Double page spread advertising was common practice in the BMJ and in line with what readers, including the complainant, would normally see. Reckitt Benckiser disagreed with the complaint.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant was very surprised to learn that an eight page supplement cost less than a two page advertisement but if the Authority was satisfied that the company was being truthful then the complainant was happy to withdraw his appeal.

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With regard to the complainant's comments about withdrawal of his appeal both parties were advised that in accordance with Paragraph 15.1 of the Constitution and Procedure the appeal must go ahead as Reckitt Benckiser had already responded to the appeal.

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APPEAL BOARD RULING

The Appeal Board noted the company's submission that it had paid £7,000 to distribute the material in the BMJ. The Appeal Board did not consider that the material in question was extreme in terms of its size, format or cost. The Appeal Board upheld the Panel's ruling of no breach of Clause 9.7. The appeal was unsuccessful.

Complaint received **9 February 2009**

Case completed **23 April 2009**

CASE AUTH/2209/2/09

PFIZER v LEO PHARMA

Promotion of Innohep

Pfizer complained about Leo Pharma's promotion of Innohep (tinzaparin sodium, a low molecular weight heparin) for extended use in the treatment of venous thromboembolism in patients with cancer. The claims at issue were referenced to Hull *et al* (2006), a direct, three month clinical comparison of Innohep vs an oral anticoagulant in cancer patients with acute symptomatic proximal vein thrombosis. There were three items at issue: a leavepiece, a cancer guidelines review and a journal advertisement. Pfizer also marketed a low molecular weight heparin, Fragmin (dalteparin sodium).

Pfizer noted that in inter-company dialogue Leo had submitted that there was no upper limit placed on the duration of Innohep therapy. However, Section 4.2 of the summary of product characteristics (SPC) stated that, for the treatment of deep vein thrombosis and pulmonary embolus Innohep should be given 'for at least 6 days and until adequate oral anticoagulation is established'. In line with clinical practice this clearly indicated that patients started on Innohep and gradually switched to oral anticoagulation over a few days (ie they did not remain on Innohep). However, if there was no transition to an oral anticoagulant then Pfizer did not consider the wording of the SPC allowed extended use of Innohep for venous thromboembolism in cancer, and as such extended treatment would be outside the current marketing authorization. Similarly the Innohep patient information leaflet (PIL) did not include guidance for cancer patients on extended use in the treatment of venous thromboembolism.

Pfizer alleged that Innohep did not have a marketing authorization for extended use and thus any promotion of the product for extended use in cancer associated venous thromoboembolism was in breach of the Code. Additionally, Pfizer considered that such activity might have significant safety implications for patients by encouraging unlicensed use of Innohep, particularly as there was no guidance for either health professionals or patients on the extended use of Innohep in patients with cancer associated venous thromboembolism in either the SPC or the PIL.

The Panel noted that the journal advertisement was headed 'Innohep – long term efficacy in treatment of [pulmonary embolism] and [deep vein thrombosis] in cancer patients' and that one page of the leavepiece, headed 'Thrombosis and Cancer', referred to 'Long-term Innohep'. The leavepiece featured a graph adapted from Hull *et al* which showed the cumulative incidence of recurrent venous thromboembolism over 300 days in cancer patients treated either with low molecular weight heparin or iv heparin/warfarin. The document reviewing the evidence and guidelines in cancer patients detailed the results from Hull *et al* and referred to the three month treatment period. It was stated that long-term Innohep was more effective than warfarin for preventing recurrent venous thromoboembolism in patients with cancer in proximal venous thrombosis. The document also gave brief details of UK guidelines on oral anticoagulation and two US guidelines on the treatment of venous thromboembolic disease. In a summary of the recommendations it was stated that the minimum duration of treatment with low molecular weight heparin was 6 months in the UK for the treatment of deep vein thrombosis and pulmonary embolism in patients with cancer. The US guidelines suggested 3-6 months' therapy for the treatment of deep vein thrombosis. For the treatment of pulmonary embolism one US guideline suggested 6-12 months' therapy and the other stated 3-6 months' therapy.

The Innohep SPC stated that therapy should be given 'for at least 6 days and until adequate oral anticoagulation is established'. There was no minimum duration of therapy stated in the Fragmin SPC. Sections 4.4 of both SPCs referred to the increased risk of hyperkalaemia with duration of therapy and the need to monitor plasma potassium particularly if therapy was prolonged beyond about 7 days. Pfizer had stated that the Medicines and Healthcare products Regulatory Agency (MHRA) required a specific licence for the extended use of Fragmin, in cancer patients with venous thromboembolism. No details were provided.

The Panel noted that although the Innohep SPC referred to therapy continuing 'for at least 6 days' there was no upper time duration given. There was an acknowledgement that therapy might be 'prolonged beyond about 7 days'. The Panel considered that although long-term therapy was not specifically referred to in the Innohep SPC there was nothing to suggest that it should not be administered for periods of longer than 6 days when there was a failure to establish adequate oral anticoagulation. The Panel considered that the claims relating to extended use were not inconsistent with the particulars listed in the SPC as alleged and ruled no breach of the Code.

Upon appeal by Pfizer, the Appeal Board noted that the Innohep SPC stated that therapy should be given 'for a least six days and until adequate oral anticoagulation is established'. There was no

upper time limit for the duration of therapy stated. Innohep had been granted a licence before long-term therapy had been contemplated. In that regard the Appeal Board considered that the data relating to side-effects and safety in the SPC was limited to that obtained only from the envisaged short-term (five to seven days) use in patients after surgery or during haemodialysis – not from long-term use in cancer patients. The Appeal Board noted Pfizer's submission that its product was indicated for extended use in a number of markets including the US. The Appeal Board noted that although clinical practice and published guidelines might support the long-term use of low molecular weight heparins in cancer patients it considered that, given the basis upon which the licence for Innohep was granted, promotion of the product for long-tern use was not in accordance with the terms of its marketing authorization and thus inconsistent with the particulars listed in the Innohep SPC. A breach of the Code was ruled.

Pfizer Limited complained about the promotion of Innohep (tinzaparin sodium) by Leo Pharma. Innohep was a low molecular weight heparin for the treatment of deep vein thrombosis and pulmonary embolus. There were three items at issue: a leavepiece (ref 1030/10191), a cancer guidelines review (ref 1030/10186) and a journal advertisement (ref 1030/10216) which had appeared in a number of oncology/cancer journals and the hospital edition of the BMJ.

Pfizer marketed Fragmin (dalteparin sodium), a low molecular weight heparin for the treatment of venous thromboembolism presenting clinically as deep vein thrombosis, pulmonary embolus or both.

COMPLAINT

Pfizer complained about claims relating to the extended use of Innohep for the treatment of venous thromboembolism in patients with cancer. The claims were referenced to Hull *et al* (2006), a clinical comparison of the extended use of Innohep vs a vitamin-K antagonist (oral anticoagulant) in cancer patients with acute symptomatic proximal vein thrombosis. Patients were randomized to receive 3 months of either treatment option. The study was not designed nor had tested a transition between low molecular weight heparin followed by a vitamin-K antagonist, but it had tested the direct head-to-head efficacy of Innohep and vitamin-K antagonist.

In inter-company dialogue Leo had stated that Innohep was licensed for the 'Treatment of deep vein thrombosis and of pulmonary embolus', with posology stating that treatment could be given for at least 6 days [following diagnosis] and until adequate oral anticoagulation was established. Leo submitted that there was no upper limit placed on the duration of Innohep therapy.

Section 4.2 of the Innohep summary of product characteristics (SPC) stated that, for the treatment of deep vein thrombosis and pulmonary embolus Innohep should be administered '…for at least 6 days and until adequate oral anticoagulation is established'. In line with clinical practice this wording clearly indicated that patients started on Innohep and gradually switched to oral anticoagulation over a few days (ie they did not remain on Innohep). However, if there was no transition to oral anticoagulation treatment then Pfizer did not consider the wording of the Innohep SCP allowed extended use of the product for venous thromboembolism in cancer, and as such extended treatment would be outside the current marketing authorization. Similarly the Innohep patient information leaflet (PIL) did not include guidance for cancer patients on extended use in the treatment of venous thromboembolism.

In inter-company dialogue Pfizer had referred to its status with the Medicines and Healthcare products Regulatory Agency (MHRA) regarding a licence application for the extended use of Fragmin, based on the CLOT study (Lee *et al* 2003), in patients with cancer associated venous thromboembolism. Pfizer was in ongoing dialogue with the MHRA regarding its licence application.

Pfizer submitted that as the MHRA required a specific licence for the extended use of Fragmin in this patient group, then by the same analogy Innohep did not have a marketing authorization to allow promotion of extended use in this patient population. Pfizer thus alleged that any materials or activities that promoted the use of Innohep for extended use in cancer associated venous thromoboembolism were in breach of Clause 3.2 of the Code.

Additionally, Pfizer considered that this promotional activity might have significant safety implications for patients by encouraging unlicensed use of Innohep, particularly as there was no guidance for either health professionals or patients on the extended use of Innohep in patients with cancer associated venous thromboembolism in either the SPC or the PIL.

RESPONSE

Leo explained that cancer patients presented a number of unique challenges in the treatment of thromboembolism. Conventional treatment with warfarin was difficult in these patients because of the need to regularly monitor the anticoagulant effect, drug interactions, recurrent thrombosis, longer admission times and disruption of invasive interventions due to normalisation of the International Normalised Ratio (INR).

A retrospective review of the practical problems and resource implications of the use of warfarin in cancer patients with venous thromboembolism (n=55), reported that 24% (n=13) of patients with metastatic disease were changed from warfarin to

low molecular weight heparin (Morris *et al* 2007). Patients were switched due to: pulmonary embolism (n=2); propagation of deep vein thrombosis (n=2) and improved patient care by facilitating home based care thus minimising hospital visits and invasive blood tests (n=9). This study also reported that there were 382 days' ward visits attributable to warfarin monitoring, with 1,379 coagulation tests performed and 21 invasive interventions required disruption of anticoagulation, with potentially longer admissions and delays in procedure due to normalisation of the INR.

Hull *et al* was a multi-centre, randomized, open-label clinical trial of acute deep vein thrombosis therapy in cancer patients to compare once daily subcutaneous Innohep with usual care warfarin therapy for 3 months. There were statistically significantly more cases of recurrent venous thromboembolism in the warfarin group compared with the Innohep group.

The 3 month duration of therapy used by Hull *et al* was in line with the three major published guidelines for the treatment of acute deep vein thrombosis in cancer patients which stated that it should be given for either up to 6 months (British Committee for Standards in Haematology (BCSH) Guidelines 2005) or for 3-6 months (US National Comprehensive Cancer Network (NCCN) 2006 and American College of Chest Physicians (ACCP) Guidelines 2008).

In the UK BCSH Guidelines 2005, the recommendation for cancer was 'Warfarin is generally inferior to therapeutic low molecular weight heparin (LMWH) for treatment of [venous thromboembolism] in patients with cancer'.

Leo submitted that Innohep was licensed for the 'Treatment of deep vein thrombosis and of pulmonary embolus', with posology stating that treatment should be given for at least 6 days [following diagnosis] and until adequate oral anticoagulation was established. There was no upper limit on the duration of Innohep therapy. Therapy should be maintained for at least 6 days and until oral anticoagulation was established. However, if progression to oral anticoagulation was not the longer term therapy of choice then the duration of therapy should be supported by clinical evidence and further endorsed by clinical guidelines. In relation to the PIL wording on duration of use, the 'How to use' section stated 'You will have one dose of Innohep each day for at least 6 days'. This was fully aligned with the duration of therapy in question and with the product SPC.

With regard to Pfizer's submission that the MHRA required a specific licence for the use of Fragmin in this group, Leo understood that Pfizer's application was initiated and submitted proactively rather than in response to a specific request or requirement from MHRA.

In conclusion Leo submitted that clinical evidence and clinical guidelines suggested that in this treatment group, low molecular weight heparins (such as Innohep) should be continued for at least 3 months, in preference to oral anticoagulation, to optimise the efficacy and safety outcomes for cancer patients. No significant safety implications had been identified for Innohep used in this way. The Innohep SPC did not preclude use in this way as it allowed for continuation of therapy until oral anticoagulation was established. Leo therefore strongly asserted that its current promotion of Innohep in cancer patients with venous thromboembolism was within the terms of the Innohep marketing authorization and consequently that it was not in breach of Clause 3.2.

PANEL RULING

The Panel noted that the journal advertisement headline claim 'Innohep – long term efficacy in treatment of [pulmonary embolism] and [deep vein thrombosis] in cancer patients' was referenced to Hull *et al*. Page 8 of the leavepiece was headed 'Thrombosis and Cancer' and referred to 'Long-term Innohep'. The page featured a graph adapted from Hull *et al* which showed the cumulative incidence of recurrent venous thromboembolism over 300 days in cancer patients treated either with low molecular weight heparin or iv heparin/warfarin. The document reviewing the evidence and guidelines in cancer patients detailed the results from Hull *et al* and referred to the three month treatment period. It was stated that long-term Innohep was more effective than warfarin for preventing recurrent venous thromoboembolism in patients with cancer in proximal venous thrombosis. The document also gave brief details of the UK BCSH guidelines on oral anticoagulation and the US NCCN and ACCP guidelines on the treatment of venous thromboembolic disease. In a summary of the recommendations it was stated that the minimum duration of treatment with low molecular weight heparin was 6 months in the UK for the treatment of deep vein thrombosis and pulmonary embolism in patients with cancer. The US guidelines suggested 3-6 months' therapy for the treatment of deep vein thrombosis. For the treatment of pulmonary embolism the NCCH guidelines suggested 6-12 months' therapy and the ACCP guideline stated 3-6 months' therapy.

The Panel noted that Section 4.2 of the Innohep SPC, Posology and Method of Administration, stated that therapy should be given 'for at least 6 days and until adequate oral anticoagulation is established'. There was no minimum duration of therapy stated in the Fragmin SPC. Sections 4.4 of both SPCs referred to the increased risk of hyperkalaemia with duration of therapy and the need to monitor plasma potassium particularly if therapy was prolonged beyond about 7 days. Pfizer had stated that the MHRA required a specific licence for the extended use of its product,

Fragmin, in cancer patients with venous thromboembolism. No details were provided.

The Panel noted that although the Innohep SPC referred to therapy continuing 'for at least 6 days' there was no upper time duration given. There was an acknowledgement in Section 4.4 that therapy might be 'prolonged beyond about 7 days'. The Panel considered that although long-term therapy was not specifically referred to in the Innohep SPC there was nothing to suggest that it should not be administered for periods of longer than 6 days when there was a failure to establish adequate oral anticoagulation. The Panel considered that the claims relating to extended use were not inconsistent with the particulars listed in the SPC as alleged and ruled no breach of Clause 3.2.

APPEAL BY PFIZER

Pfizer noted that the Innohep SPC for the treatment of deep vein thrombosis and pulmonary embolus stated that treatment should be given for at least 6 days **and** until adequate oral anticoagulation was established. It did not state **or** until adequate oral anticoagulation was established.

Standard practice for treatment of deep vein thrombosis was to commence low molecular weight heparin and oral anticoagulation (most commonly warfarin) simultaneously because warfarin usually took 5-7 days to become therapeutic. Once warfarin became therapeutic the low molecular weight heparin was stopped.

Pfizer noted warfarin was a difficult medicine to use, particularly in cancer patients for all the reasons outlined above. This was the rationale for designing the 3 month Hull *et al* study (using Innohep as the heparin) and the 6 month CLOT study (Lee *et al*) (using Fragmin as the heparin). In both studies the comparator arm (or usual care) was short-term heparin which was stopped as soon as the oral anticoagulation became therapeutic. Both studies demonstrated a reduction in recurrence of thrombosis in the active arm and these data had been reflected in several haematology and oncology guidelines specifically for treatment in patients with cancer.

Nevertheless, Pfizer alleged that medicines could not be promoted simply because clinical data and guidelines supported an indication. The SPC must be updated with the new information to gain this indication. The Innohep SPC only allowed for treatment for at least 6 days and until adequate oral anticoagulation was established; a licence variation would be required in order to promote extended treatment with Innohep instead of using oral anticoagulation as per Hull *et al*.

Pfizer had proactively approached the MHRA to apply for a licence variation for Fragmin based on the 6 month data from the CLOT study. The application was in its final stages but throughout the process over many months the MHRA had indicated repeatedly that granting an extended use licence was not straightforward and was a significant departure from the standard practice of short-term use until effective oral anticoagulation was achieved. The application had required detailed risk benefit analysis of extended use and particular thinking had been required around risk minimisation for patients who were likely to self-inject over an extended period.

In summary, whilst Pfizer accepted there were robust data and clinical guidelines supporting the extended use of low molecular weight heparin in cancer associated deep vein thrombosis, it did not agree that Leo could promote this use based on its current SPC without applying for a licence variation. The key wording was the fact that the Innohep SPC stated that treatment should be given for at least 6 days **and** until adequate oral anticoagulation was established. It did not state **or** until adequate oral anticoagulation was established. The SPC wording clearly indicated the intention to transition to oral therapy. Where no such intention existed, as in Leo's promotional material, then this was outside the Innohep licence. For these reasons Pfizer repeated its allegation of a breach of Clause 3.2.

COMMENTS FROM LEO

Leo was pleased that Pfizer had accepted that there were robust data and clinical guidelines to support the continued use of low molecular weight heparins in preference to switching to treatment with warfarin in patients with cancer associated deep vein thrombosis.

Leo understood the difficulty that Pfizer had with the CLOT study (Lee *et al*). Although this study initiated treatment with the licensed dose of 200 IU/kg of Fragmin (dalteparin sodium), the dose was reduced to approximately 150 IU/kg after the first month. Such a step type treatment regimen was not within the SPC for Fragmin and thus the requirement for a licence variation would apply.

Leo submitted that it had only promoted Innohep for the treatment of venous thromboembolism using the approved treatment dose of 175 IU/kg which was the dose used in Hull *et al*. As the Panel noted, the Innohep SPC did not give an upper time limit for the duration of treatment if it was not followed by oral anticoagulation, thus treatment with a low molecular weight heparin for 3-6 months, as supported by the robust data and clinical guidelines agreed by Pfizer, was not inconsistent with the Innohep SPC. As the Panel also noted within Section 4.4 of the Innohep SPC, advice was given on management if treatment was extended beyond seven days.

Leo therefore submitted that its current promotion of Innohep in patients with cancer associated venous thromboembolism was within the terms of

the marketing authorization for Innohep and, consequently, it was not in breach of Clause 3.2.

FINAL COMMENTS FROM PFIZER

Pfizer alleged that the use of low molecular weight heparins for extended duration in oncology patients with venous thromboembolism was a completely new regimen for these medicines. Any variation in the recommended dosage of the medicine was only one aspect of the overall new regimen, and other important aspects which also needed to be considered included the duration of treatment and the types of patients receiving the medicines. The MHRA had clearly indicated to Pfizer that the duration of therapy and the patient population were crucial determinants of the risk benefit profile.

The Fragmin (Lee *et al*) and Innohep (Hull *et al*) clinical trials that evaluated the effectiveness of these medicines in an oncology population were designed as head-to-head trials comparing short-term low molecular weight heparins transitioning onto warfarin (usual care) vs extended use of low molecular weight heparins throughout the 3-6 month study duration. The latter was the alternative and a new regimen to the current product SPC, and therefore Pfizer proactively approached the MHRA to apply for a licence variation for Fragmin.

For the reasons mentioned above Pfizer alleged a breach of Clause 3.2.

APPEAL BOARD RULING

The Appeal Board noted that Section 4.2 of the Innohep SPC, Posology and Method of Administration, stated that therapy should be given 'for a least six days and until adequate oral anticoagulation is established'. There was no upper time limit for the duration of therapy stated. Leo's representatives at the appeal confirmed that Innohep had been granted a licence before long-term therapy in any patient group had been contemplated. In that regard the Appeal Board considered that the data relating to side-effects and safety in the SPC was limited to that obtained only from the envisaged short-term (five to seven days) use in patients after surgery or during haemodialysis – not from long-term use in cancer patients. The Appeal Board noted Pfizer's submission that its product was indicated for extended use in a number of markets including the US. The Appeal Board noted that although clinical practice and published guidelines might support the long-term use of low molecular weight heparins in cancer patients it considered that, given the basis upon which the licence for Innohep was granted, the promotion of Innohep for long-tern use was not in accordance with the terms of its marketing authorization and thus inconsistent with the particulars listed in the Innohep SPC. A breach of Clause 3.2 was ruled. The appeal was successful.

During its consideration of this case the Appeal Board noted that, regardless of the Innohep marketing authorization, the three month data (the primary outcome data from Hull *et al*) relied upon by Leo to substantiate its claims showed no statistically significant difference between Innohep and usual care (short-term low molecular weight heparin with a transition to warfarin therapy) with regard to bleeding complications during the three month treatment interval. Study medicines were discontinued at 12 weeks unless oral anticoagulation was indicated. At 12 month follow-up there was a statistically significant difference in recurrent venous thromboembolism between the two treatment groups in favour of Innohep (p=0.044). The Appeal Board requested that Leo be advised of its concerns.

Complaint received	**23 February 2009**
Case completed	**15 May 2009**

CASE AUTH/2212/3/09

TAKEDA v MERCK SHARP & DOHME

Promotion of Cozaar

Takeda complained about a Cozaar (losartan) advertisement issued by Merck Sharp & Dohme. The advertisement, *inter alia*, compared the antihypertensive efficacy of Cozaar (losartan) with other angiotensin II antagonists (AIIA) stating that 'Losartan is as effective as other leading AIIAs and gives 24-hour blood pressure control' referenced to a meta-analysis by Conlin *et al* (2000) and to Baguet *et al* (2007). Beneath the claim the weighted average reduction in diastolic blood pressure from 43 published, double-blind, randomised, controlled trials was given in a table for losartan (50-100mg), candesartan (8-16mg) (Takeda's product Amias), valsartan (80-160mg) and irbesartan (150-500mg).

Takeda was concerned about the presentation of data from Conlin *et al* and its use to substantiate the claim 'Losartan is as effective as other leading AIIAs …'.

Takeda alleged that readers were unable to understand the clinical relevance of the data presented as the dose ranges cited for the four AIIAs were not like for like. Readers were unable to draw appropriate and accurate conclusions from the information, or form their own opinion of the therapeutic value of each of the medicines. Takeda detailed what it considered were inconsistencies in the stated doses and noted that readers could not be expected to know the full range of licensed doses for every AIIA and which doses were comparable (eg which was the usual maintenance dose or maximum dose for each).

Further, Takeda alleged that Conlin *et al* was out-of-date and did not reflect the current balance of evidence or support the claim in question. Conlin *et al* only included pre October 1998 studies by which time there had only been 4 head to head studies of losartan vs the other AIIAs.

Since then there had been a further 10 studies comparing losartan with either irbesartan or valsartan and a further 11 head to head studies that compared the effects of candesartan with losartan in patients with essential hypertension. The largest of these, two identical head to head studies demonstrated a significant blood pressure reduction advantage for candesartan compared with losartan. These data were submitted to the regulatory authorities and reflected in the candesartan summary of product characteristics (SPC).

With regard to hierarchy of evidence when comparing two medicines, head to head, randomised, controlled trials were more robust and meaningful than indirect comparisons such as Conlin *et al*. Individual head to head, randomised, controlled trials were only superseded with respect to hierarchy of evidence by a systematic review of all head to head, randomised, controlled trials that compared two medicines.

Furthermore, Conlin *et al* used to substantiate the claim concluded that there was no difference between the AIIAs this was not the same as stating they were as effective which could only be demonstrated in a study specifically designed to assess equivalence. The claim 'Losartan is as effective as other leading AIIAs …' was also all embracing. Losartan was as effective as other AIIAs at doing what? There were many ways to demonstrate the antihypertensive efficacy of medicines eg clinic blood pressure (BP), 24 hour ambulatory BP, diastolic and/or systolic BP, peak BP lowering effect, trough BP lowering effect, pulse pressure.

Takeda's second concern was that the quotation from the Cochrane review which appeared beneath the table of data 'there are no clinically meaningful BP lowering differences between available [AIIAs]' was taken in isolation, out of context and did not reflect the entirety of the review. For example, Cochrane *et al* stated:

'For many of the drugs, there are insufficient data for a full range of doses. Therefore it remains possible that there could be differences between some of the drugs. However, the data are most consistent with the near maximum BP lowering effect of each of the drugs being the same. *It would require head-to-head trials of different [AIIAs] at equivalent BP lowering doses to assess whether or not there are differences in the BP lowering efficacy between different drugs.* This review provides useful dose-response information for estimating equivalent doses …' (emphasis added by Takeda).

Takeda submitted that, when available, head to head studies should be considered when determining the balance of evidence. There was sufficient head to head evidence between losartan and several of the other AIIAs (including candesartan) that demonstrated that losartan was not as effective at lowering blood pressure as these other AIIAs. The use of the quotation from the Cochrane review and the claim 'Losartan is as effective as other leading AIIAs …' was an inaccurate, unbalanced and misleading representation of the full evidence base.

The Panel noted that the claim 'Losartan is as effective as other leading AIIAs and gives 24-hour

blood pressure control' appeared above a table which compared the blood pressure lowering effects of losartan, candesartan, valsartan and irbesartan as adapted from Conlin *et al*.

Conlin *et al* was a meta-analysis which compared the antihypertensive efficacy of losartan, valsartan, irbesartan and candesartan by evaluating 43 randomised, controlled trials. These trials compared AIIAs with placebo, other antihypertensive classes and direct head to head comparisons. The study concluded that the analysis suggested that AIIAs lowered blood pressure with similar efficacy when administered at their usual recommended doses for the treatment of hypertension. The study authors noted that four of the 42 studies were head to head studies where losartan was compared with valsartan, irbesartan and candesartan; these contributed less than 20% of all the available evidence on blood pressure efficacy. The Panel noted that little detail about the statistical analysis appeared in the published paper.

The Panel noted Takeda's comments about meta-analysis but considered that they were an established and valid methodology, particularly in the absence of head to head trials. Nonetheless, 'Losartan is as effective as other leading AIIAs …' was an unequivocal claim and readers might expect the supporting data to include head to head studies rather than a meta-analysis. There was no information in the advertisement that told readers that Conlin *et al* was a meta-analysis and thus that the data published in the advertisement were indirect comparisons. The Panel further noted the conclusion of Conlin *et al* was that the data suggested the AIIAs had similar efficacy.

The Panel noted each party's submission about the doses presented in the advertisement. The Panel noted that according to the valsartan and candesartan SPCs the maximum antihypertensive doses were 320mg and 32mg once daily respectively. These doses did not feature in the advertisement. The Panel noted Merck Sharp & Dohme's submission that candesartan 32mg currently represented less than 5% of total candesartan volume prescribed in the UK. Merck Sharp & Dohme had not submitted what percentage of patients received the maximum dose of losartan, which was included in the Conlin *et al* meta-analysis. Conlin *et al* stated that some of the four published studies in which losartan had been compared directly with valsartan, irbesartan and candesartan had suggested differences in efficacy or responder rates but that the results of the present meta-analysis showed no difference in blood pressure efficacy or responder rates. Conlin *et al* concluded that 'This analysis suggests that AIIA lower blood pressure with similar efficacy when administered at their *usual recommended doses'* (emphasis added).

The Panel considered that the information about the source of the data, the tentative nature of the conclusion and about the doses of the AIIAs ie starting, usual maintenance, maximum etc was not sufficiently complete and the material was misleading in this regard. Breaches of the Code were ruled.

The Panel noted that Conlin *et al* assessed data published up to October 1998. The Panel noted both parties' submissions about subsequent publication of head to head data. The Panel noted Merck Sharp & Dohme's submission that the findings of Conlin *et al* had been confirmed by subsequent meta-analyses; Cochrane (2008) and Baguet *et al*. The Cochrane meta-analysis only included clinical trials comparing AIIAs with placebo. Patients could have co-morbid conditions whereas the patient population in Conlin *et al* could have no concomitant disease. The Panel noted that whilst presentation of data from Conlin *et al* must comply with the Code it did not consider on the evidence presented that publication of subsequent relevant data rendered Conlin *et al* out-of-date and thus misleading as alleged. No breach of the Code was ruled on this narrow point.

The Panel did not consider the claim 'Losartan is as effective as other leading AIIAs …' all embracing as alleged. In the context in which it appeared it was clear that the claim referred to the lowering of blood pressure. No breach of the Code was ruled on this point.

The Panel noted that the Cochrane analysis stated that the evidence suggested that there were no clinically meaningful differences between available AIIAs for lowering blood pressure. The study authors noted there was a similarity in BP lowering effects at trough. However for many of the medicines there was insufficient data for a full range of doses and thus it was possible that there could be differences between some of the medicines. It would require head to head trials of different AIIAs at equivalent BP lowering doses to assess whether there were differences in the BP lowering efficacy of different medicines. The study authors also noted that the review provided useful dose response information for estimating equivalent doses and thus designing trials to compare different AIIAs. The Panel considered that the claim 'A new independent Cochrane review suggests that 'there were no clinically meaningful BP lowering differences between available [AIIAs]' inferred that it had been proven that there were no clinically meaningful blood pressure lowering differences between available AIIAs which was not so. The use of the word 'suggests' was insufficient to negate such an inference which was misleading and not a fair reflection of the Cochrane review as alleged. A breach of the Code was ruled.

Upon appeal by Merck Sharp & Dohme the Appeal Board noted that the authors of the Cochrane analysis stated that 'The evidence from this review suggests that there are no clinically meaningful BP lowering differences between available [AIIAs]'.

The advertisement at issue, however, had only reproduced the second half of this statement as a quotation ie 'there are no clinically meaningful BP lowering differences between available [AIIAs]'. Although 'suggests' was included outside the quotation the Appeal Board considered that by not faithfully reproducing the authors' statement the quotation cited in the advertisement gave a more unequivocal overview of the Cochrane analysis than had been given by its authors.

The Appeal Board noted that the Code required claims, *inter alia*, to be based on an up-to-date evaluation of *all* the evidence and to reflect that evidence clearly. The Appeal Board recognised the value of meta-analysis but noted that only indirect comparisons of AIIAs were possible from the Cochrane analysis. Glenny *et al* (2005) had stated that when comparing competing interventions direct evidence from good quality, randomized, controlled trials should be used wherever possible. Without this evidence it might be necessary to look for indirect comparisons from randomized, controlled trials. The Appeal Board noted that there were some direct comparisons of the AIIAs and so in that regard it did not consider that the results of the Cochrane analysis could be viewed in isolation.

The Appeal Board noted that the Cochrane analysis had only included placebo controlled trials in which patients had been treated to target. In that regard the analysis had shown that all of the AIIAs were able to treat to target but beyond that it had not investigated any additional BP lowering efficacy. Conversely Bakris *et al* and Vidt *et al*, forced titrations of candesartan and losartan (Cozaar), showed that candesartan was more effective than losartan in lowering BP when both were administered once daily at maximum doses. Bakris *et al* reported that candesartan lowered mean sitting trough BP by 13.3/10.9mmHg compared with a mean reduction of 9.8/8.7mmHg by losartan at week 8 – a difference of 3.5/2.2mmHg. The difference between the two products with regard to mean sitting trough BP as reported by Vidt *et al* was 3.3/1.4mmHg.

The Appeal Board noted that small differences in BP lowering, such as reported by Bakris *et al* and Vidt *et al* could be clinically meaningful. In that regard the Appeal Board noted that a table of results in the Cochrane analysis showed similar differences between some of the AIIAs albeit by indirect comparison.

The Appeal Board considered the claim 'A new independent Cochrane review suggests that "there were no clinically meaningful BP lowering differences between available [AIIAs]"' inferred that it had been proven that there were no clinically meaningful blood pressure lowering differences between available AIIAs which was not so especially in light of the evidence from Bakris *et al* and Vidt *et al* which directly compared candesartan and losartan. The Appeal Board considered that the claim did not reflect the totality of the available evidence and it was misleading. The Appeal Board upheld the Panel's ruling of breaches of the Code. The appeal was unsuccessful.

Takeda UK Limited complained about an advertisement (ref 10-09 CZR.08.GB.10728.J) for Cozaar (losartan) issued by Merck Sharp & Dohme Limited which appeared in The Pharmaceutical Journal, 8 November. Inter-company dialogue had not resolved matters.

The advertisement was headed 'advertisement feature' followed by 'IMPORTANT: information that may impact PCT [primary care trust] finances'. The advertisement discussed the incidence of hypertension and that Cozaar would be the first angiotensin II antagonist (AIIA) to come off patent with an expected consequent price reduction and thus savings. The final section compared the antihypertensive efficacy of Cozaar with other AIIAs stating that 'Losartan is as effective as other leading AIIAs and gives 24-hour blood pressure control'. The claim that losartan was as effective as other leading AIIAs was referenced to a meta-analysis by Conlin *et al* (2000) and to Baguet *et al* (2007). Beneath the claim the weighted average reduction in diastolic blood pressure from 43 published, double-blind, randomised, controlled trials was given in a table for losartan (50-100mg), candesartan (8-16mg) (Takeda's product Amias), valsartan (80-160mg) and irbesartan (150-500mg*).

COMPLAINT

Takeda was concerned about the presentation of data from Conlin *et al* and its use to substantiate the claim 'Losartan is as effective as other leading AIIAs …'.

Takeda alleged that readers were unable to understand the clinical relevance of the information presented as the dose ranges included for the different AIIAs were not like for like. Unless this was made clear the readers were unable to draw appropriate and accurate conclusions from the information, or form their own opinion of the therapeutic value of each of the medicines. For example, the current licensed maximum doses for candesartan (32mg) and valsartan (320mg) were not included. The doses cited for losartan were the starting and usual maintenance dose (50mg) and maximum dose (100mg), whereas for candesartan and valsartan only the usual starting and maintenance doses were included. Readers could not be expected to know the full range of licensed doses for every AIIA and which doses were comparable (eg which was the usual maintenance dose or maximum dose for each). A breach of Clauses 7.2 and 7.3 was alleged.

Further, Takeda alleged that Conlin *et al* was out-of-date and did not reflect the current balance of evidence or support the claim 'Losartan is as

effective as other leading AIIAs …' and therefore there was a breach of Clauses 7.2 and 7.3.

Although published in 2000, Conlin *et al* only included studies that were published prior to October 1998. At the time, there had only been 4 head to head studies. Conlin *et al* stated:

'There have been four published studies in which losartan has been compared directly with valsartan, irbesartan and candesartan. Some of these trials have suggested differences in efficacy or responder rates between the agents tested. The results of the present meta-analysis show no difference in blood pressure efficacy or responder rates. Because these direct comparative studies contributed less than 20% of all available evidence on blood pressure efficacy, a meta-analysis of the sort provided in this paper might be regarded as a stronger basis for understanding the comparative efficacy of drugs in this class.'

When Conlin *et al* was published this might well have been correct. However, since October 1998 a significant number of head to head studies had compared the AIIAs, many of which had demonstrated differences in efficacy and therefore Takeda believed that the authors' assumption was no longer accurate. Specifically, there had been a further 10 studies comparing losartan with either irbesartan or valsartan and a further 11 head to head studies that compared the effects of candesartan with losartan in patients with essential hypertension (Takeda provided a list of candesartan vs losartan studies). The largest of these, two identical head to head studies comparing candesartan 32mg (the dose not included in Conlin *et al*) with losartan 100mg in 1,268 patients, demonstrated a significant reduction in trough systolic and diastolic blood pressure in favour of candesartan. These data were submitted to the regulatory authorities and included within the candesartan summary of product characteristics (SPC) 'The antihypertensive effect and tolerability of candesartan and losartan were compared in two randomised, double-blind studies in a total of 1,268 patients with mild to moderate hypertension. The trough blood pressure reduction (systolic/diastolic) was 13.1/10.5mmHg with candesartan cilexetil 32mg once daily and 10.0/8.7mmHg with losartan potassium 100mg once daily (difference in blood pressure reduction 3.1/1.8mmHg, $p<0.0001$).'

With regard to hierarchy of evidence when comparing two medicines, head to head, randomised, controlled trials were more robust and meaningful than an indirect comparison such as that used in Conlin *et al*. Individual head to head, randomised, controlled trials were only superseded with respect to hierarchy of evidence by a systematic review of all head to head, randomised, controlled trials that compared two medicines.

Furthermore, Conlin *et al* was used to substantiate the claim 'Losartan is as effective as other leading AIIAs …'. The analysis conducted by Conlin *et al* concluded that there was no difference between the AIIAs. This was not the same as stating they were as effective. This could only be demonstrated in a study specifically designed to assess equivalence. The claim 'Losartan is as effective as other leading AIIAs …' was also all embracing. Losartan was as effective as other AIIAs at doing what? There were many measurements that could be used to assess the antihypertensive efficacy of medicines eg clinic blood pressure (BP), 24 hour ambulatory BP, diastolic and/or systolic BP, peak BP lowering effect, trough BP lowering effect, pulse pressure.

Takeda stated its second concern was that the quotation from the Cochrane review which appeared beneath the table of data 'there are no clinically meaningful BP lowering differences between available [AIIAs]' was taken in isolation, out of context and did not reflect the entirety of the review. For example, the first section within the discussion section of the Cochrane Review was entitled 'Is there a difference in magnitude of BP lowering effect between individual drugs in the [AIIA] class?'. This section stated:

'For many of the drugs, there are insufficient data for a full range of doses. Therefore it remains possible that there could be differences between some of the drugs. However, the data are most consistent with the near maximum BP lowering effect of each of the drugs being the same. **It would require head-to-head trials of different [AIIAs] at equivalent BP lowering doses to assess whether or not there are differences in the BP lowering efficacy between different drugs.** This review provides useful dose-response information for estimating equivalent doses …' (emphasis added by Takeda).

Therefore, as discussed above when available, head to head studies between losartan and other AIIAs should be considered when determining the balance of evidence. Takeda believed that there was sufficient head to head evidence between losartan and several of the other AIIAs (including candesartan) that demonstrated that losartan was not as effective at lowering blood pressure as these other AIIAs. Takeda therefore believed that the use of the quotation from the Cochrane review and the claim 'Losartan is as effective as other leading AIIAs …' was an inaccurate, unbalanced and misleading representation of the full evidence base in breach of Clauses 7.2 and 7.3.

RESPONSE

Merck Sharp & Dohme noted that throughout inter-company dialogue and in the complaint Takeda had opposed Merck Sharp & Dohme's use of meta-analyses of randomised controlled trials to support claims of equivalence between AIIAs. In this context, Takeda had stated repeatedly that the company's use of meta-analysis data was inappropriate or outdated. This was not so.

Merck Sharp & Dohme considered that meta-analyses had a valid role in supporting promotional activities:

- They could compare large numbers of patients in a manner that head to head clinical trials could not.
- They provided an overview of all available data within the selection criteria (including unpublished data where available, thereby avoiding publication bias).
- Meta-analysis of the phase III data that formed part of a marketing authorization file often provided the best or only opportunity to generate 'placebo corrected' data, since placebo arms were rarely included in post-launch comparative studies.
- They were the preferred method of comparing products for medicines management groups, NHS pharmaceutical advisors and other key healthcare decision makers. In this instance, the use of such data to support a promotional item was particularly appropriate in that readers of The Pharmaceutical Journal included many in this group.

As Takeda had described it, the hierarchy of evidence ranked systemic reviews and meta-analysis as the highest levels of evidence. The National Institute for health and Clinical Excellence (NICE) ranked meta-analysis data as Class 1, ie a highest level of evidence. The European Medicines Evaluation Agency (EMEA) praised meta-analysis as a method of summarizing efficacy results and analysing less frequent safety issues.

The Authority had reviewed several complaints during the last year that had included consideration of promotional activities based on the results of meta-analyses, including two against the complainant. In each of these the Authority had not objected to the general principle of the use of such data to support claims; however, some complaints had been upheld where such data had been used inappropriately.

Conlin *et al* meta-analysis

Merck Sharp & Dohme had used Conlin *et al* in Cozaar promotional material for approximately 8 years. Takeda had not complained to the PMCPA about its use before.

Merck Sharp & Dohme explained that previous inter-company dialogue with Takeda about Merck Sharp & Dohme's use of Conlin *et al* had reached agreement. Merck Sharp & Dohme provided details including the agreement to an amended claim that Merck Sharp & Dohme could use in association with Conlin *et al*. The wording agreed with Takeda then was identical to that used in the item now at issue.

Takeda objected to Merck Sharp & Dohme's use of Conlin *et al*. In its opinion Merck Sharp & Dohme should not use Conlin *et al* to support a claim that 'Losartan is as effective as other leading AIIAs …' (in the context of BP lowering) on three grounds that. Merck Sharp & Dohme responded to these points in order:

1 The doses used in the study were not the full dose ranges for all of the comparators

Merck Sharp & Dohme agreed that not all currently available doses of all the current AIIAs were included in Conlin *et al*. This did not affect the company's ability to use the study in promotional material and the company believed that the PMCPA's findings in Merck Sharp & Dohme's recent complaint against Takeda supported this. Although Conlin *et al* did not include the 32mg dose of candesartan (which was not a licensed dose at the time of the analysis), subsequent meta-analyses, including the largest and most recent Cochrane review, had included it and come to the same conclusion. The more recent reports did not alter the validity, accuracy or context in which Conlin *et al* was used. In any case, the use of candesartan 32mg in the UK currently represented less than 5% of total candesartan volume prescribed in the UK (IMS UK BPI data, Jan 2009), and its clinical relevance was therefore limited.

Merck Sharp & Dohme submitted that the material had been transparent on the subject of the doses used in the meta-analysis; these were printed in full in the table describing results. Health professionals knew they should consult the relevant SPC before treating. In this context, sufficient information was provided for readers of The Pharmaceutical Journal to make up their minds about whether the claim was appropriate on the grounds of doses studied.

2 The study was out-of-date having been superseded by a number of head to head efficacy studies

To support its second point, Takeda stated it had supplied 11 head to head studies demonstrating superiority for candesartan over losartan in the management of hypertension whereas 12 references had been provided. Many of these studies were small; they frequently failed to reach statistical significance for all blood pressure variables (systolic and diastolic), and some were designed to assess endpoints other than blood pressure. Merck Sharp & Dohme did not believe that these invalidated the meta-analyses of 46 randomised, controlled trials in the Cochrane review (13,451 patients) or the 43 trials in Conlin *et al* (11,281 patients), or the claims it had based upon them.

The findings of Conlin *et al* had been confirmed by, and were in line with, subsequent meta-analyses (Cochrane (2008) and Baguet *et al*). The authors' findings remained valid and hence Merck Sharp & Dohme's continued use of this report in supporting promotional activities remained appropriate.

3 The study concluded that there was no difference between the AIIAs reviewed

Takeda had objected to the use of the phrase 'as effective as other leading AIIAs …' to describe the findings of a study which found no difference between the four comparators studied. This exact wording had been agreed during inter-company dialogue in November 2007; Merck Sharp & Dohme believed that the complaint was therefore inappropriate (having been the subject of agreement at inter-company dialogue) and meaningless. The meta-analyses found no meaningful difference in the BP lowering effectiveness of the four leading AIIAs. 'As effective as ….' seemed synonymous with that finding.

To summarise, whilst Merck Sharp & Dohme agreed that there might be times when it was not appropriate to use older scientific publications to support promotional activities, it believed it was permissible to do so where it could be shown to remain valid, for example where more recent publications continued to support the original conclusions. Merck Sharp & Dohme believed this to be true in its use of Conlin *et al*.

Cochrane Review

Takeda's complaint stated that Merck Sharp & Dohme had quoted the report in a manner that was out of context, and not reflective of the entirety of the review and noted that the review suggested that further studies were required to further evaluate the differences in efficacy.

Many of the points at issue had been covered above. Merck Sharp & Dohme remained unclear as to what Takeda's objection was to using the Cochrane Review in the way it had and to which area of the Code the alleged breaches referred.

The Cochrane Collaboration was acknowledged as the leading source of quality meta-analyses and its reports were used by regulatory authorities and medicines management groups, including NICE and the Scottish Intercollegiate Guidelines Network (SIGN), throughout the UK and the rest of the world. The Collaboration's review of AIIAs corroborated Conlin *et al* and added even more studies to the pool of patients reviewed by meta-analysis with the conclusion that there were no significant differences between the medicines in this class.

Takeda had complained that the report had been quoted out of context and in a way that did not reflect the entirety of the review.

The principal finding from the 2008 Cochrane review was crystal clear that 'The evidence from this review suggests that there are no clinically meaningful BP lowering differences between available [AIIAs].'

Takeda's contention that meta-analysis was an invalid support for promotional activities once head to head, randomised, clinical trials were available was flawed. Merck Sharp & Dohme had already pointed out to Takeda in inter-company dialogue the largest study comparing candesartan and losartan included 332 and 322 patients respectively. The equivalent figures in the Cochrane Review were 762 and 2,134.

Merck Sharp & Dohme therefore did not agree that its use of the Cochrane Review was in breach of the Code. The conclusions supported a claim that 'Losartan is as effective as other leading AIIAs …' and Merck Sharp & Dohme considered that this type of review was an entirely valid comparison.

* * * * *

The Director noted Merck Sharp & Dohme's submission that the wording agreed with Takeda in inter-company dialogue 'Losartan is as effective as other leading AIIAs …' was identical to that used in the material at issue. The Director noted that agreement had been reached during inter-company dialogue in relation to an allegation and similar claim neither of which were at issue in the present case. The complaint was thus referred to the Panel for consideration.

PANEL RULING

The Panel noted that the claim 'Losartan is as effective as other leading AIIAs and gives 24-hour blood pressure control' appeared above a table which compared the weighted average reduction in diastolic blood pressure from 43 published double-blind, randomised, controlled trials of losartan (-10mmHg, 50-100mg, n=2,217) candesartan (-9.5mmHg, 8-16mg, n=593), valsartan (-9.6mmHg, 80-160mg, n=855) and irbesartan (-10.4mmHg, 150-500mg, n=610). The data was stated to be adapted from Conlin *et al*.

Conlin *et al* was a meta-analysis which compared the antihypertensive efficacy of losartan, valsartan, irbesartan and candesartan by evaluating 43 randomised, controlled trials. These trials compared AIIAs with placebo, other antihypertensive classes and direct head to head comparisons. The study concluded that the analysis suggested that AIIAs lowered blood pressure with similar efficacy when administered at their usual recommended doses for the treatment of hypertension. The study authors noted that four of the 42 studies were head to head studies where losartan was compared with valsartan, irbesartan and candesartan; these contributed less than 20% of all the available evidence on blood pressure efficacy. The Panel noted that little detail about the statistical analysis appeared in the published paper.

The Panel noted Takeda's comments about meta-analysis but considered that they were an established and valid methodology, particularly in the absence of head to head trials. Nonetheless,

'Losartan is as effective as other leading AIIAs …' was an unequivocal claim and readers might expect the supporting data to include head to head studies rather than a meta-analysis. There was no information in the advertisement that told readers that Conlin *et al* was a meta-analysis and thus that the data published in the advertisement were indirect comparisons. The Panel further noted the conclusion of Conlin *et al* was that the data *suggested* the AIIAs had similar efficacy.

The Panel noted each party's submission about the doses presented in the advertisement. The Panel noted that according to the valsartan and candesartan SPCs the maximum doses for treatment of hypertension were 320mg and 32mg once daily respectively. These doses did not feature in the advertisement. The Panel noted Merck Sharp & Dohme's submission that candesartan 32mg currently represented less than 5% of total candesartan volume prescribed in the UK. Merck Sharp & Dohme had not submitted what percentage of patients received the maximum dose of losartan, which was included in the Conlin *et al* meta-analysis. Conlin *et al* stated that some of the four published studies in which losartan had been compared directly with valsartan, irbesartan and candesartan had suggested differences in efficacy or responder rates but that the results of the present meta-analysis showed no difference in blood pressure efficacy or responder rates. Conlin *et al* concluded that 'This analysis **suggests** that AIIA lower blood pressure with similar efficacy when administered at their **usual recommended doses**' (emphasis added).

The Panel considered that the information about the source of the data, the tentative nature of the conclusion and about the doses of the AIIAs ie starting, usual maintenance, maximum etc was not sufficiently complete and the material was misleading in this regard. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that Clause 7.2 required, *inter alia*, that claims had to be based on an up-to-date evaluation of all the evidence. Conlin *et al* assessed data published up to October 1998. The Panel noted both parties' submissions about subsequent publication of head to head data. The Panel noted Merck Sharp & Dohme's submission that the findings of Conlin *et al* had been confirmed by subsequent meta-analyses; Cochrane (2008) and Baguet *et al*. The Cochrane meta-analysis only included clinical trials comparing AIIAs with placebo. Patients could have co-morbid conditions whereas the patient population in Conlin *et al* could have no concomitant disease. The Panel noted that whilst presentation of data from Conlin *et al* must comply with the Code it did not consider on the evidence presented that publication of subsequent relevant data rendered Conlin *et al* out-of-date and thus misleading as alleged. No breach of Clauses 7.2 or 7.3 was ruled on this narrow point.

The Panel did not consider the claim 'Losartan is as effective as other leading AIIAs …' all embracing as alleged. In the context in which it appeared it was clear that the claim referred to the lowering of blood pressure. No breach of Clauses 7.2 and 7.3 was ruled on this point.

The Panel noted that the Cochrane analysis stated that the evidence suggested that there were no clinically meaningful differences between available AIIAs for lowering blood pressure. The study authors noted there was a similarity in BP lowering effects at trough. However for many of the medicines there was insufficient data for a full range of doses and thus it was possible that there could be differences between some of the medicines. It would require head to head trials of different AIIAs at equivalent BP lowering doses to assess whether there were differences in the BP lowering efficacy of different medicines. The study authors also noted that the review provided useful dose response information for estimating equivalent doses and thus designing trials to compare different AIIAs. The Panel considered that the claim 'A new independent Cochrane review suggests that 'there were no clinically meaningful BP lowering differences between available [AIIAs] 'inferred that it had been proven that there were no clinically meaningful blood pressure lowering differences between available AIIAs which was not so. The use of the word 'suggests' was insufficient to negate such an inference which was misleading and not a fair reflection of the Cochrane review as alleged. A breach of Clauses 7.2 and 7.3 was ruled.

During the consideration of this case the Panel noted Merck Sharp & Dohme's submission that sufficient information was provided such that readers could make up their minds about whether the claim was appropriate on the grounds of the doses studied. In the Panel's view this was unacceptable. Companies must always ensure that claims made for their medicines were appropriate. The Panel requested that Merck Sharp & Dohme be advised of its views in this regard.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme noted that this complaint was about how its journal advertisement had reported the Cochrane review of medicines in Cozaar's therapeutic class (AIIAs). The review analysed the results of 42 randomised, controlled clinical trials of seven AIIAs. The objective of the review was to quantify the dose-related systolic and/or diastolic BP lowering efficacy of AIIAs vs placebo in the treatment of primary hypertension.

Merck Sharp & Dohme submitted that in most therapy areas, relative efficacy was difficult to assess because of the number of head to head clinical studies, many performed in small numbers of subjects, some of which would show differences between comparators going either way, some of which would not. Meta-analysis was a valid tool for providing valid comparisons of therapeutic

outcomes. The Cochrane Collaboration was globally acknowledged by clinicians and medicines management groups for producing the highest quality of meta-analysis available to prescribing decision-makers. The claim 'A new independent Cochrane review suggests that there are no clinically meaningful BP lowering differences between available [AIIAs] appeared in the advertisement at issue. As would be discussed later, what might not have been made evident to the Panel in its ruling was that the advertisement tracked the phraseology used in the review, including use of the word 'suggests'.

Takeda had referred to a particular quotation from the review's discussion section, but only used the second half of one paragraph in isolation. It would probably be appropriate to put the authors' opinions into context by quoting the entire paragraph: 'This review provides a reasonable amount of data to assess the trough BP lowering effect of 9 different [AIIAs]. When the different [AIIAs] are compared, there is a similarity in their BP lowering effects at trough. When the best estimate of the near maximal BP lowering efficacy of these 9 drugs is compared, they range from -6/-3 mm Hg to -10/-7 mm Hg. For many of the drugs, there are insufficient data for a full range of doses. Therefore it remains possible that there could be differences between some of the drugs. However, the data are most consistent with the near maximum BP lowering effect of each of the drugs being the same. It would require head-to-head trials of different [AIIAs] at equivalent BP lowering doses to assess whether or not there are differences in the BP lowering efficacy between different drugs. This review provides useful dose-response information for estimating equivalent doses and thus designing trials to compare different [AIIAs]'.

Merck Sharp & Dohme noted that this was the only instance in the report where comments were expressed by the authors that the review might not represent a comprehensive assessment of relative efficacy and the only mention of a need to perform head to head comparative studies.

Merck Sharp & Dohme submitted that on checking the full report for the authors' claim above that 'For many of the drugs, there are insufficient data for a full range of doses', it appeared that the following factors had influenced their concerns on this matter:

- Eprosartan had no reports relating to efficacy at the highest recommended daily dose, 800mg, although data were provided on unlicensed higher doses. Because of this the report concluded that 'the true near maximal BP lowering efficacy of eprosartan cannot be estimated'.

- Olmesartan, in the authors' opinion, had insufficient published data at doses above 20mg/day. Although data did exist, they concluded once again 'that the true near maximal BP lowering efficacy cannot be estimated'.

Merck Sharp & Dohme concluded was that the authors' comments about insufficient data across all licensed dose ranges of all AIIAs represented a, perhaps arguable, concern about insufficient data at the upper dose range only in just two of the seven AIIAs reviewed.

Elsewhere there were at least six references to equivalence in efficacy of the various AIIAs in controlling hypertension. These included the following sections of the review and the relevant quotation:

- Study abstract: main results. 'The data do not suggest that any one [AIIAs] is better or worse at lowering BP'
- Study abstract: authors' conclusions. 'The evidence from this review suggests that there are no clinically meaningful BP lowering differences between available [AIIAs]
- Full report: plain language summary. 'No [AIIA] appears to be any better or worse than others in terms of blood pressure lowering ability'.
- Discussion: 'is there a difference in the magnitude of BP lowering effect between individual drugs in the [AIIA] class? When the different [AIIAs] are compared, there is a similarity in their BP lowering effects at trough'
- Authors' conclusions, implications for practice: specific findings (1). 'The data do not suggest that any one [AIIA] is better or worse than any other at lowering blood pressure when used at maximal recommended doses'
- Authors' conclusions, implications of these findings. See below.

The last of these, in authors' conclusions: implications of these findings included the most emphatic statement on how the review could best be interpreted: 'This systematic review provides the best available published evidence about the dose-related blood pressure lowering efficacy of [AIIAs] for the treatment of primary hypertension. These findings have the potential to change prescribing behaviour and drug funding policies around the world. The evidence from this review suggests that there are no clinically meaningful differences between available [AIIAs] for lowering blood pressure. Thus, substantial cost savings can be achieved by prescribing the least expensive [AIIA].'

Merck Sharp & Dohme submitted that these last comments, despite the use of the word 'suggests' but importantly included under a heading 'implication of these findings', put the authors' commitment to the review's findings into the context of a firm conclusion which was reflected in the advertisement in question.

The authors had listed the main reasons why they believed their review might not constitute a comprehensive review of class efficacy. These were covered in a specific section and included:

- **Publication bias.** The authors considered that there was selection of reports for publication with

a potential bias towards more favourable results. This was based on analysis of result scatter, a belief that much of the data used to support licensing was unpublished and lack of public domain data to support some dose schedules licensed in some countries.

- **Selection bias**. A common exclusion criterion in the studies reviewed was hypersensitivity to ACE-inhibitors. The authors believed this could indicate investigators having sufficient knowledge of the patients' treatment history to provide an opportunity to select patients more amenable to treatment.

- **Other sources**. The authors criticized the reports for generally providing insufficient information to reassure the reader that the methods used for randomizing patients and blinding subjects and/or treatments were adequate to eliminate selection or observer bias.

Merck Sharp & Dohme submitted that it was important to note that the authors' general conclusion in this section was that, although these factors might have resulted in an overall increase in apparent efficacy for the AIIA class, they were unlikely to have favoured any one agent within the class or invalidated the conclusion that the AIIAs had similar efficacy.

Merck Sharp & Dohme submitted that in pursuing this complaint against it, Takeda had only focussed on half of one paragraph in a 103 page document.

Merck Sharp & Dohme hoped that by noting all the points made by the Cochrane Collaboration authors, including the strength of their conclusions despite recognising potential bias, Merck Sharp & Dohme had provided context and reassurance that the claims made in relation to this meta-analysis were appropriate. The advertisement tracked the phraseology used in the review, including use of the word 'suggests'. In addition, it made clear that the comment was made in the context of that specific paper. Merck Sharp & Dohme submitted that the advertisement fairly represented the authors' conclusions from what was a robust and generally well respected report.

Merck Sharp & Dohme submitted that the Cochrane Collaboration made much of its independent status and scientific approach. Caveats referring to a need for further studies were not unusual in academic environments such as theirs. Three sentences in a 103 page report warning that further studies might be required needed to be put into context alongside five fairly unequivocal statements supporting a balanced final conclusion suggesting no meaningful differences within a class of medicine. Under the circumstances, Merck Sharp & Dohme submitted that it did not seem unreasonable to use the statement in a journal advertisement without fear of misleading readers.

For the reasons listed above, Merck Sharp & Dohme submitted that the use of this claim represented a measured, balanced, accurate and up-to-date assessment of the situation which did not mislead and was a fair reflection of the review's findings.

Merck Sharp & Dohme therefore disagreed that this aspect of the advertisement was in breach of Clauses 7.2 or 7.3 of the Code.

COMMENTS FROM TAKEDA

Takeda noted that the basis of its complaint which was upheld by the Panel in relation to the Cochrane review was two-fold:

Firstly, Takeda alleged that the claim in the advertisement relating to the Cochrane review, 'there are no clinically meaningful BP lowering differences between available [AIIAs]', was taken in isolation, out of context and did not reflect the entirety of the review.

Secondly, Takeda alleged that due to the availability of head to head studies comparing losartan with candesartan the use of the quotation relating to the Cochrane review (together with the other claim 'Losartan is as effective as other leading AIIAs') was an inaccurate, unbalanced and misleading representation of the full evidence base.

Takeda therefore alleged that the use of the claim 'A new independent Cochrane review suggests that "there are no clinically meaningful BP lowering differences between available [AIIAs]"' was in breach of Clauses 7.2 and 7.3.

As detailed by Merck Sharp & Dohme, the objective of the review was to quantify the dose-related systolic and/or diastolic BP lowering efficacy of the AIIAs vs placebo in the treatment of primary hypertension. It was not to formally assess whether differences existed between the AIIAs. The quotation used by Merck Sharp and Dohme; 'there are no clinically meaningful BP lowering differences between available [AIIAs], did not accurately reflect the objective of the review nor did it make it clear that the Cochrane review was an indirect meta-analysis which used placebo as the common comparator. When taken at face value with no further information on the methodology used in the Cochrane review, the reader could incorrectly conclude that the Cochrane Review was a direct comparison of the different AIIAs. Even if the results of the analysis were quoted accurately, it could still be misleading to use them promotionally without making the limitations of the analysis clear. This indirect analysis specifically excluded the direct head to head evidence available. By using it in isolation, Merck Sharp & Dohme had deliberately ignored the wealth of robust head to head data that existed. The authors were entitled to draw conclusions on their analysis alone. Merck Sharp & Dohme, however, not only had a responsibility to ensure that any promotional claims accurately reflected the paper being quoted, but also that it

accurately reflected the balance of evidence.

Takeda agreed with Merck Sharp & Dohme that when direct head to head clinical studies were not available, an indirect meta-analysis could be a valuable tool to help clinicians make prescribing decisions. However, when well conducted head to head randomised trials were available then this provided the most robust evidence. This was clearly the position of the Cochrane Collaboration and leading experts in the field. A recent article by the Cochrane Collaboration (Song *et al* 2009a,) assessed the validity of indirect meta-analysis and stated: 'Well designed randomised controlled trials (RCTs) generally provide the most valid evidence of relative efficacy of competing interventions, in which the possibility of selection bias is minimised (Kunz 2007). However, many competing interventions have not been compared directly (head-to-head) in RCTs. Even when different interventions have been directly compared in RCTs such direct evidence is often limited and insufficient. Lack of evidence from direct comparison between active interventions makes it difficult for clinicians to choose the most effective treatment for patients.'

The same authors had also published on the specific merits of head to head RCTs compared to indirect meta-analysis (Glenny *et al*, 2005). The introduction stated 'Well-designed randomised controlled trials (RCTs) generally provide the most reliable evidence of effectiveness as observed differences between the trial arms can, in general, be confidently attributed to differences in the treatment(s) being evaluated. However, in many areas, available trials may not have directly compared the specific treatments or regimens of interest. A common example is where there is a class of several drugs, each of which has been studied in placebo-controlled RCTs, but there are no trials (or very few) in which the drugs have been directly compared with each other'. The authors discussed this issue further in a recent publication on the methodological problems of using indirect comparisons for evaluating healthcare interventions published in the BMJ (Song *et al* 2009b).

Takeda alleged that the authors of the Cochrane Review on AIIAs were clear to reinforce that the findings of their indirect meta-analysis were not definitive and that; 'It would require head-to-head trials of different [AIIAs] at equivalent BP lowering doses to assess whether or not there are differences in the BP lowering efficacy between different drugs.'

As previously detailed Takeda noted that there were several well-conducted head to head randomised controlled trials involving over 3,000 patients directly comparing losartan with candesartan. The balance of this evidence was that losartan was not as effective as candesartan in lowering blood pressure. For example, the largest of these was the CLAIM study (Bakris *et al* 2001, Vidt *et al* 2001) programme which, as stated in the Amias SPC, compared the antihypertensive effect and tolerability of candesartan and losartan (both at their maximum licensed dose) in two identical randomised, double-blind studies in a total of 1,268 patients with mild to moderate hypertension. The trough blood pressure reduction was 13.1/10.5mmHg with candesartan and 10.0/8.7mmHg with losartan (difference of 3.1/1.8mmHg; $p<0.0001/p<0.0001$).

Takeda noted that the Cochrane review only included placebo-controlled studies which were usually conducted early in the development of a product and primarily for the purposes of registration. Subsequently, head to head studies directly comparing one medicine with another were then conducted. If an indirect meta-analysis of placebo controlled trials were the 'gold standard' for comparing one medicine with another then it would negate the need for head to head RCTs to be conducted

Takeda alleged that Merck Sharp and Dohme had implied that it had not provided the full detail of the Cochrane Review to the Panel. Although Takeda had referred to a particular part of the discussion had it provided the full Cochrane Review to the Panel for reference and review so that it could make a full assessment of the information. The most important limitation of this analysis was not mentioned by Merck Sharp & Dohme at any stage in its appeal, nor in the advertisement at issue. This analysis was indirect, and therefore excluded the extensive direct head to head evidence that existed comparing Losartan to several of the other AIIAs, including candesartan. Previous cases had reviewed and accepted the superiority data for a number of the AIIAs compared with losartan (eg Cases AUTH/1510/8/03, AUTH/1501/8/03). It would therefore seem at odds to agree that the direct evidence on the one hand showed superiority of other treatments, but that this indirect comparison justified a claim of no difference. This was not a criticism of the Cochrane review, merely an acknowledgement of the limitations of this kind of indirect analysis.

APPEAL BOARD RULING

The Appeal Board noted that the authors of the Cochrane analysis stated that 'The evidence from this review suggests that there are no clinically meaningful BP lowering differences between available [AIIAs]'. The advertisement at issue, however, had only reproduced the second half of this statement as a quotation ie 'there are no clinically meaningful BP lowering differences between available [AIIAs]'. Although 'suggests' was included outside the quotation the Appeal Board considered that by not faithfully reproducing the authors' statement the quotation cited in the advertisement gave a more unequivocal overview of the Cochrane analysis than had been given by its authors.

The Appeal Board noted that the Code required

claims, *inter alia*, to be based on an up-to-date evaluation of *all* the evidence and to reflect that evidence clearly. The Appeal Board recognised the value of meta-analysis but noted that only indirect comparisons of AIIAs were possible from the Cochrane analysis. Glenny *et al* (2005) had stated that when comparing competing interventions direct evidence from good quality, randomized, controlled trials should be used wherever possible. Without this evidence it might be necessary to look for indirect comparisons from randomized, controlled trials. The Appeal Board noted that there were some direct comparisons of the AIIAs and so in that regard it did not consider that the results of the Cochrane analysis could be viewed in isolation.

The Appeal Board noted that the Cochrane analysis had only included placebo controlled clinical trials in which patients with primary hypertension had been treated to target with an AIIA. In that regard the analysis had shown that all of the AIIAs were able to treat to target but beyond that it had not investigated any additional BP lowering efficacy. Conversely Bakris *et al* and Vidt *et al*, forced titrations of candesartan and losartan (Cozaar), showed that candesartan was more effective than losartan in lowering BP when both were administered once daily at maximum doses. Bakris *et al* reported that candesartan lowered mean sitting trough BP by 13.3/10.9mmHg compared with a mean reduction of 9.8/8.7mmHg by losartan at week 8 – a difference of 3.5/2.2mmHg. The difference between the two products with regard to mean sitting trough BP as reported by Vidt *et al* was 3.3/1.4mmHg.

The Appeal Board noted that small differences in BP lowering, such as reported by Bakris *et al* and Vidt *et al* could be clinically meaningful. In that regard the Appeal Board noted that a table of results in the Cochrane analysis showed similar differences between some of the AIIAs albeit by indirect comparison.

The Appeal Board considered the claim 'A new independent Cochrane review suggests that "there were no clinically meaningful BP lowering differences between available [AIIAs]"' inferred that it had been proven that there were no clinically meaningful blood pressure lowering differences between available AIIAs which was not so especially in light of the evidence from Bakris *et al* and Vidt *et al* which directly compared candesartan and losartan. The Appeal Board considered that the claim did not reflect the totality of the available evidence and it was misleading. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3 of the Code. The appeal was unsuccessful.

Complaint received **6 March 2009**

Case completed **12 June 2009**

CASE AUTH/2215/3/09

MERZ PHARMA v ALLERGAN

Promotion of Botox

Merz Pharma complained about a Botox (botulinum neurotoxin) product monograph and an objection handler issued by Allergan. Merz marketed Xeomin (botulinum neurotoxin). Allergan stated that both items had been withdrawn following Case AUTH/2183/11/08.

The product monograph contained the claim that Botox was '… approved in over 70 countries, with 20 licensed indications …'. The objection handler contained the claim 'Worldwide, Botox currently has 20 licensed indications, whilst Xeomin has only 2 licensed indications'.

Merz submitted that whilst Botox might be approved in 70 countries with an extensive range of indications there were only 7 on the UK summary of product characteristics (SPC). To imply that there were 20 in the UK was untrue and misleading. To advertise that there were 20 indications worldwide was an attempt to solicit questions about the other, currently unauthorized indications, thus constituting promotion inconsistent with the SPC.

The Panel considered that although both the product monograph and the objection handler listed the six indications approved in the UK for Botox, reference to the 20 licensed indications worldwide in both documents might solicit questions about indications not licensed in the UK. No details of these indications were given in the documents. Nonetheless, the Panel considered that claims about the number of worldwide indications for Botox were inconsistent with the UK SPC and misleading and thus represented promotion which was not consistent with the particulars listed in the Botox SPC. Breaches of the Code were ruled.

In relation to the product monograph, the Panel noted that there were 20 licensed indications and thus this claim could be substantiated; no breach of the Code was ruled in that regard.

Merz noted that the headline on the front cover of the objection handler was 'A BIG difference' with the Botox product logo in the bottom right hand corner. The claim was not referenced but was clearly intended to position Botox as having a 'big difference' over its competitors and implied that there was some special merit to Botox. Clinically there was no difference in efficacy and safety between Botox and Xeomin (Benecke *et al* 2005, Roggenkamper 2006). The claim was therefore inaccurate and incapable of substantiation.

The Panel noted that all claims in promotional material were assumed to relate to the clinical situation unless otherwise specified. The Panel noted Allergan's submission that Botox differed from Xeomin in terms of the quantity and quality of clinical data. There appeared to be no clinical data, however, to suggest that Botox was a clearly 'different' botulinum neurotoxin. The Panel thus considered that the claim 'A BIG difference' for Botox was misleading and exaggerated and implied a special merit for Botox which could not be substantiated. Breaches of the Code were ruled.

Merz Pharma UK Ltd complained about the promotion of Botox (botulinum neurotoxin) by Allergan Ltd. The materials at issue were a product monograph (ref ACA/0343/2007/UK) and an objection handler ref ACA/1303/2006). Merz marketed Xeomin (botulinum neurotoxin).

Allergan stated that both items had been withdrawn as a result of rulings made in Case AUTH/2183/11/08. Given that both pieces had thus been in use until at least November 2008 this case was considered under the 2008 Code.

On examining the response from Allergan the Director decided that a number of allegations had been successfully addressed in inter-company dialogue and these matters were not dealt with as part of the complaint.

1 Claims about the number of Botox indications

Page 22 of the product monograph contained the claim that Botox was '… approved in over 70 countries, with 20 licensed indications …'.

Page 10 of the objection handler contained the claim 'Worldwide, Botox currently has 20 licensed indications, whilst Xeomin has only 2 licensed indications'.

COMPLAINT

Merz submitted that whilst Botox might be approved in 70 countries with an extensive range of indications there were only 7 on the UK summary of product characteristics (SPC). To imply that there were 20 in the UK was untrue and misleading. To advertise that there were 20 indications worldwide could only be considered an attempt to solicit a question about the other, currently unauthorized indications, thus constituting promotion inconsistent with the SPC. Merz alleged breaches of Clauses 3.2, 7.2 and 7.4 of the Code with regard to the product monograph.

With regard to the claim in the objection handler Merz repeated its allegation of a breach of Clause 3.2.

RESPONSE

Allergan submitted that the exact sentence at issue in the conclusion of the product monograph, 'It is approved in 70 countries, with 20 licensed indications and is approved for use by many hospital formularies.' summarised the data presented. The adjacent page contained the prescribing information for Botox, detailing the licensed indications. Earlier in the monograph the development of Botox had been covered. The specific UK licensed indications for Botox were detailed in a table and associated text.

Allergan submitted that it had not implied there were 20 indications for Botox in the UK.

Similarly, on an earlier page of the objection handler the specific UK licensed indications for Botox were detailed in a table and associated text.

The statement at issue clearly referred to worldwide indications. Allergan had not implied there were 20 indications for Botox in the UK and the company thus denied a breach of Clause 3.2.

PANEL RULING

The Panel noted both the product monograph (page 2) and the objection handler (page 4) listed the six indications approved in the UK for Botox. The Panel considered that to refer to the 20 licensed indications worldwide in both documents might solicit questions about indications not licensed in the UK but licensed elsewhere. No details of these indications were given in the documents. Clause 3.2 required that promotion of a medicine had to be in accordance with its marketing authorization and not be inconsistent with the SPC. The Panel considered that the claims at issue with regard to the number of worldwide indications for Botox were inconsistent with the UK SPC and misleading and thus represented promotion which was not consistent with the particulars listed in the Botox SPC. Breaches of Clause 3.2 were ruled with regard to both the product monograph and the objection handler. Additionally the product monograph was also ruled in breach of Clause 7.2.

With regard to the alleged breach of Clause 7.4 in relation to the product monograph, the Panel noted that there were 20 licensed indications and thus this claim could be substantiated and thus no breach of Clause 7.4 was ruled.

2 Claim 'A BIG difference'

COMPLAINT

Merz noted that the headline on the front cover of the objection handler was 'A BIG difference' with the Botox product logo in the bottom right hand corner. 'Big' was capitalised which gave it increased emphasis. The claim was not referenced but was clearly intended to position Botox as having a 'big difference' over its competitors in the botulinum toxin market. This implied that there was some special merit to Botox which was unclear and unreferenced. Clinically it had been demonstrated that there was no difference in efficacy and safety between Botox and Xeomin (Benecke *et al* 2005, Roggenkamper 2006). The claim was therefore inaccurate, incapable of substantiation and suggested that Botox had special merit which could not be substantiated. Breaches of Clauses 7.2, 7.4 and 7.10 were alleged.

RESPONSE

Allergan submitted that in the context of the now withdrawn objection handler, 'A BIG difference' was qualified within the piece with:

- The wealth and breadth of studies for Botox vs Xeomin, including the largest meta-analysis in the botulinum toxin therapy field (Allergan Data on File; Naumann and Jankovic, 2004).
- The length of studies with Botox vs Xeomin (Mejia *et al*, 2005; Benecke *et al*, 2005).
- The clinical evidence with Botox supporting a very low incidence of neutralising antibodies (Jankovic *et al*, 2003; Naumann *et al*, 2005; Yablon *et al*, 2005) whilst no such data currently existed for Xeomin (Xeomin SPC).

Allergan noted that Merz had stated that 'clinically it had been demonstrated that there was no difference in efficacy between Botox and Xeomin'. This was not the case. The two cited non-inferiority studies (Benecke *et al*, Roggenkamper *et al*) demonstrated similar efficacy and safety profiles; they did not demonstrate equivalence.

Allergan denied breaches of Clauses 7.2, 7.4 or 7.10.

PANEL RULING

The Panel noted that all claims in promotional material were assumed to relate to the clinical situation unless otherwise specified. The Panel noted Allergan's submission that Botox differed from Xeomin in terms of the quantity and quality of clinical data. There appeared to be no clinical data, however, to suggest that Botox was a clearly 'different' botulinum neurotoxin. The Panel thus considered that the claim 'A BIG difference' for Botox was misleading and exaggerated and implied a special merit for Botox which could not be substantiated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

Complaint received **12 March 2009**

Case completed **7 May 2009**

CASE AUTH/2216/3/09

PROSTRAKAN v CEPHALON

Promotion of Effentora

ProStrakan complained about a 'Titration Guidelines' booklet to support the promotion of Effentora (fentanyl buccal tablet) by Cephalon. ProStrakan marketed Abstral (sublingual fentanyl citrate tablet). Effentora and Abstral were used to treat breakthrough cancer pain (BTcP) in patients already receiving maintenance opioid therapy.

The detailed response from Cephalon is given below.

The front cover of the booklet featured the claim 'A dose for each BTcP patient With a range of 5 doses, Effentora allows you to individualise the treatment of BTcP'. ProStrakan submitted that the published data for Effentora showed that a significant proportion of patients that entered the titration phase would fail to successfully complete titration. For example, Zeppetella *et al* 2008 showed that of 248 patients who commenced titration, 84 did not successfully complete the titration process. ProStrakan therefore alleged that the claim 'A dose for each patient' was inaccurate and could not be substantiated.

The Panel noted that the Effentora summary of product characteristics (SPC) stated that Effentora should be individually titrated to an effective dose that provided adequate analgesia and minimised undesirable effects. Details were given including the ability to titrate upwards as necessary through the range of available strengths.

The Titration Guidelines booklet included instructions for treatment of five BTcP episodes. The page showing the 5th BTcP episode stated that if inadequate analgesia was obtained 30 minutes after 800mcg then alternative treatment options were needed.

The Panel noted the Zepetella *et al* had combined data from two published studies of fentanyl buccal tablets in opioid-tolerant cancer patients with breakthrough pain. Of the 252 patients enrolled, 66% (167) were successfully titrated to an effective dose. For the full analysis set (n=150) the successful doses were 100mcg (9%), 200mcg (13%), 400mcg (22%), 600mcg (21%) and 800mcg (35%). In the Panel's view the data demonstrated that different patients might require up to an 8 fold difference in dose but that with five tablet strengths available prescribers had flexibility as to the dose prescribed.

The Panel noted that not all of the patients enrolled in Zeppetella *et al* were successfully treated with fentanyl buccal tablets and in the open label dose titration phase 28 (11%) dropped out due to lack of efficacy. Nonetheless, the Panel did not consider that in the context of analgesia prescribers would assume that the claim 'A dose for each BTcP patient' meant that Effentora was effective in all patients; no medicine was effective in everybody. The remainder of the claim 'With a range of 5 doses Effentora allows you to individualise the treatment of BTcP' provided further context.

Overall, the Panel did not consider that the claim 'A dose for each BTcP patient' was inaccurate as alleged or could not be substantiated. No breaches of the Code were ruled.

ProStrakan alleged that a descending scale on the front cover of the booklet implied that Effentora resulted in complete pain relief within 10 minutes and was reinforced by the scale being superimposed on an image of two people who were clearly not in any pain. The published data for Effentora showed that there was a statistically significant pain intensity difference vs placebo from 10 minutes but it did not show that patients would be pain free within this time. ProStrakan alleged that the graphic was in breach of the Code as it misled as to the efficacy of Effentora.

The Panel noted a statement in the SPC that statistically significant improvements in pain intensity difference was seen with Effentora vs placebo as early as ten minutes in one study and as early as fifteen minutes (earliest time point measured) in another study.

The Panel noted that on the front cover of the booklet the descending scale started with 10 minutes and a 9mm vertical red line at the left hand side. Thereafter each regressive minute was marked with vertical red lines which gradually decreased in height until at zero, on the right hand side, there was no red line at all. In the Panel's view this implied that whatever was present at 10 minutes was completely gone at zero. Given its inclusion in a promotional piece about Effentora, the Panel considered that some readers would assume that the sliding scale meant that Effentora produced complete pain relief in 10 minutes which was not so. The graphic was superimposed over a visual of a couple looking relaxed and happy. The Panel considered that the descending scale misled as to the efficacy of Effentora as alleged. A breach of the Code was ruled.

The company logo and strapline 'deliver more' appeared in the lower left hand corner of the front cover of the booklet. The product logo was in the

lower right hand corner. ProStrakan stated that the company logo was adjacent to the product logo and on the front cover of an Effentora promotional item. 'Deliver more' was therefore a hanging comparison in breach of the Code.

The Panel considered that the corporate logo was sufficiently separated from the product logo such that 'deliver more' would not be regarded as a claim for Effentora. No breach of the Code was ruled.

For each titration dose (100mcg/200mcg/400mcg/600mcg and 800mcg) the booklet featured diagrams of a patient's face with tablets superimposed around the jaw line. ProStrakan noted that the graphics indicated the required positioning of tablets for all doses. The images for the 600mcg (3x200mcg tablets) and 800mcg (4x200mcg tablets) doses clearly showed some tablets in the upper part of the mouth and some in the lower part of the mouth (particularly the 3x200mcg image). The Effentora SPC stated that tablets should be placed in the upper part of the buccal cavity. Thus, the information in the dose titration guide was inconsistent with the particulars in the SPC, in breach of the Code. ProStrakan was concerned that this discrepancy might pose a safety hazard for patients.

The Panel considered that the images were misleading. Where more than two tablets were to be used (ie 600mcg and 800mcg doses) some of the tablets were placed on the diagram such that they appeared over the lower buccal cavity. The SPC clearly stated that tablets were to be placed in the upper portion of the buccal cavity (above an upper rear molar between the cheek and gum). The Panel considered that the images were inconsistent with the particulars listed in the Effentora SPC. A breach of the Code was ruled.

ProStrakan noted that the prescribing information on the inside back covers of the booklet did not list the frequency of the application site reactions. According to the SPC these were 'very common' and so this information should have been included. The frequency of other adverse events was listed, therefore this omission appeared to be trying to minimise the significance of application site reactions.

The Panel noted that one of the elements of prescribing information listed in the Code was 'a succinct statement of common side-effects likely to be encountered in clinical practice'. The prescribing information at issue stated 'Application site reactions including pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles' but did not attribute any frequency to these side-effects. The Effentora SPC listed these effects as being very common. Immediately following the statement regarding application site reactions the prescribing information stated 'Very common effects (>10%) – nausea and dizziness. Common (<1%-10%) – Dysgensia, Somnolence …'. Given that frequencies of other adverse events had been stated it thus appeared that application site reactions occurred at a frequency that was something other than very common or common which was not so. To state the frequency for some adverse events but not for others was not helpful. Nonetheless the information listed in the Code had been provided and so no breach of the Code was ruled.

ProStrakan Group Plc complained about the promotion of Effentora (fentanyl buccal tablet) by Cephalon Limited. The material at issue was a 'Titration Guidelines' booklet (ref CE/FE-08031/Dec08). ProStrakan marketed Abstral (sublingual fentanyl citrate tablet). Effentora and Abstral could be used to treat breakthrough cancer pain (BTcP) in patients already receiving maintenance opioid therapy.

1 Claim 'A dose for each BTcP patient'

The front cover of the booklet featured the claim 'A dose for each BTcP patient With a range of 5 doses, Effentora allows you to individualise the treatment of BTcP'.

COMPLAINT

ProStrakan submitted that the published data for Effentora showed that a significant proportion of patients that entered the titration phase would fail to successfully complete titration. For example, Zeppetella *et al* 2008 showed that of 248 patients who commenced titration, 84 did not successfully complete the titration process. ProStrakan therefore alleged that the claim 'A dose for each patient' was in breach of Clause 7.2 of the Code as it was inaccurate and was also a breach of Clause 7.4 as it could not be substantiated.

RESPONSE

Cephalon did not dispute that a proportion of patients entering the titration phase would not achieve an effective dose. However, within the context of the process of titration (as outlined in the Titration Guidelines booklet), this was completed by the statement 'With a range of 5 doses, Effentora allows you to individualise the treatment of BTcP'.

The claim at issue referred to using the range of tablet strengths to find a suitable dose, to individualise the dose for each patient during the titration phase. For all patients for whom the decision had been made to prescribe Effentora, the essence of titration required that each patient received a dose, to establish their effective maintenance dose.

The reference quoted was consistent with other

studies on successfully completing titration. This figure was not dissimilar to general response rates with many commonly prescribed medicines.

Cephalon contended that, based on these points, the claim was not inaccurate and so not in breach of Clause 7.2; the alleged breach of Clause 7.4 was not applicable.

PANEL RULING

The Panel noted that the Effentora summary of product characteristics (SPC) stated that Effentora should be individually titrated to an effective dose that provided adequate analgesia and minimised undesirable effects. Details were given including the ability to titrate upwards as necessary through the range of available strengths.

The Titration Guidelines booklet included instructions for treatment of five BTcP episodes. The page showing the 5th BTcP episode stated that if inadequate analgesia was obtained 30 minutes after 800mcg then alternative treatment options were needed.

The Panel noted the Zepetella *et al* had combined data from two published studies of fentanyl buccal tablets in opioid-tolerant cancer patients with breakthrough pain. Of the 252 patients enrolled, 66% (167) were successfully titrated to an effective dose. For the full analysis set (n=150) the successful doses were 100mcg (9%), 200mcg (13%), 400mcg (22%), 600mcg (21%) and 800mcg (35%). In the Panel's view the data demonstrated that different patients might require up to an 8 fold difference in dose but that with five tablet strengths available the prescribers had flexibility as to the dose prescribed.

The Panel noted that not all of the patients enrolled in Zeppetella *et al* were successfully treated with fentanyl buccal tablets and in the open label dose titration phase 28 (11%) dropped out due to lack of efficacy. Nonetheless, the Panel did not consider that in the context of analgesia prescribers would assume that the claim 'A dose for each BTcP patient' meant that Effentora was effective in 100% of patients; no medicine was effective in everybody. The remainder of the claim 'With a range of 5 doses Effentora allows you to individualise the treatment of BTcP' provided further context.

Overall, the Panel did not consider that the claim 'A dose for each BTcP patient' was inaccurate as alleged or could not be substantiated. No breaches of Clauses 7.2 and 7.4 respectively were ruled.

2 Descending scale of 10 minutes to zero

The front cover of the booklet included a descending scale marked '10 minutes' with a 9mm vertical red line at the left hand side and 'O' with no vertical red line at the right hand side.

COMPLAINT

ProStrakan alleged that the descending scale clearly implied that Effentora resulted in complete pain relief within 10 minutes. This implication was reinforced by the scale being superimposed on an image of two people who were clearly not in any pain. The published data for Effentora showed that there was a statistically significant pain intensity difference vs placebo from 10 minutes but it did not show that patients would be entirely pain free within this time. ProStrakan alleged that the graphic was in breach of Clause 7.8 of the Code as it misled as to the efficacy of Effentora.

RESPONSE

Cephalon submitted that the 10 minute scale was not associated with any claim or indications that complete pain relief was achieved within 10 minutes. The implication of an association with 'complete pain relief' was only alleged by ProStrakan. The scale only highlighted 10 minutes, with otherwise the period divided into minutes without providing any further information. The 10 minutes represented an artistic interpretation at which statistical significance for numerous end-points was achieved (in a placebo-controlled trial, Slatkin *et al,* 2007). No other meaning was given to the scale.

Cephalon contended in view of the fact that the images, individually or in combination, did not indicate patients were entirely pain free within 10 minutes the alleged breach of Clause 7.8 was unfounded.

PANEL RULING

The Panel noted a statement in the SPC that statistically significant improvements in pain intensity difference was seen with Effentora vs placebo as early as ten minutes in one study and as early as fifteen minutes (earliest time point measured) in another study.

The Panel noted that on the front cover of the booklet the descending scale started with 10 minutes and a 9mm vertical red line at the left hand side. Thereafter each regressive minute was marked with vertical red lines which gradually decreased in height until at zero, on the right hand side, there was no red line at all. In the Panel's view this implied that whatever was present at 10 minutes was completely gone at zero. Given its inclusion in a promotional piece about Effentora, the Panel considered that some readers would assume that the sliding scale meant that Effentora produced complete pain relief in 10 minutes which was not so. The graphic was superimposed over a

visual of a couple looking relaxed and happy. The Panel considered that the descending scale gave a misleading impression about the efficacy of Effentora as alleged. A breach of Clause 7.8 was ruled.

3 Cephalon company logo with strapline 'deliver more'

The company logo and strapline appeared in the lower left hand corner of the front cover of the booklet. The product logo was in the lower right hand corner.

COMPLAINT

ProStrakan stated that the company logo was adjacent to the product logo and on the front cover of an Effentora promotional item. The 'deliver more' text was therefore a hanging comparison in breach of Clause 7.2 of the Code.

RESPONSE

Cephalon submitted that the corporate logo/statement and Effentora logo were not within sufficient proximity of each other to be considered adjacent. This alone clearly suggested that the allegation that 'deliver more' constituted a hanging comparison in relation to Effentora was unfounded and so there was no breach of Clause 7.2. Furthermore, the statement 'deliver more' was a corporate claim, and as such was not associated with the promotion of a specific medicine. It therefore fell outside the scope of the Code.

Cephalon stated that it was unfortunate that ProStrakan had complained on this point. Cephalon had responded through inter-company correspondence that an internal decision had already been made to phase out the use of this corporate claim for other reasons.

PANEL RULING

The Director noted that in inter-company dialogue Cephalon had agreed to phase out the use of the strapline 'deliver more'; the company had not agreed to stop using it with immediate effect. Inter-company dialogue had thus been unsuccessful and so the complaint on this point could proceed.

The Panel noted Cephalon's contention that the strapline 'deliver more' was a corporate claim and thus not subject to the Code. The Panel considered, however, that in a promotional piece for a medicine a corporate strapline might be regarded as a promotional claim for that medicine. Each case would have to be judged on its own merits. In this instance the Panel considered that the corporate logo was sufficiently separated from the product logo such that 'deliver more' would not be regarded as a claim for Effentora. No breach of Clause 7.2 was ruled.

4 Images of tablet placement

For each titration dose (100mcg/200mcg/400mcg/600mcg and 800mcg) the booklet featured diagrams of a patient's face with tablets superimposed around the jaw line.

COMPLAINT

ProStrakan noted that the graphics indicated the required positioning of tablets for all doses. The images for the 600mcg (3x200mcg tablets) and 800mcg (4x200mcg tablets) doses clearly showed some tablets in the upper part of the mouth and some in the lower part of the mouth (particularly the 3x200mcg image). The Effentora SPC stated that tablets should be placed in the upper part of the buccal cavity. Thus, the information in the dose titration guide was inconsistent with the particulars in the SPC, in breach of Clause 3.2 of the Code. ProStrakan was concerned that this discrepancy might pose a safety hazard for patients.

RESPONSE

Cephalon submitted that following ProStrakan's original inter-company complaint, it had reviewed the images at issue and considered that they could be misconstrued as representing placement of Effentora in both the upper and lower portions of the buccal cavity. However, adverse events were typical of opioids and there was no evidence from safety monitoring that such placement was occurring and was associated with additional risk.

The images did not clearly show some tablets in the lower part of the mouth. The graphical representation showed that if three or four tablets were required, placement on both sides of the mouth would be necessary, and this should be two on each side. As a 2-D image, it was a challenge to demonstrate the true positioning of the buccal tablets.

In light of ProStrakan's initial inter-company complaint, Cephalon had offered to review the graphical images. Unfortunately, since the correspondence, Cephalon had already approved internally new graphical images to address this, solely in the interests of clarifying the point of buccal tablet placement rather than acceding to the alleged breach.

Therefore, Cephalon refuted the alleged breach of Clause 3.2, but considered additional clarity could be provided through re-drafting of the appropriate images.

PANEL RULING

The Director noted that in inter-company dialogue Cephalon had agreed to review the images but had not agreed to stop using them. Inter-company dialogue had thus been unsuccessful and so the complaint on this point could proceed.

The Panel considered that the images were misleading. Where more than two tablets were to be used (ie 600mcg and 800mcg doses) some of the tablets were placed on the diagram such that they appeared over the lower buccal cavity. The SPC clearly stated that tablets were to be placed in the upper portion of the buccal cavity (above an upper rear molar between the cheek and gum). The Panel considered that the images were inconsistent with the particulars listed in the Effentora SPC. A breach of Clause 3.2 was ruled.

5 Prescribing information

COMPLAINT

ProStrakan noted that the prescribing information on the inside back covers of the Titration Guidelines booklet did not list the frequency of the application site reactions. According to the SPC these were 'very common' and so this information should have been included. The frequency of other adverse events was listed, therefore this omission appeared to be trying to minimise the significance of application site reactions. A breach of Clause 4.2 was alleged.

RESPONSE

Cephalon submitted that there was no absolute requirement to state frequencies in the prescribing information. Clause 4.2 required '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 product characteristics, together with a statement that prescribers should consult the summary of product characteristics in relation to other side effects'.

The prescribing information fulfilled these requirements. The statement relating to application site reactions stood alone for emphasis. Cephalon thus denied a breach of Clause 4.2

PANEL RULING

The Panel noted that one of the elements of prescribing information listed in Clause 4.2 was 'a succinct statement of common side-effects likely to be encountered in clinical practice'. The prescribing information at issue stated 'Application site reactions including pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles' but did not attribute any frequency to these side-effects. The Effentora SPC listed these effects as being very common. Immediately following the statement regarding application site reactions the prescribing information stated 'Very common effects (>10%) – nausea and dizziness. Common (<1%-10%) – Dysgensia, Somnolence …'. Given that frequencies of other adverse events had been stated it thus appeared that application site reactions occurred at a frequency that was something other than very common or common which was not so. To state the frequency for some adverse events but not for others was not helpful. Nonetheless the information listed in Clause 4.2 had been provided. Clause 4.2 did not require frequencies to be stated – just that common side effects be listed. Clause 4.1 required that the elements of prescribing information listed in Clause 4.2 be provided and so no breach of Clause 4.1 was ruled.

Complaint received **11 March 2009**

Case completed **6 May 2009**

CASE AUTH/2218/3/09

VOLUNTARY ADMISSION BY ASTRAZENECA

Promotion of Nexium

AstraZeneca voluntarily submitted that its promotion of Nexium 40mg (esomeprazole) was inconsistent with Section 4.2 of the Nexium summary of characteristics (SPC). In support of its submission AstraZeneca cited a Nexium detail aid and two independently produced treatment pathways distributed by the company.

AstraZeneca explained that during a review of its Nexium campaign it was considered that some materials did not take into account the entire wording in Section 4.2 of the SPC for the 40mg dose.

Section 4.1 of the Nexium SPC included the indication:
'Gastro-Oesophageal Reflux Disease
- **treatment of erosive reflux oesophagitis**
- **long-term management of patients with healed oesophagitis to prevent relapse**
- **symptomatic treatment of gastro-oesophageal reflux disease.'**

AstraZeneca's promotion was in line with this but in Section 4.2 of the SPC a distinction was made between the doses used for the different subsets of GORD:

'Gastro-Oesophageal Reflux Disease (GORD)
- **<u>treatment of erosive reflux oesophagitis</u>**
  40mg once daily for 4 weeks.

- **<u>long-term management of patients with healed oesophagitis to prevent relapse</u>**
  20mg once daily.

- **<u>symptomatic treatment of gastro-oesophageal reflux disease</u>**
  20mg once daily in patients without oesophagitis. If symptom control has not been achieved after four weeks, the patient should be further investigated.'

GORD encompassed a spectrum of disorders from erosive oesophagitis to symptomatic disease without oesophagitis, from severe to mild.

AstraZeneca's interpretation of Section 4.2 was that the 40mg dose was only indicated in GORD patients who had a specific diagnosis of oesophagitis. When the licence was filed in 2000, oesophagitis was normally diagnosed by upper gastro-endoscopy albeit with an appreciation of a move to the current practice of a more symptomatic based approach.

In the promotional materials at issue the 40mg Nexium dose was promoted for all unresolved GORD, unresponsive to first line proton pump inhibitor (PPI) therapy. Unresolved GORD encompassed patients with or without oesophagitis.
- **Specifically, in the detail aid 40mg Nexium was positioned for reflux oesophagitis but also for symptomatic treatment in GORD (which, by implication, could include patients who might or might not have oesophagitis).**
- **In addition, two sets of independently produced local treatment guidelines for GORD, distributed by AstraZeneca, positioned Nexium 40mg for patients with unresolved GORD who had not responded to a four week course of a generic PPI. The guidelines referred to GORD patients (including those with or without oesophagitis) with no distinction made on the appropriate dose.**

AstraZeneca considered the material to be in breach of the Code; however, it believed that the error was made in good faith and noted the following:-

- **GORD was an ill defined term that was often misused in practice with other terms referring to gastro-intestinal pathology.**
- **During the initial assessment of the Nexium filing in 2000, the regulatory agencies questioned the value of upper gastro-endoscopy in the diagnosis and management of GORD and decided that the clinician should ultimately make this decision. This led to endoscopy not being mandatory prior to treatment with Nexium.**
- **International leading gastroenterologists had produced two sets of guidelines for the management of GORD in the past 10 years which questioned the value of subjecting GORD patients to an endoscopy and proposed empiric treatment with a PPI.**
- **The National Institute for health and Clinical Excellence (NICE) recommended that routine endoscopic evaluation of patients was not necessary and instead recommended empiric treatment with PPIs for reflux type dyspepsia (further confusing terminology).**
- **The materials were subject to close and considered scrutiny by senior medical personnel at AstraZeneca. Their opinion was that the materials were consistent with accepted clinical practice but, nevertheless, could be interpreted as not fully consistent with the licence.**

National and international guidelines and routine clinical practice recognised that GORD (with or without oesophagitis) might be managed without routine endoscopic evaluation favouring instead a symptomatic diagnosis for the GORD spectrum.

Despite the potential for ambiguity in its materials vis-à-vis the wording on the licence and current clinical practice, AstraZeneca believed it was appropriate to take this conservative view and accordingly all relevant promotional material for Nexium ceased on 25 February 2009 while clinical discussions were carried out. New materials would take account of the full wording of the license.

The detailed response from AstraZeneca is given below.

The Authority's Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potential serious breach of the Code or if the company failed to take appropriate action to address the matter. Promotion that was inconsistent with the SPC was a potentially serious matter and the Director thus decided that the admission must be treated as a complaint.

* * * * *

The Panel noted that GORD encompassed a spectrum of disorders ranging from symptoms of acid reflux only without oesophagitis to erosive reflux oesophagitis where the stomach acid had damaged the lining of the oesophagus.

The Panel noted that in the Nexium SPC GORD was subdivided into treatment of erosive reflux oesophagitis (40mg once daily – an additional 4 weeks of treatment was recommended for patients in whom oesophagitis had not healed or who had persistent symptoms); long-term management of patients with healed oesophagitis to prevent relapses (20mg once daily) and symptomatic treatment of GORD (20mg once daily in patients without oesophagitis). If symptom control was not achieved after 4 weeks the patient should be further investigated. Once symptoms had resolved subsequent symptom control could be achieved using 20mg once daily. The Panel considered that before treatment with 40mg Nexium could begin, patients had to have a diagnosis of erosive reflux oesophagitis.

The Panel noted AstraZeneca's submission that Nexium 40mg was indicated, *inter alia*, for symptomatic treatment of GORD in patients whose symptoms were not controlled after 4 weeks on 20mg once daily. The Panel noted the SPC stated that such patients should be further investigated after 4 weeks but did not refer to the 40mg dose. The Panel considered the SPC meant that further clinical investigation was required at 4 weeks. This did not necessarily preclude the subsequent administration of the 40mg dose in those patients in whom a diagnosis of erosive reflux oesophagitis was made at 4 weeks.

The Panel noted AstraZeneca's submission that the diagnosis and management of GORD had evolved since the original Nexium regulatory filing in 2000. Current clinical practice generally relied on a symptomatic diagnosis for the GORD spectrum, rather than endoscopic diagnosis. The Panel noted the recommendations and evolving use of clinical terms by various national and international guidelines. AstraZeneca referred to an ambiguity in its materials vis-à-vis the wording on the licence and current clinical practice. The Panel noted that irrespective of current clinical practice promotional material must be in accordance with the medicine's marketing authorization and must not be inconsistent with the particulars listed in its SPC.

The Panel noted the detail aid at issue was entitled 'Unresolved GORD corrodes peoples lives' included bar charts headed 'Reducing symptom frequency' and 'Reducing heartburn severity' respectively beneath the heading 'Nexium 40mg provides a solution for patients with unresolved GORD by …'. The Panel noted that patients with unresolved GORD might or might not have oesophagitis. Nexium 40mg was indicated for treatment of erosive reflux oesophagitis. The Panel considered that the detail aid was thus inconsistent with the particulars listed in the Nexium SPC as admitted by AstraZeneca. A breach of the Code was ruled.

The Panel noted that the two sets of guidelines had each been independently developed and subsequently distributed by AstraZeneca. Each bore prescribing information for Nexium 20-40mg. Each guideline referred to second line treatment with Nexium 40mg for patients with unresolved reflux-type dyspepsia. It was thus not sufficiently clear that a diagnosis of erosive reflux oesophagitis was needed before 40mg therapy could begin. The guidelines were thus inconsistent with the particulars listed in the Nexium SPC as admitted by AstraZeneca. A breach of the Code was ruled in relation to each document.

AstraZeneca voluntarily submitted that its promotion of Nexium 40mg (esomeprazole) was inconsistent with Section 4.2 of the Nexium summary of characteristics (SPC). In support of its submission AstraZeneca cited a Nexium detail aid and two independently produced treatment pathways distributed by the company.

COMPLAINT

AstraZeneca explained that during a review of its campaign material it was queried whether the proposed positioning of the 40mg dose of Nexium for gastro-oesophageal reflux disease (GORD) was in line with the SPC. This led to an internal review of existing Nexium materials. The majority of materials were found to be consistent with the licensing particulars, however, in AstraZeneca's view certain materials did not take into account the entire wording in Section 4.2 of the SPC for the 40mg dose.

Licensing particulars

Section 4.1 of the Nexium SPC included the indication:
'Gastro-Oesophageal Reflux Disease
- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease.'

AstraZeneca's promotion was in line with this indication, however, within Section 4.2 of the SPC a distinction was made between the doses used for the different subsets of GORD:

'Gastro-Oesophageal Reflux Disease (GORD)
- treatment of erosive reflux oesophagitis
  40mg once daily for 4 weeks.

- long-term management of patients with healed oesophagitis to prevent relapse
  20mg once daily.

- symptomatic treatment of gastro-oesophageal reflux disease
  20mg once daily in patients without oesophagitis. If symptom control has not been achieved after four weeks, the patient should be further investigated.'

The term GORD encompassed a spectrum of disorders which ranged from erosive oesophagitis to symptomatic disease without oesophagitis, from severe to mild.

AstraZeneca's interpretation of Section 4.2 was that the 40mg dose was only indicated in GORD patients who had a specific diagnosis of oesophagitis. At the time of filing for a licence in 2000, oesophagitis was normally diagnosed by upper gastro-endoscopy albeit with an appreciation of a move to the current practice of a more symptomatic based approach.

Promotional materials

In the promotional materials at issue the 40mg Nexium dose was promoted for all unresolved GORD, unresponsive to first line generic proton pump inhibitor (PPI) therapy. Unresolved GORD encompassed those patients with or without oesophagitis.

- Specifically, in the detail aid 40mg Nexium was positioned for reflux oesophagitis but also for symptomatic treatment in GORD (which, by implication, could include patients who might or might not have oesophagitis).
- In addition, two sets of independently produced local treatment guidelines for GORD were distributed by AstraZeneca. These guidelines positioned Nexium 40mg for patients with unresolved GORD who had not responded to a four week course of a generic PPI. The guidelines referred to GORD patients (including patients with or without oesophagitis) with no distinction made on the appropriate dose.

AstraZeneca judgement

AstraZeneca considered the material to be in breach of Clause 3.2; however, it believed that no other section of the Code was breached and that the error was made in good faith.

In particular, AstraZeneca noted the following:-

- GORD was an ill defined term that was often misused in practice with other terms referring to gastro-intestinal pathology.
- During the initial assessment of the Nexium filing in 2000, the regulatory agencies questioned the value of upper gastro-endoscopy in the diagnosis and management of GORD and decided that the clinician should ultimately make this decision. This led to endoscopy not being mandatory prior to treatment with Nexium.
- International leading gastroenterologists had produced two sets of guidelines for the management of GORD in the past 10 years. These guidelines questioned the value of subjecting GORD patients to an endoscopy and proposed empiric treatment with a PPI.
- The National Institute for health and Clinical Excellence (NICE) recommended that routine endoscopic evaluation of patients was not necessary and instead recommended empiric treatment with PPIs for reflux type dyspepsia (further confusing terminology).
- The materials were subject to close and considered scrutiny by senior medical personnel at AstraZeneca. Their opinion was that the materials were consistent with accepted clinical practice but, nevertheless, could be interpreted as not fully consistent with the licence.

National and international guidelines and routine clinical practice recognised that clinicians might decide to manage GORD (with or without oesophagitis) without the need for routine endoscopic evaluation and current practice favoured a symptomatic diagnosis for the GORD spectrum rather than an endoscopic intervention.

Despite the potential for ambiguity in its materials vis-à-vis the wording on the licence and current clinical practice, AstraZeneca believed it was appropriate to take this conservative view and accordingly all relevant promotional material for Nexium ceased on 25 February 2009 while clinical discussions were carried out. New materials would take account of the full wording of the license.

* * * * *

Paragraph 5.4 of the Authority's Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potential serious breach of the Code or if the

company failed to take appropriate action to address the matter. Promotion that was inconsistent with the SPC was a potentially serious matter and the Director thus decided that the admission must be treated as a complaint.

AstraZeneca was asked to comment in relation to Clause 3.2 of the Code.

* * * * *

RESPONSE

AstraZeneca provided further information about Nexium and GORD.

Nexium SPC and explanation of terms within the indications and posology section

In normal circumstances, the lower oesophageal sphincter at the top of the stomach prevented stomach acid from passing back into the oesophagus. There were a number of reasons for this to fail. Repeated reflux of acid into the lower oesophagus gave rise to GORD. The term GORD encompassed a spectrum of disorders that ranged from symptoms of acid reflux only to erosive reflux oesophagitis, where the stomach acid had damaged the lining of the oesophagus.

AstraZeneca reiterated the licensed indications as set out in the Nexium SPC.

The SPC, like other PPI SPCs did not state that endoscopy was required before commencing therapy with Nexium. Erosive reflux oesophagitis (RO) and RO were both classified using the Los-Angeles grading system. Any patient graded A-D was included in trials assessing the effectiveness of Nexium 40mg for RO. When these key phase III trials were published, they referred to these patients as having either RO or erosive RO therefore erosive RO and RO were used interchangeably, although reflux oesophagitis was a more accepted clinical term. It was noted that the latest international consensus publication recommended the use of RO over erosive RO as the latter was now an outdated term.

AstraZeneca interpreted Section 4.2 of the SPC to mean that 40mg Nexium was indicated in GORD patients who had a diagnosis of reflux oesophagitis and in GORD patients in whom an initial four-week course of Nexium 20mg had not provided sufficient response where further investigation was recommended.

The evolution of the diagnosis and management of GORD and RO

The management of GORD had varied and attempts had been made to standardise approaches to its management.

In 1999 the Genval guidelines were the first attempt to standardise management of GORD. Thirty-five doctors from 16 counties assessed the evidence for the diagnosis and treatment of patients with GORD: The group offered a definition of GORD and stated that endoscopy was thought to be of limited use in the routine management of most patients who presented with reflux symptoms and no alarm symptoms (symptoms that suggested a diagnosis of cancer). Empirical treatment was proposed as a first line of therapy.

In 2000 AstraZeneca obtained a licence for Nexium 20 and 40mg tablets for *inter alia* treatment of GORD, during the assessment process there was a reflection that the diagnosis of GORD might be made clinically without the need for endoscopy and that the treating clinician should ultimately make the decision.

In 2004, NICE issued guidelines for the management of dyspepsia in adults in primary care and recommended endoscopy and treatment with PPIs for patients with (reflux like) dyspepsia and GORD (including RO).

NICE advocated empirical therapy with PPIs for reflux type dyspepsia ie the types of patients that would present and likely to be clinically diagnosed with GORD. NICE also recommended that routine endoscopic evaluation of most patients was not necessary, rather, a list of alarm symptoms identified patients that would be suitable for referral. NICE also stated that early endoscopy had not demonstrated better patient outcomes than empirical treatment and that test and endoscopy had not been demonstrated to produce better patient outcomes than empirical treatment. The associated impact on patient safety was also assessed when making these recommendations.

Hence NICE supported empirical treatment with PPIs and reserved endoscopic evaluation to a limited group of patients identified at highest risk of other significant pathology.

To support clinical diagnosis of GORD a number of symptom-based questionnaires had been developed and validated for use, these included the reflux disease questionnaire (RDQ), GORD impact scale (GIS), ReQuest and GERD-Q.

In 2006, 44 experts from 18 countries produced the Montreal classification and definition of GORD. It defined GORD as a condition which developed when the reflux of stomach contents caused troublesome symptoms and/or complications. It also recommended the term reflux oesophagitis was used in preference to erosive oesophagitis.

In summary, GORD (including RO) could be diagnosed by endoscopy or clinically based on a symptomatic approach. NICE recommended the use of empiric therapy with PPIs rather than endoscopic evaluation for most patients.

Nexium materials and claims

The internal review revealed that the Nexium

detail aid, and the two sets of guidelines positioned Nexium 40mg for the treatment of GORD. However in AstraZeneca's view these materials were not sufficiently clear about whether patients referred to had reflux oesophagitis and did not provide advice to refer patients for investigation in line with the wording in the licence. AstraZeneca submitted that its positioning reflected clinical practice but did not take into account the full wording of the licence and that it should have advised further investigation in those patients with symptomatic GORD when considering escalating treatment to 40mg Nexium or use in RO.

Nexium detail aid (NEX12765a)

This detail aid was used between August 2007 to February 2009 and positioned Nexium for uncontrolled GORD; such positioning was covered by the licence. On page 6 Nexium 40mg was referred to in a meta-analysis assessing healing rates in patients with RO, again such use was covered within the scope of the licence. On pages 7 and 11, a trial called RESPONSE (then data on file but now published) was referred to showing how Nexium 40mg provided a solution for patients with unresolved GORD. In this trial patients were included if they had been diagnosed with GORD (and it was not clear which of these patients had been diagnosed with reflux oesophagitis or further investigated) and had unresolved symptoms despite 8 weeks' treatment with a full dose of another PPI. Upon entry into the trial patients were assigned to 8 weeks of treatment with Nexium 40mg. Page 12 again referred to Nexium's superiority for healing RO consistent with the information presented on page 6. Therefore although Nexium 40mg had been positioned for the treatment of RO in the detail aid it had also been positioned for the treatment of GORD where it was not clear which patients did or did not have RO or should be further investigated.

The two sets of guidelines had been developed independently of AstraZeneca; the company was given permission to distribute them in September 2007 and October 2008 respectively. These local treatment pathways had positioned Nexium as second line treatment for patients with suspected GORD. Nexium 40mg was positioned for those patients who had not had their GORD symptoms resolved after an initial trial with a generic PPI. However, again it was not clear whether these GORD patients would have RO or should be further investigated after their trial with generic PPI. Therefore AstraZeneca felt it inappropriate to distribute these guidelines and ceased this activity in February 2009.

Although clinical practice for GORD had evolved over the last 20 years, these materials had only been in use since August 2007 when it was considered that the materials would be in line with current clinical practice. Previous materials positioned Nexium 40mg for patients with RO. The review of AstraZeneca's internal materials was conducted in February 2009 when all current promotional activity for Nexium was also ceased.

Thus although these three promotional pieces were in line with current clinical practice and supported the clinical diagnosis of GORD, there were aspects in these pieces that did not extend to diagnosing RO or recommending further investigation before initiating treatment with Nexium 40mg. Thus, it in AstraZeneca's view these pieces were not strictly in line with the licensing particulars of Nexium and were in breach of Clause 3.2.

PANEL RULING

The Panel noted that GORD encompassed a spectrum of disorders ranging from symptoms of acid reflux only without oesophagitis to erosive reflux oesophagitis where the stomach acid had damaged the lining of the oesophagus.

The Panel noted that in the Nexium SPC GORD was subdivided into treatment of erosive reflux oesophagitis (40mg once daily – an additional 4 weeks of treatment was recommended for patients in whom oesophagitis had not healed or who had persistent symptoms); long-term management of patients with healed oesophagitis to prevent relapses (20mg once daily) and symptomatic treatment of GORD (20mg once daily in patients without oesophagitis). If symptom control was not achieved after 4 weeks the patient should be further investigated. Once symptoms had resolved subsequent symptom control could be achieved using 20mg once daily. The Panel considered that before treatment with 40mg Nexium could begin, patients had to have a diagnosis of erosive reflux oesophagitis.

The Panel noted AstraZeneca's submission that Nexium 40mg was indicated, *inter alia*, for symptomatic treatment of GORD in patients whose symptoms were not controlled after 4 weeks on 20mg once daily. The Panel noted the SPC stated that such patients should be further investigated after 4 weeks but did not refer to the 40mg dose. The Panel considered the SPC meant that further clinical investigation was required at 4 weeks. This did not necessarily preclude the subsequent administration of the 40mg dose in those patients in whom a diagnosis of erosive reflux oesophagitis was made at 4 weeks.

The Panel noted AstraZeneca's submission that the diagnosis and management of GORD had evolved since the original Nexium regulatory filing in 2000. Current clinical practice generally relied on a symptomatic diagnosis for the GORD spectrum, rather than endoscopic diagnosis. The Panel noted the recommendations and evolving use of clinical terms by the Genval guidelines, NICE and the Montreal classification. AstraZeneca referred to an ambiguity in its materials vis-à-vis

the wording on the licence and current clinical practice. The Panel noted that irrespective of current clinical practice promotional material must be in accordance with the medicine's marketing authorization and must not be inconsistent with the particulars listed in its SPC.

The Panel noted the detail aid at issue was entitled 'Unresolved GORD corrodes peoples lives'. Page 7 featured two bar charts headed 'Reducing symptom frequency' and 'Reducing heartburn severity' respectively beneath the heading 'Nexium 40mg provides a solution for patients with unresolved GORD by …'. The Panel noted that identical data also appeared on page 13 of the detail aid rather than page 11 referred to by AstraZeneca. The Panel noted that patients with unresolved GORD might or might not have oesophagitis. Nexium 40mg was indicated for treatment of erosive reflux oesophagitis. The Panel considered that pages 7 and 13 of the detail aid were thus inconsistent with the particulars listed in the Nexium SPC as admitted by AstraZeneca. A breach of Clause 3.2 was ruled.

The Panel noted that the two sets of guidelines had each been independently developed and subsequently distributed by AstraZeneca. Each bore prescribing information for Nexium 20-40mg. Each guideline referred to second line treatment with Nexium 40mg for patients with unresolved reflux-type dyspepsia. It was thus not sufficiently clear that a diagnosis of erosive reflux oesophagitis was needed before 40 mg therapy could begin. The guidelines were thus inconsistent with the particulars listed in the Nexium SPC as admitted by AstraZeneca. A breach of Clause 3.2 was ruled in relation to each document.

Proceeding commenced 18 March 2009

Case completed 24 April 2009

ANONYMOUS GENERAL PRACTITIONER v BOEHRINGER INGELHEIM

Conduct of representative

An anonymous non-contactable general practitioner complained that he had been unwittingly drawn into an industrial dispute between Boehringer Ingelheim and one of its representatives. The complainant was led to believe that as a result of the company conducting market research, he was asked to provide written evidence that he had seen this representative. The complainant later discovered from another pharmaceutical company's representative that this formed part of this individual's defence in a disciplinary procedure.

The complainant stated he was very selective about seeing representatives; however this dishonest incident had thrown into question his relationship with the pharmaceutical industry and he was disgusted with this type of conduct. Doctors should not be used as pawns and trivialised in this way.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that the complainant was anonymous and non-contactable. The representative had left Boehringer Ingelheim and there was no direct account from him as to what had occurred. When an allegation had been made about a representative's conduct it was difficult to determine precisely what had occurred. In this instance there were few details and no way to ask those directly involved for more information.

The complainant stated that he was asked to provide written evidence that he had seen the representative in question in relation to market research being carried out by Boehringer Ingelheim. The company stated that there was no market research and that the representative had contacted doctors during a period of sick leave. The Panel considered that Boehringer Ingelheim was responsible for the conduct of its employee regardless of whether or not that employee was on sick leave. The Panel was concerned that if the circumstances were as outlined by the complainant then high standards had not been maintained. However the Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. The Panel had some concerns about the arrangements and noted that it appeared that the representative had contacted doctors despite being on sick leave. Nonetheless with regard to the interaction between the representative and the doctor there was no way of knowing what had been said and in that regard the Panel did not consider that evidence had been provided to show that on the balance of probabilities the representative had behaved inappropriately and thus no breach of the Code was ruled.

An anonymous non-contactable general practitioner complained about the conduct of a representative from Boehringer Ingelheim Limited.

COMPLAINT

The complainant stated that he had been unwittingly drawn into an industrial dispute between the representative and Boehringer Ingelheim, whereby he was led to believe that as a result of the company carrying out market research, he was asked to provide written evidence that he had seen this representative. The complainant later discovered from another representative of another pharmaceutical company, that this letter formed part of the defence for this individual in a disciplinary procedure.

The complainant stated he was very selective about seeing representatives; however this dishonest incident had thrown into question his relationship with the pharmaceutical industry and he was quite disgusted with this type of conduct. Doctors should not be used as pawns and trivialised in this way.

When writing to Boehringer Ingelheim the Authority asked it to respond in relation to Clauses 2, 9.1, 12.2 and 15.2 of the Code.

RESPONSE

Boehringer Ingelheim denied a breach of Clauses 9.1, 12.2, 15.2 and 2.

Despite the anonymity of the complainant, Boehringer Ingelheim knew who the representative was. When Boehringer Ingelheim received the complaint, the representative in question was already suspended and under investigation due to concerns regarding communication with doctors.

The representative in question joined Boehringer Ingelheim in 2003 and was trained on the Code and Boehringer Ingelheim's Standard Operating Procedures in 2003, 2006 and 2007. This included internal training meetings and on-line training.

The representative was on sick leave from October

2008 until March 2009 and as stated above, had received full training until his period of absence. During the period of sick leave, the representative did not undertake any duties on behalf of Boehringer Ingelheim. This included all elements of his position as a medical representative and any contact with customers was without the company's authorization or knowledge.

Despite the extensive training mentioned above and the fact he was on sick leave, he contacted customers and in the interests of partnership and transparency, Boehringer Ingelheim included anonymised copies of the communications from the doctors that it had sourced through the investigation.

With regard to the market research that the representative had advised he was undertaking, Boehringer Ingelheim submitted that there was not any market research.

Boehringer Ingelheim believed its processes and training were robust. This was an unfortunate and regrettable incident that was isolated and unforeseeable. Boehringer Ingelheim did not believe that it had brought the industry into disrepute as this activity was not associated with promotion; it was one representative who had acted outside company procedures and standards.

Integrity and honesty were very important to Boehringer Ingelheim as reflected in the company code of conduct. Boehringer Ingelheim was investigating this thoroughly and the outcome of a disciplinary hearing was awaited.

In response to a request for further information, Boehringer Ingelheim stated that the representative was on sick leave from early October 2008 to early March 2009. The letters from doctors referred to visits made in September and early October 2008 that were part of standard promotional activity. However, the representative had visited these customers in February 2009 to obtain those letters. It was these later visits that the complaint referred to and not the visits in September and October last year.

Boehringer Ingelheim submitted that it was widely held that when an employee was off sick, they ceased to perform all functions for the company. The company's absence policy stated that during sickness employees should remain at home resting. The representative had not raised his intention to visit these doctors and it was a reasonable expectation, on the grounds above, that the representative would not have worked while off sick.

In response to a request to advise precisely what the representative asked the doctors in order for them to write the letters, Boehringer Ingelheim stated that it was unable to provide this information as the representative left the company before its internal investigation had been completed. The company did not therefore have an official account from the representative regarding this matter.

As previously stated, there was no market research being performed. There were no records of the visits in Boehringer Ingelheim's system as the employee was off sick during the time of the alleged incidents.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. Shortly after the company had submitted its initial response the representative had left Boehringer Ingelheim and there was no direct account from him as to what had occurred. When an allegation had been made about a representative's conduct it was difficult to determine precisely what had occurred. In this instance there were few details and no way to ask those directly involved for more information.

The Panel noted that it was a well established principle under the Code that pharmaceutical companies were responsible for the conduct of their representatives even if they acted outside the company's instructions.

There was insufficient detail to determine precisely what had happened. The complainant stated that he was asked to provide written evidence that he had seen the representative in question in relation to market research being carried out by Boehringer Ingelheim. The company stated that there was no market research and that the representative had contacted doctors during a period of sick leave. The Panel considered that Boehringer Ingelheim was responsible for the conduct of its employee regardless of whether or not that employee was on sick leave. The Panel was concerned that if the circumstances were as outlined by the complainant then high standards had not been maintained. However the Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. The Panel had some concerns about the arrangements and noted that it appeared that the representative had contacted doctors despite being on sick leave. Nonetheless with regard to the interaction between the representative and the doctor there was no way of knowing what had been said and in that regard the Panel did not consider that evidence had been provided to show that on the balance of probabilities the representative had behaved inappropriately and thus no breach of Clauses 2, 9.1, 12.2 and 15.2 was ruled.

Complaint received	**19 March 2009**
Case completed	**12 May 2009**

CASE AUTH/2220/3/09

ANONYMOUS v LILLY

Conduct of representative

An anonymous and non contactable complainant who described himself as a member of a practice based prescribing commissioning consortia (PBC) in a local primary care trust (PCT) complained an Eli Lilly representative had set up a six day diabetes training course for the complainant's group without the permission of the local diabetes team. He had the trainers discuss mostly his company's products.

The detailed responses from Lilly are given below.

The Panel noted that, according to Lilly, prior permission for the course was obtained from the local PCT. No breach of the Code was ruled.

The Panel noted that the Type 2 Diabetes Foundation Course was five separate days of education aimed at primary care and produced by a university. The course was sponsored by Lilly which met room rental and speaker costs. The course covered various aspects of diabetes diagnosis, lifestyle issues, treatment and complications.

The Panel noted that references to Lilly's or other companies' medicines appeared in some of the material provided. The Panel noted that some of the slide sets used came from clearly identified third party sources. Some of these slides referred to therapies either by brand name or non-proprietary name and it was not surprising, given Lilly's commercial interest in the area, that its medicines were named along with those from other companies. Similarly, a large proportion of slides which were not accredited to any organization or individual, also referred to Lilly's products. The Panel did not know if Lilly had influenced the content of these slides in any way.

Day three of the course, however, featured a presentation from a member of Lilly's staff using the company's own slides 'Initiating and Managing Injectable Therapy in [Type 2 Diabetes Mellitus]. An Electronic Pathway'. The title slide clearly stated 'Sponsored by Eli Lilly & Company Limited' and each slide featured the company logo in the bottom right hand corner. Given that this was thus a promotional presentation on behalf of Lilly, the company had to be responsible for it under the Code. The presentation promoted Humalog (insulin lispro), Humalin (insulin) and Byetta (exenatide), prescribing information for which was included in the material. The Panel noted that on the agenda although the presenter was named the fact that she was employed by Lilly was not; the presentation thus appeared to be an integral part of the university course which was not so. The Panel did not know what delegates were told about the provenance and status of the material and presentation. The Panel queried whether the presentation had been approved by the university for inclusion as part of its course. The Panel noted Lilly's submission that its presentation supplemented the university course.

The Panel noted the complainant's allegation that the trainers mostly discussed Lilly's products. The Panel noted that the audience comprised prescribers. The Panel considered, on balance, that the inclusion of the Lilly promotional presentation and material as an apparently integral part of an otherwise well-recognized independent educational course was inappropriate such that the representative had not maintained high standards. A breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

The complainant alleged that the representative had brought in a diabetes specialist nurse from elsewhere to some practices in his group and had the nurse see patients and change their medicine to Lilly's product Byetta. At one particular practice the patient was then seen at the hospital following complications.

The representative brought in other people to run audits and then pushed his medicines for the people as 'not controlled'. He had done this in nearly all of the GP practices in the group.

The Panel noted that the service implemented by a third party reviewed type 2 diabetics who were sub-optimally controlled on maximally tolerated doses of more than one oral therapy in line with National Institute for Health and Clinical Excellence (NICE)/local guidelines and/or practice agreed protocols. A service booklet described the service and featured a treatment flowchart reproduced from NICE Guideline 2008. The third treatment stage ie when oral therapy with metformin and a sulphonylurea had failed (HbA1c ≥7.5% or as individually agreed) was stated to be 'Add thiazolidinedione or insulin with active dose titration' but adjoining this was a highlighted box which read 'Exenatide may be considered here when body weight is a special problem and recommendations in the guideline are met'. The Panel noted that whilst this was an accurate reproduction of the NICE guidance it queried whether the reference to exenatide (Byetta) was appropriate in a booklet introducing a non promotional service. The flowchart otherwise referred to classes of product.

The representative introduced the service at an

initial meeting with the GP and completed the practice authorization form. The practice then contacted the third party which thereafter ran the service. The authorization form referred to the practice confirming both the treatment protocol and the nurse implementation of any actions that the practice requested.

One of the elements of the service was a third party nurse-facilitated 3 hour education and training workshop on the management of type 2 diabetes tailored to practice requirements. The workshop incorporated a case note review on patients suboptimally controlled on the maximally tolerated dose of more than one oral therapy in line with NICE guidelines. The practice staff thereafter conducted review clinics with the nurse in attendance.

The Panel noted that according to its summary of product characteristics (SPC) Byetta was indicated for treatment of type 2 diabetes in combination with metformin and/or sulphonylureas in patients who had not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

The Panel noted that the NICE Guideline on the management of type 2 diabetes stated that exenatide was not recommended for routine use in type 2 diabetes. It could be considered as an option only if the patient satisfied each of four requirements relating to body mass index; specific problems of psychological biochemical or physical nature arising from high body weight; inadequate glucose control with conventional oral agents after a trial of metformin and sulphonylurea; and other high cost medication, such as thiazolidinedione or insulin injection therapy would otherwise be started.

The training materials discussed the role of the representative, it was made clear that the service should be introduced briefly during a promotional call. A detailed discussion could only take place during a non promotional call which should take place at least 24 hours later. The requirements of the Code and its relevant supplementary information were discussed. One document referred to the representative providing administrative support. The material did not make it abundantly clear that the representative should be mindful of the requirements of the Code during the implementation of the audit.

The Panel noted that the material referred to exenatide and/or its licensed indication. The Panel noted that the practice confirmed the treatment protocol and authorized the activities of the nurse. The Panel noted that there was no evidence before it that the audit was inappropriate or that patients had been inappropriately switched to exenatide as alleged. Nor was there any evidence that the representative had pushed his medicines for uncontrolled patients as alleged. The Panel noted that the complainant was anonymous and non contactable. No additional material had been submitted. The complaint had the burden of proving their complaint on the balance of probabilities. The Panel ruled no breach of the Code including Clause 2.

The complainant alleged that the representative pushed GPs and practice nurses to prescribe insulin when not comfortable to do so (his company's of course) and not refer to specialists in the community. The reason was the specialists didn't use his.

The Panel considered that the complainant had not established that the representative had inappropriately promoted products as alleged. No breach of the Code were ruled.

The complainant alleged that the representative had funded the writing of the local PBC business plan and the diabetes protocol; this was unethical. The representative had acted via the PBC lead whom he had seen at least 15-20 times and taken out for many meals.

The Panel noted Lilly's submission that neither it nor the representative had funded the writing of the PBC business plan or diabetes protocol, and no breach was ruled.

The Panel was very concerned that Lilly's call record system did not detail whether a call was at the request of a health professional. It was thus difficult to see how Lilly could demonstrate compliance with the Code. Although Lilly had provided a copy of a field force presentation this only demonstrated that relevant training had been provided; it did not establish whether the number of calls upon a specific health professional complied with the Code.

The Panel noted Lilly's submission that the vast majority of the 17 calls in 2008 were solicited and was confident that its representative had not breached the Code. Records submitted by Lilly showed that the representative had face-to-face contact with the PBC lead seven times over the course of the nine weeks. Three of the meetings took place in the private rooms of restaurants. All but one of the meetings appeared to have been recorded as a 'group sell'. The remaining meeting was a 1:1 meeting during which the representative detailed the 'entire portfolio of insulins and Byetta'. The Panel was concerned about the arrangements and noted that the impression created by the arrangement of any meeting must be kept in mind. Nonetheless the burden of proof fell on the complainant. Lilly had submitted that the vast majority of calls were solicited. The Panel did not consider that it had been established on the balance of probabilities, that the calls by the representative on the PBC lead were inconsistent with the requirements of the Code and no breach was ruled.

The complainant alleged that the representative

had an accomplice, a local hospital diabetes consultant. This doctor always used Lilly products, did many talks for the representative who the complainant alleged remunerated him well. The complainant had seen them together at least 10 times in the last 6 months. The complainant was sure in the diabetes consultants area, if the Authority looked at Lilly insulin sales, there would be a huge increase. How could this be allowed to happen?

The Panel noted its critical comments about Lilly's call record system above and considered they were relevant here. In the last 6 months the consultant had presented at 11 Lilly sponsored meetings and had 17 1:1 meetings with the representative. The Panel noted Lilly's submission that its internal policies required 1:1 calls by the representatives to arrange the meeting and sign anticorruption and due diligence forms. The Panel queried whether a 1:1 meeting was indeed necessary to sign an anticorruption form on each occasion when the same speaker spoke at a series of company meetings in the same therapeutic area and was no doubt already familiar with the company's policies and procedures. Irrespective of the company's internal policy it was very difficult to see how 17 1:1 meetings in a six month period could meet the requirements of the Code.

Unlike its response above Lilly did not quantify the number of calls solicited by the consultant. The Panel considered the arrangements unacceptable. The Panel considered that the totality of the evidence was such that on the balance of probabilities the number of meetings with the hospital consultant was inconsistent with the Code and a breach of the Code was ruled. The Panel did not consider that there was evidence to establish that the meetings amounted to an inducement to prescribe Lilly's products or that the honoraria were otherwise unacceptable as alleged. No breaches of the Code were ruled.

The complainant alleged that the representative pushed the local GPs to refer to the diabetes consultant at a local hospital, because he used Lilly products, and not to its local specialist team for insulins and diabetes management.

The Panel considered that there was no evidence that the representative had inappropriately pushed the complainant's GPs to refer patients to the hospital consultant as alleged. No breach of the Code was ruled.

The complainant alleged that the representative constantly criticised its local diabetes service, the members of its secondary care team and their competency in doing their jobs.

The Panel considered that there was no evidence that the representative had behaved as alleged. No breaches of the Code were ruled.

The complainant alleged that the representative had on many occasions taken GPs from the complainant's group out for a meal with no education – just a free meal.

The Panel noted that each of the meetings was arranged by the PBC and sponsored by Lilly. The company was unable to provide copies of the agendas or invitations. The representative gave a promotional talk at each meeting. Lilly should be able to demonstrate that the meetings were appropriate to sponsor and that the arrangements complied with the Code including the invitation and agenda. It was difficult to see how such meetings could be approved as submitted by Lilly without sight of the agenda or invitation. The Panel was very concerned about the apparent lack of control. There was, however, no evidence to support the allegation that the meetings comprised a free meal with no education. No breaches of the Code were ruled.

The complainant alleged that the representative constantly pushed many of the local complainant's GPs to switch their patients from a competitor insulin to a Lilly insulin.

The Panel again noted that the complainant had not established that the representative had inappropriately promoted his products as alleged. No breach of the Code was ruled.

An anonymous and non contactable complainant who described himself as a member of a practice based prescribing commissioning consortia (PBC) in a primary care trust (PCT) complained about the conduct of a representative from Lilly.

When writing to Lilly, the Authority asked it to respnd in relation to Clauses 2, 8.2, 15.2, 15.3, 18.1, 18.4 and 19.1 of the Code.

1 Diabetes training course

COMPLAINT

The complainant alleged that the representative had set up a six day diabetes training course for the complainant's group without the permission of the local diabetes team. He had the trainers discuss mostly his company's products.

RESPONSE

Lilly explained that the representative was approached by the PBC lead and asked if he/Lilly could help with diabetes education within the PBC. As a consequence, the representative contacted another doctor, to run the university course which was proposed, with assistance from a consultant in diabetes.

It subsequently transpired, before the commencement of the course that although local

approval was to be sought, permission to run the course had not been obtained. The course was therefore put on hold until approval was obtained.

The six day Type 2 Diabetes Foundation Course was subsequently accredited by the Royal College of Nursing (RCN) and was run between 20 October 2007 and 14 June 2008 – by a university accredited trainer and diabetes education facilitator (nurse consultant), the local professor of diabetes and the local diabetes consultant. Lilly provided copies of course documentation. The course covered a wide range of diabetes-related topics. The slides used were checked and approved by one of the company's clinical research physicians (CRPs). The agendas and slide-sets used did not refer to Lilly's (or any other company's) medicines, since the course was solely educational, not promotional. Day Six was set aside for end of course exams.

The agenda for day one stated that 'This meeting has been sponsored by an Educational Grant provided by Lilly', which was not so; the meeting was sponsored by Lilly and subsequent agendas stated 'This Educational Event is sponsored by Lilly'. Lilly explained that the 6 day course, the Type 2 Diabetes Foundation Course, was facilitated by a university accredited trainer (nurse consultant). On completion of the course, each delegate received a certificate, an example of which was provided.

With regard to the slides sets used, these were all approved in advance of the course by one of Lilly's CRPs. It was not possible to determine which of the slides was used with each part of the agenda, since, being a training course, the nurse consultant as the educational facilitator, would have moved between the available slides, dependent on the discussion. The additional Lilly material was presented by, a medical liaison officer and a member of Lilly's medical department. The Lilly materials were clearly branded as such and did not form part of the university accredited course facilitated by the nurse consultant, but supplemented it.

PANEL RULING

The Panel noted that on receipt of Lilly's response it had become apparent that the five day course at issue had been held on various dates between 20 October 2007 and June 2008 and thus the requirements of the 2006 Code applied. However the clauses cited by the Authority were the same in the 2006 Code as in the 2008 Code. The case was thus considered under the 2008 Code.

The Panel noted that the complainant was anonymous and non contactable. The complainant had not provided any additional material to support their allegations. The complainant had the burden of proving their complaint on the balance of probabilities.

The complainant had alleged that the course was run without the permission of the local diabetes team. The Panel noted that, according to Lilly, prior permission for the course was obtained from the local PCT. No breach of Clause 15.2 was ruled on this point.

The Panel noted that the Type 2 Diabetes Foundation Course was five separate days of education aimed at primary care and produced by a university. The course was sponsored by Lilly which met room rental and speaker costs. The course covered various aspects of diabetes diagnosis, lifestyle issues, treatment and complications. The Panel noted that it was possible for a company to sponsor material or an activity produced and provided by a third party which mentioned its own products and not be liable under the Code, but only if, *inter alia*, there had been a strictly arm's length arrangement between the parties. In practical terms the arrangements must be such that there could be no possibility that the pharmaceutical company had been able to exert any influence or control over the final content and provision of the material or activity.

The Panel noted that contrary to Lilly's submission that the slide sets used did not refer to Lilly's or other companies' medicines such references did appear in some of the material provided. The Panel noted that some of the slide sets used came from clearly identified third party sources. Some of these slides referred to therapies either by brand name or non-proprietary name and it was not surprising, given Lilly's commercial interest in the area, that its medicines were named along with those from other companies. Similarly, a large proportion of slides which were not accredited to any organization or individual, also contained references to Lilly's products. The Panel did not know if Lilly had influenced the content of these slides in any way.

Day three of the course, however, featured a one and a half hour presentation from a member of Lilly's staff using the company's own slides 'Initiating and Managing Injectable Therapy in [Type 2 Diabetes Mellitus]. An Electronic Pathway' (ref DBT148 June 2008). The title slide clearly stated 'Sponsored by Eli Lilly & Company Limited' and each slide featured the company logo in the bottom right hand corner. Given that this was thus a promotional presentation on behalf of Lilly, the company had to be responsible for it under the Code. The presentation promoted Humalog (insulin lispro), Humalin (insulin) and Byetta (exenatide), prescribing information for which was included in the material. The Panel noted that on the agenda although the presenter was named the fact that she was employed by Lilly was not; the presentation thus appeared to be an integral part of the university course which was not so. The Panel did not know what delegates were told about the provenance and status of the material and presentation. The Panel queried whether the presentation had been approved by the university for inclusion as part of its course. The Panel noted Lilly's submission that its presentation supplemented the university course.

The Panel noted the complainant's allegation that the trainers mostly discussed Lilly's products. The Panel noted that the audience comprised prescribers. The Panel considered, on balance, that the inclusion of the Lilly promotional presentation and material as an apparently integral part of an otherwise well-recognized independent educational course was inappropriate such that the representative had not maintained high standards. A breach of Clause 15.2 was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 and no breach of that Clause was ruled.

2 Diabetes specialist nurse and audit

COMPLAINT

The complainant alleged that the representative had brought in a diabetes specialist nurse from elsewhere to some practices in his group and had the nurse see patients and change their medicine to Lilly's product Byetta. At one particular practice the patient was then seen at the hospital following complications.

The representative brought in other people to run audits and then pushed his medicines for the people as 'not controlled'. He had done this in nearly all of the GP practices in the group.

RESPONSE

Lilly explained that it offered GPs a service, called the Enhanced Management of Type 2 Diabetes (EMD), in accordance with the provisions of the Code, including Clauses 18.1 and 18.4. It was intended to assist GP practices to implement the National Institute for health and Clinical Excellence (NICE)/local guidelines and/or practice protocols by reviewing type 2 diabetics who were sub-optimally controlled on maximally tolerated doses of more than one oral therapy. The service was provided via a third party which supplied IT and nurse resources across the UK for the appropriate identification and review of patients. The service was a therapy review, not switch, service: the representative had confirmed his understanding that this was how the EMD has worked; accordingly there was no question of the representative or 'pushing' Lilly medicines as alleged.

Since this service was unconnected with the promotion of any medicine, there was no obligation on a practice to participate unless practice staff wished to do so.

The programme worked by the practice being offered the service and it being explained to them. The nurse provided by the third party visited the practice and, working with practice staff, ran an educational and training workshop for them on the management of type 2 diabetes. The workshop was tailored to meet the individual practices' requirements: the 'Miquest' audit tool performed a search of all diabetic patients in the practice regardless of their current management. A case note review was conducted to identify patients with sub-optimally controlled diabetes, as described above: the practice determined the type of patients that it was most interested in reviewing; whilst those failing on oral therapies were one group, it might choose others. As with all the elements of this service, this decision was entirely in the hands of the participating practice and was documented as such in the practice authorisation form (a copy of which was provided). The practice staff then determined which patients to invite into the clinic, and conducted the therapy reviews, supported by the nurse advisor. Although the third party nurse advisor might offer support, it was the practice staff who decided on and initiated treatment, or made changes.

This service was offered to the PBC lead, and the service was run in ten local practices.

In response to a request for further information, Lilly provided copies of the representatives' training materials.

Accordingly, Lilly denied the allegations.

PANEL RULING

The Panel noted that medical and educational goods and services had to enhance patient care, or benefit the NHS and maintain patient care. With regard to therapy review services the supplementary information to Clause 18.4 provided helpful guidance. A therapeutic review which aimed to ensure that patients received optimal treatment following a clinical assessment was a legitimate activity for a pharmaceutical company to support and/or assist. The results of such clinical assessments might require, amongst other things, possible changes of treatment including changes of dose or medicine or cessation of treatment. A genuine therapeutic review should include a comprehensive range of relevant treatment choices including non medicinal choices and should not be limited to the medicines of the sponsoring pharmaceutical company. The arrangements for therapeutic review must enhance patient care, or benefit the NHS and maintain patient care. The decision to change or commence treatment must be made for each individual patient by the prescriber and every decision to change an individual's treatment must be documented with evidence that it was made on rational grounds. The supplementary information also stated that sponsored health professionals should not be involved in the promotion of specific products. Nurses were required to comply with the Nursing and Midwifery Council Code of Professional Conduct which required that registration status was not used in the promotion of medicines.

The Panel noted that the service implemented by the third party reviewed type 2 diabetics who were sub-optimally controlled on maximally tolerated doses of more than one oral therapy in line with NICE/local guidelines and/or practice agreed protocols. A service booklet described the service and featured a treatment flowchart reproduced from NICE Guideline 2008. The third treatment stage ie when oral therapy with metformin and a sulphonylurea had failed (HbA1c ≥7.5% or as individually agreed) was stated to be 'Add thiazolidinedione or insulin with active dose titration' but adjoining this was a highlighted box which read 'Exenatide may be considered here when body weight is a special problem and recommendations in the guideline are met'. The Panel noted that whilst this was an accurate reproduction of the NICE guidance it queried whether the reference to exenatide (Byetta) was appropriate in a booklet introducing a non promotional service. The flowchart otherwise referred to classes of product. Clause 18.4 stated that medical and educational goods and services must not bear the name of any medicine. The supplementary information to that clause made it clear that this requirement did not apply when the goods consisted of independently produced textbooks or journals which included as part of their texts the names of medicines.

The representative introduced the service at an initial meeting with the GP and completed the practice authorization form. The practice then contacted the third party which thereafter ran the service. The authorization form referred to the practice confirming both the treatment protocol and the nurse implementation of any actions that the practice requested.

One of the elements of the service was a nurse-facilitated 3 hour education and training workshop on the management of type 2 diabetes run by the third party and tailored to practice requirements. The workshop incorporated a case note review on patients suboptimally controlled on the maximally tolerated dose of more than one oral therapy in line with NICE guidelines. The practice staff thereafter conducted review clinics with the nurse in attendance.

The Panel noted that according to its summary of product characteristics (SPC) Byetta was indicated for treatment of type 2 diabetes in combination with metformin and/or sulphonylureas in patients who had not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

The Panel noted that Section 1.6.3 of the NICE Guideline 66 on the management of type 2 diabetes stated that exenatide was not recommended for routine use in type 2 diabetes. It could be considered as an option only if the patient satisfied each of four requirements relating to body mass index; specific problems of psychological biochemical or physical nature arising from high body weight; inadequate glucose control with conventional oral agents after a trial of metformin and sulphonylurea; and other high cost medication, such as thiazolidinedione or insulin injection therapy would otherwise be started.

The training materials discussed the role of the representative, it was made clear that the service should be introduced briefly during a promotional call. A detailed discussion could only take place during a non promotional call which should take place at least 24 hours later. The requirements of Clause18.4 and its relevant supplementary information were discussed. One document referred to the representative providing administrative support. The material did not make it abundantly clear that the representative should be mindful of the requirements of the Code during the implementation of the audit.

The Panel noted that the material referred to exenatide and/or its licensed indication. The Panel noted that the practice confirmed the treatment protocol and authorized the activities of the nurse. The Panel noted that there was no evidence before it that the audit was inappropriate or that patients had been inappropriately switched to exenatide as alleged. Nor was there any evidence that the representative had pushed his medicines for uncontrolled patients as alleged. The Panel noted that the complainant was anonymous and non contactable and noted its comments at point 1 above about the burden of proof. The Panel ruled no breach of Clauses 18.1 and 18.4. The Panel consequently ruled no breach of Clause 2.

3 Conduct of the representative

COMPLAINT

The complainant alleged that the representative pushed GPs and practice nurses to prescribe insulin (Lilly's of course) even when not comfortable to do so and not to refer to specialists in the community because the specialists didn't use his medicines.

RESPONSE

Lilly explained that health professionals with adequate knowledge and training might prescribe a range of medicines according to local guidelines and formularies. Lilly understood that local GPs in this area might only initiate insulin with local PCT approval. Such GPs apparently acquired accreditation by attendance on the 'Insulins for Life' programme run by a diabetes consultant at a local hospital.

If a GP was accredited to prescribe insulins, then the representative might appropriately call on this GP to promote Lilly products, and using only materials certified in accordance with the Code. Lilly could provide copies of representatives' promotional materials if required.

Lilly submitted that the representative did not seek to hinder internal referral processes or pressurise staff into prescribing Lilly medicines when they were not comfortable to do so.

Lilly also referred to its response at point 6, below.

Accordingly, Lilly denied this allegation.

PANEL RULING

The Panel noted that the representative's primary role was to promote and inform health professionals about Lilly products. Such activity had to comply with the Code. The complainant had not established that the representative had inappropriately promoted his products as alleged. No breach of Clause 15.2 was ruled.

4 Funding of business plan and protocol

COMPLAINT

The complainant alleged that the representative had funded the writing of the local PBC business plan via the PBC lead. The representative had seen the PBC lead on at least 15-20 occasions and taken him out for many meals. He had funded the writing of the diabetes protocol, which the complainant alleged was totally unethical.

RESPONSE

Lilly submitted that neither the representative personally, nor the company, funded the writing of the PBC business plan or diabetes protocol. Accordingly, Lilly was unable to provide a copy of the protocol. There was no evidence of any other funding from Lilly for this activity via its Grants and Donations Committee, which administered grants and donations in response to unsolicited requests.

In 2008, the representative saw the PBC lead 17 times in 1:1 calls, the vast majority of which were at his request. These were not only promotional calls, but calls to help organise and run the six day training course, referred to at point 1, above. Unfortunately however, Lilly's call record system did not detail whether a call was at the request of the health professional or the company, so Lilly was unable to give the precise details in this regard. Lilly was however confident that the representative had not breached the requirements of Clause 15, including those of Clause 15.4.

So far in 2009 the representative had had one 1:1 call with the PBC lead at the surgery to promote Lilly medicines. Additionally, there had been 5 group sell meetings with members of this PBC, three of which had been at restaurants and two at the surgery.

Accordingly, Lilly denied the allegation.

In response to a request for further information about its call record system and whether such data was recorded in any other format to demonstrate compliance with Clause 15.4, Lilly stated that, as might be seen from the representatives' materials provided in relation to point 2 above, all of its representatives were trained on the Code and its internal SOPs. The requirements of Clause 15.4 ('Frequency and manner of calls on doctors and other prescribers') were specifically addressed as part of that training. Such data was not otherwise presently recorded in the call record system.

PANEL RULING

The Panel noted Lilly's submission that neither it nor the representative had funded the writing of the PBC business plan or diabetes protocol. It was unclear whether the diabetes plan had been discussed at any of the six group meetings held with members of the PBC. The Panel ruled no breach of Clauses 15.2 and 18.1 of the Code on this point.

The Panel noted that the allegation about the number of calls upon the PBC lead concerned Clause 15.4 of the Code. Whilst Lilly had not been asked to address this clause, it had, nonetheless, cited Clause 15.4 and responded in relation to its requirements. The Panel thus decided to rule under this clause.

The supplementary information to Clause 15.4 provided that the number of calls on, *inter alia*, a doctor by a representative each year should not normally exceed three on average, excluding attendance at group meetings, a visit requested by a doctor or call to respond to a specific enquiry or a visit to follow up a report of an adverse reaction. The Panel noted Lilly's account of the number of visits. The Panel was very concerned that Lilly's call record system did not detail whether a call was at the request of a health professional. It was thus difficult to see how Lilly could demonstrate compliance with Clause 15.4 of the Code. Lilly had explained that such compliance was demonstrated by reference to its representatives' training materials. That was not so. Lilly had provided a copy of a presentation 'The ABPI Code of Practice. Focus on Field Activities' (ref DBT 188) which discussed at slide 21 the requirements of Clause 15.4. Whilst such material demonstrated that relevant training had been provided it did not establish whether the number of calls upon a specific health professional complied with Clause 15.4.

The Panel noted Lilly's submission that the vast majority of the 17 calls in 2008 were solicited and was confident that its representative had not breached Clause 15.4 of the Code. Records submitted by Lilly showed that the representative had face-to-face contact with the PBC lead seven times over the course of the nine weeks. Three of

the meetings took place in the private rooms of restaurants. All but one of the meetings appeared to have been recorded as a 'group sell'. The remaining meeting was a 1:1 meeting during which the representative detailed the 'entire portfolio of insulins and Byetta'. The Panel was concerned about the arrangements and noted that the impression created by the arrangement of any meeting must be kept in mind. Nonetheless the burden of proof fell on the complainant. Lilly had submitted that the vast majority of calls were solicited. The Panel did not consider that it had been established on the balance of probabilities, that the calls by the representative on the PBC lead were inconsistent with the requirements of Clause 15.4 and its supplementary information. No breach of Clause 15.4 was thus ruled.

5 Meetings with a hospital consultant

COMPLAINT

The complainant alleged that the representative had an accomplice, a consultant in diabetes at a local hospital. This doctor always used Lilly products, did many talks for the representative who, the complainant alleged, remunerated him well. The complainant stated that the Authority would need to investigate how many times the representative had seen him. The complainant had seen them together on at least 10 occasions in the last 6 months. The complainant was sure in the diabetes consultant's area there would be a huge increase in the sales of Lilly's insulins. How could this be allowed to happen?

RESPONSE

Lilly stated that the diabetes consultant was, and had been, a speaker for Lilly, and also often asked the representative to visit. The consultant had presented at eleven Lilly sponsored meetings in the last 6 months and the representative had visited the consultant for 1:1 calls on 17 occasions during this time: in order to comply with Lilly's company policies and procedures, arrangement of a speaker meeting by a representative necessitated 1:1 calls to arrange the meeting, and sign anti-corruption due diligence forms before setting up the speaker contract. Lilly provided details of the speaker fees paid to the consultant in the last 6 months.

Lilly submitted that it did not know whether the consultant used its medicines to the exclusion of all others (although, from a practical standpoint, it doubted it). The representative's promotion of Lilly medicines to the consultant was within the Code and neither the representative nor the company would seek in any way to interfere with his prescribing decisions.

Lilly denied breaches of Clauses 18.1 and 19.1 of the Code.

PANEL RULING

The Panel noted its comments about Clause 15.4 at point 4 above and considered that they applied here. Whilst Lilly had not cited Clause 15.4 it had nonetheless responded in relation to the requirements of that clause.

The Panel noted its critical comments about Lilly's call record system at point 4 above and considered they were relevant here. In the last 6 months the consultant had presented at 11 Lilly sponsored meetings and had 17 1:1 meetings with the representative. The Panel noted Lilly's submission that its internal policies required 1:1 calls by the representatives to arrange the meeting and sign anticorruption and due diligence forms. The Panel queried whether a 1:1 meeting was indeed necessary to sign an anticorruption form on each occasion when the same speaker spoke at a series of company meetings in the same therapeutic area and was no doubt already familiar with the company's policies and procedures. Irrespective of the company's internal policy it was very difficult to see how 17 1:1 meetings in a six month period could meet the requirements of Clause 15.4 and its supplementary information.

Unlike its response at point 4 above Lilly did not quantify the number of calls solicited by the consultant. The Panel considered the arrangements unacceptable. The Panel considered that the totality of the evidence was such that on the balance of probabilities the number of meetings with the hospital consultant was inconsistent with Clause 15.4 and its supplementary information. A breach of Clause 15.4 was ruled. The Panel did not consider that there was evidence to establish that the meetings amounted to an inducement to prescribe Lilly's products or that the honoraria were otherwise unacceptable as alleged. No breach of Clauses 18.1 and 19.1 were ruled.

6 Referral to a hospital consultant

COMPLAINT

The complainant alleged that the representative pushed the local GPs to refer to the diabetes consultant at a local hospital who used Lilly products, and not to its local specialist team for insulins and diabetes management.

RESPONSE

Lilly understood that there were two local hospitals. A 'choose and book' system was used, whereby the GP and patient together could determine where the patient would like to obtain treatment.

Lilly also understood that the PBC had, until

recently, chosen the diabetes consultant as its lead consultant, but that at a meeting, in February 2009, members of the PBC group decided to work with a different diabetes consultant (of another hospital) (details of meetings 2 and 6, were provided).

Lilly had been unable to find anything to substantiate the allegation and the representative denied it.

Accordingly, this allegation was denied.

PANEL RULING

The Panel noted the complainant was anonymous and its comments in this regard at point 1 above. The Panel considered that there was no evidence that the representative had inappropriately pushed the complainant's GPs to refer patients to the hospital consultant as alleged. No breach of Clause 15.2 was ruled.

7 Alleged disparagement of diabetes service

COMPLAINT

The complainant alleged that the representative constantly criticised the local diabetes service, the members of its secondary care team and their competency in doing their jobs.

RESPONSE

The representative denied this accusation and Lilly would further note that several of the local clinicians – including the local diabetes consultant – participated in the diabetes course referred to at Point 1, which ran counter to this point.

Accordingly, this allegation was denied and Lilly denied breaching either Clause 2 of Clause 8.2 of the Code, or at all.

PANEL RULING

The Panel noted the complainant was anonymous and its comments in this regard at point 1 above. There was no evidence that the representative had behaved as alleged. No breach of Clauses 8.2 and 2 were ruled.

8 Hospitality

COMPLAINT

The complainant alleged that the representative had on many occasions taken GPs from the complainant's group out for a meal with no education – just a free meal.

RESPONSE

The representative denied this allegation. The representative had conducted 'group sells' in private rooms at local restaurants. Lilly enclosed details of the representative's group sells recorded on its call record system: all such group sells were conducted in accordance with the company's internal processes and procedures, had clear objectives and content. The provision of food or hospitality without associated educational content was not permitted under its internal rules and procedures or the Code. The representative knew this and his most recent training – on Lilly's Red Book, which underlined the company's core values of respect for people, integrity and excellence – was completed on 26 January 2009. The representative originally did his ABPI Code training in 1999, passing the exam in May 1999. The representative most recently had an update on the Code in September 2009.

Lilly stated that the three group sells which took place in restaurants (details of which were provided), were all approved, had clear objectives and content and fell within Lilly guidelines. In each case, the hospitality was secondary to the main purpose of the event. Lilly also enclosed copies of the Byetta (exenatide) group sell slides.

Accordingly, this allegation was denied.

In response to a request for further information Lilly explained that meetings in two named restaurants took place in private rooms at those restaurants. Each of the meetings was arranged by the PBC and sponsored by Lilly. As part of this sponsorship, the representative undertook a group sell presentation for the products mentioned in the screen shots supplied previously. The representative had confirmed that the invitations were sent by the PBC with a clear declaration of Lilly sponsorship. Consequently Lilly did not have copies of either the invitations or the agendas but offered to obtain them if required.

PANEL RULING

The Panel noted Lilly's submission that each of the meetings was arranged by the PBC and sponsored by Lilly. The company was unable to provide copies of the agendas or invitations. The representative gave a promotional talk at each meeting. Lilly should be able to demonstrate that the meetings were appropriate to sponsor and that the arrangements complied with the Code including the invitation and agenda. It was difficult to see how such meetings could be approved as submitted by Lilly without sight of the agenda or invitation. The Panel was very concerned about the apparent lack of control. There was, however, no evidence to support the allegation that the meetings comprised a free meal with no education. No breach of Clauses 2 and 19.1 were ruled.

9 Conduct of the representative

COMPLAINT

The representative also pushed constantly many of the complainant's GPs to switch their patients from a competitor insulin to a Lilly insulin.

RESPONSE

As a pharmaceutical diabetes representative, a key part of the representative's role was the promotion of patient safety and well-being, in addition to the promotion of Lilly medicines. As part of his work, where the health professional asked for suggestions as to how the care of an individual patient might be improved, the representative might legitimately properly promote a Lilly product, within the scope of the Code: he and Lilly would, however, not advocate switching patients from one therapy to another if they were well-controlled on their current regime. Lilly enclosed copies of promotional materials used by its representatives.

The allegation was denied.

Lilly stated that it strove to ensure that its dealings with health professionals were ethical, complied with the Code and of the highest professional standards. The company had concluded, from its investigation into the matters above, that the representative at issue had not acted unethically or breached Clauses 15.2 or 15.3 of the Code; Lilly had not brought discredit to the pharmaceutical industry at (Clause 2).

PANEL RULING

The Panel considered its ruling at point 3 above was relevant here. The Panel ruled no breach of Clause 15.2 of the Code.

Complaint received **25 March 2009**

Case completed **24 June 2009**

PUBLIC HEALTH REGISTRAR v RECKITT BENCKISER

Promotion of Gaviscon Advance

A public health registrar alleged a breach of Clause 2 in that Reckitt Benckiser's promotion of Gaviscon Advance (sodium alginate and potassium bicarbonate) had brought discredit to, and reduced confidence in, the pharmaceutical industry because of its cumulative breaches of a similar and serious nature over the past few months.

In Case AUTH/2138/7/08 two advertisements that had appeared in the BMJ were ruled to be misleading in breach of the Code. Case AUTH/2205/2/09 referred to a third advertisement which had breached the Code.

The detailed response from Reckitt Benckiser is given below.

The Panel noted that in both Case AUTH/2138/7/08 and Case AUTH/2205/2/09 it had ruled breaches of the Code. The supplementary information to Clause 2 stated, as one example of an activity likely to be in breach of Clause 2, multiple/cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time.

The Panel was concerned that both the previous cases demonstrated an apparent poor knowledge of the requirements of the Code. In that regard the Panel noted that Reckitt Benckiser had initiated a compliance programme which included in-house training by an external consultant.

A ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. Despite its concerns about the previous cases the Panel did not consider that their cumulative effect was such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry as alleged. No breach of Clause 2 was ruled.

A public health registrar complained about the promotion of Gaviscon Advance (sodium alginate and potassium bicarbonate) by Reckitt Benckiser Healthcare (UK) Limited.

COMPLAINT

The complainant alleged a breach of Clause 2 of the Code by Reckitt Benckiser in its promotion of Gaviscon Advance in recent months.

In Case AUTH/2138/7/08, which referred to two advertisements for Gaviscon Advance that appeared in the BMJ last year, the Panel ruled that both advertisements were misleading in breach of the Code.

Case AUTH/2205/2/09 referred to a third advertisement for the same product, which appeared a few months later in the same journal, and had breached Clauses 6.3, 7.2, 9.10 and 12.1 of the Code. [When the Panel considered the complaint now before it, Reckitt Benckiser had accepted the Panel's rulings of breaches of the Code in Case AUTH/2205/2/09 although the complainant's appeal of a ruling of no breach of the Code had yet to be considered.]

The complainant considered that Reckitt Benckiser's activities had brought discredit to, and reduced confidence in, the pharmaceutical industry because of its cumulative breaches of a similar and serious nature in the promotion of Gaviscon Advance over the past few months.

RESPONSE

Reckitt Benckiser strongly disputed the allegation. While it had fully accepted and addressed the previous Panel rulings it did not believe the two cases were connected or could, in combination, bring discredit upon the pharmaceutical industry.

Previous cases and Panel rulings

The two cases in question were Case AUTH/2138/7/08 and Case AUTH/2205/2/09. The former was in respect of two advertisements featured in the BMJ on 22 March 2008 and 12 April 2009, the latter concerned a supplement distributed in the BMJ on 7 February 2009 that presented the findings of an advisory board meeting, this case was not yet concluded but the information presented here was based on the Panel ruling received on 18 March 2009.

Case AUTH/2138/7/08

This case concerned two advertisements reporting *in vitro* experiments that had shown Gaviscon Advance Aniseed Suspension could impede the reflux of bile and pepsin and inhibit the activity of pepsin. It was alleged that the two advertisements had presented *in vivo* conclusions based on *in vitro* experimental data. Reckitt Benckiser refuted the claim stating that the data had been presented with full experimental detail and numerous references to the fact that the studies were conducted *in vitro*. The advertisements were included in a professional journal where it was reasonable to expect the audience to understand the material presented without drawing misleading conclusions.

The Panel ruled that aspects of the material appeared to relate directly to the clinical situation and that this was misleading. A breach of Clause 7.2 was ruled in respect of each advertisement.

Case AUTH/2205/2/09

This case concerned a supplement distributed with the BMJ that reported the findings of an advisory board – a multidisciplinary group of experts brought together to discuss laryngopharyngeal reflux. The complainant questioned whether the advisory meeting had in fact taken place and was a genuine advisory board meeting. It was further alleged that the findings reported were disguised promotion. Reckitt Benckiser again disputed all the allegations and believed that the supplement, that had been reviewed and accepted by the BMJ, written by a third party and reviewed and approved by the advisory board members, was an educational supplement and not an advertisement for Gaviscon Advance.

The Panel found that Reckitt Benckiser was not sufficiently at 'arm's length' from the meeting, subsequently the supplement was ruled in breach of Clauses 6.3 and 12.1. The sponsorship declaration was not sufficient and a breach of Clause 9.1 was ruled. A breach of Clause 7.2 was also ruled as it was considered that the supplement had not fully covered all aspects noted in the introduction. No breach of Clause 9.7 was ruled as the supplement was not an extreme format or could be confused to be part of the BMJ as alleged; this was subject to an as yet unconsidered appeal by the complainant.

Action taken to ensure future compliance

Reckitt Benckiser had already taken substantial action with regard to the Case AUTH/2138/7/08 to ensure future compliance. Case AUTH/2205/2/09 was not yet concluded but steps had been taken in response to the Panel's ruling and these would be reviewed after the appeal had been heard.

Case AUTH/2138/7/08 was found in breach due to the extrapolation of *in vitro* data to suggest that Gaviscon Advance Aniseed Suspension might protect the oesophagus from the reflux of bile and pepsin in the clinical setting. Subsequently Reckitt Benckiser had amended the Gaviscon licence accordingly and updated Sections 4.1 and 5.1 of the summary of product characteristics (SPC) to include references to bile and pepsin.

As noted, Case AUTH/2205/2/09 was unresolved but Reckitt Benckiser had committed to review and improve its current processes, particularly in relation to activities with external groups. Previous cases on advisory boards and subsequent documents arising from them were under review and the company intended to consult the Authority if there was any ambiguity in its interpretation. In addition it had committed to hold regular meetings of the relevant regulatory and medical team members to examine the Code of Practice Review as a group and to record learnings from this more formally.

In the broader context of compliance, and although not specifically relevant to these cases, a wide reaching compliance programme was in progress to ensure there was a thorough knowledge of the Code and full understanding of its implementation in practice throughout the organisation. Already this year the annual NHS commercial team meeting was largely dedicated to training on the Code. The 2008 Code was presented and a full day's training was given by an external expert consultant. The company intended to repeat this process within six months with relevant marketing staff.
Reckitt Benckiser was committed to reviewing and enhancing approval and compliance procedures. Regulatory and medical staff, who were fully trained on the Code, would continue to attend repeat sessions on a regular basis, every 2-3 years to maintain an expert knowledge of the Code. To add context to the control exercised by the regulatory and medical teams, regarding production of copy, the items referred to in the complaint were two of many that were certified within the organisation. Reckitt Benckiser took the approval and certification processes very seriously and always maintained a high level of integrity when doing so. In the last twelve months nearly 600 pieces had been certified, of which around 100 had been subject to the Code. Reckitt Benckiser was predominantly an over-the-counter company and as such the remainder of items were more commonly subject to the Proprietary Association of Great Britain Code.

The implications of the breaches ruled

Both cases at issue had highlighted areas in which the Reckitt Benckiser should, and had, taken action to ensure Code compliance was maintained. Any breach of the Code was significant and the company took complaints very seriously. The complainant noted that it was the serious nature of both breaches that should result in a subsequent breach of Clause 2. There were degrees of severity depending on the implications of different breaches, which was further borne out by reviewing previous cases ruled in breach of Clause 2. Reckitt Benckiser considered that the breaches ruled in the two cases at issue were not of such severity that any discredit had been brought upon the pharmaceutical industry or that confidence in the industry had been undermined, particularly in light of the rulings of the previous case.

In Case AUTH/2138/7/08 the breach resulted from issues relating to the extrapolation of data; in Case AUTH/2205/2/09 the breaches related to the means in which information was communicated. In neither case was the accuracy of the data or information at fault. Consequently these breaches had not resulted in inappropriate prescribing or use of Gaviscon Advance, either in isolation or in preference to a

more suitable product. More importantly there was never even minimal risk to patient safety. In Case AUTH/2138/7/08 claims about protection of the oesophagus from the reflux of bile and pepsin were found to be misleading. The product licence for Gaviscon Advance Aniseed Suspension had subsequently been updated and similar claims could be fully substantiated. In Case AUTH/2205/2/09 the report of the advisory board, comprising expert health professionals was approved by the advisory board members prior to publication. This focussed on laryngopharyngeal reflux and currently Gaviscon Advance Aniseed Suspension was the only product licensed for the symptomatic relief of this condition. Notably in neither case was the information made available to patients or the public, it was only available to health professionals via a distinguished medical journal that had approved the material.

Furthermore, the complainant suggested that these were cumulative breaches of a similar and serious nature. Indeed, if Case AUTH/2205/2/09 was to represent a breach of undertaking of Case AUTH/2138/7/08 this would be a reasonable assertion and would demonstrate disregard for previous rulings and a serious failing that might bring the industry into disrepute. This was not the case however and the two cases were quite unrelated and occurred almost a year apart.

Reckitt Benckiser accepted that in both cases a breach of Clause 7.2 was ruled, however in Case AUTH/2138/7/08 this related to a claim that was deemed unsubstantiated by the data, due to its extrapolation to the clinical situation. In Case AUTH/2205/2/09 no similar or related material had been used, the topic of the piece was completely different and the breach was not related to any claims. The medical writer had suggested in the introduction to the supplement that management of gastro-oesophageal reflux disease would be discussed alongside a number of other topics but this was not accurate as the focus of the piece was laryngopharyngeal reflux.

To state, therefore, that these breaches were of a cumulative, similar and serious nature misrepresented the cases and the previous findings of the Panel. Reckitt Benckiser stressed that these breaches were not acceptable and would not be repeated, but it would further assert that they were not of a similar nature that would suggest a disregard for previous rulings. They did not therefore bring discredit upon or reduce confidence in the industry.

The previous cases ruled in breach of Clause 2

The breaches of Clause 2 ruled in the last two years generally fell into a number of categories where:

- action resulting in a breach of the Code directly impacted patients or the public
- action resulting in a breach of the Code directly impacted prescribing habits
- there had been a breach of previous undertaking
- promotion of medicines had occurred without a marketing authorization.

Impact on patients might have occurred either by direct promotion to the patients or the public, by offering patients incentives to request a particular medicine or even risking their safety. Direct impact on the prescribing of a medicine might have resulted in its inappropriate use, either by misrepresentation of a medicine, or its features comparative to other therapies or by attempting to offer incentives to health professionals to prescribe a certain product. A breach of previous undertaking was deemed to show serious disregard for authority rulings; be that the Authority or the Medicines and Healthcare products Regulatory Agency. Promotion without a marketing authorization had occurred due to activity prior to the grant of a licence.

There were undoubtedly serious consequences that might be expected to bring discredit upon the pharmaceutical industry and in all these previous cases the impact of the activity found to be in breach far outweighed any implications of the breaches ruled in Case AUTH/2138/7/08 and AUTH/2205/2/09.

It was feasible that a pharmaceutical company could misinterpret the Code without bringing the industry into disrepute or undermining confidence, which would imply serious misconduct or deliberate deception. Occasional breaches were not uncommon; many companies were subject to multiple breaches without ever bringing the industry into disrepute and thus being ruled in breach of Clause 2. While it was not acceptable to be found in breach of the Code, Reckitt Benckiser considered that the breaches described in Cases AUTH/2138/7/08 and AUTH/2205/2/09 were not of such serious or similar nature that they could, even in combination, constitute a breach of Clause 2. Furthermore, it was noted in the supplementary information to Clause 2 that 'A ruling of a breach of this clause is a sign of particular censure and is reserved for such circumstances'.

Examples of activities that were likely to be in breach of Clause 2 included prejudicing patient safety and/or public health, excessive hospitality, inducements to prescribe, inadequate action leading to a breach of undertaking, promotion prior to the grant of a marketing authorization, conduct of company employees/agents that fell short of competent care and multiple/cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time.

Neither the material at issue nor any of the breaches ruled in Cases AUTH/2138/7/08 and AUTH/2205/2/09 could fall within any of the examples given above.

In conclusion, the cases cited in the complaint had been reviewed and significant action had, and was, being taken to ensure no breach of undertaking was

possible. Steps were being taken to tighten control and improve compliance with the Code; this was and would continue to be taken very seriously at Reckitt Benckiser. It was committed to abiding by the Code now and in the future.

PANEL RULING

The Panel noted that in Case AUTH/2138/7/08 it had ruled breaches of the Code because data presented in support of clinical conclusions was from *in-vitro* studies. Furthermore, in its consideration of the case the Panel had noted that the two advertisements at issue were essentially scientific abstracts as originally presented at scientific meetings. The Panel had noted its concerns that the abstracts, although written for a scientific purpose, had been used unchanged for a promotional purpose.

In Case AUTH/2205/2/09, the proceedings of a Reckitt Benckiser advisory board had been presented as an apparently independent educational supplement in the BMJ. The Panel had considered *inter alia*, that the material was a disguised advertisement for Gaviscon Advance.

The Panel noted that the supplementary information to Clause 2 stated, as one example of an activity likely to be in breach of Clause 2, multiple/cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time.

The Panel was concerned that both the previous cases demonstrated an apparent poor knowledge of the requirements of the Code. In that regard the Panel noted that Reckitt Benckiser had initiated a compliance programme which included in-house training by an external consultant.

A ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. Despite its concerns about the previous cases the Panel did not consider that their cumulative effect was such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry as alleged. No breach of Clause 2 was ruled.

Complaint received **20 March 2009**

Case completed **12 May 2009**

ANONYMOUS LILLY EMPLOYEE v LILLY and DAIICHI-SANKYO

Efient press release

An anonymous Lilly employee stated that he was increasingly frustrated at his company and had reached his limit with the consumer press release issued by Lilly and Daiichi-Sankyo to mark the launch of Efient (Prasugrel).

Prasugrel was a good medicine but needed to be used with caution. There could be significant issues with bleeding but these could be minimised by carefully considering the patient. Indeed, the marketing authorization required a risk minimisation programme to be carried out. The consumer press release, emphasised the deserved superior efficacy of prasugrel over clopidogrel [Plavix, marketed by Sanofi-Aventis] but made a cheap point about 25% resistance when it was well known that this study was from a 60 patient study in primary percutaneous coronary intervention (PCI). The safety section described bleeding as epistaxis, haematuria when actually there were significant higher fatal and life threatening and minor and major bleeds. In an attempt to dislodge clopidogrel from its pedestal, Lilly appeared ready to sacrifice safety, pushing the use of this medicine beyond its PCI indication.

The Panel noted that the press release briefly described the indications for Efient and the efficacy data which had led to the approval of the medicine by the regulatory authorities. Some background information was given as to the prevalence of acute coronary syndrome (ACS) and the economic impact of heart disease. The press release was not an advertisement per se for Efient and so in that regard the Panel ruled no breach of the Code.

Readers were informed that despite current guidelines, and evidence of efficacy, therapy was underused. The National Institute for Clinical Excellence had recommended that patients with ACS be treated with aspirin and clopidogrel. It was noted, however, that up to 25% of patients did not respond adequately to clopidogrel.

In response to a request for further information, Lilly and Daiichi-Sankyo had submitted that although it was clear that there was a variability of response to clopidogrel, the percentage variability varied widely because there was no agreed threshold of platelet inhibition below which a patient would be considered a non-responder and no one standardized method by which to measure platelet inhibition. The companies had cited what they considered to be a relatively conservative estimate with regard to the percentage of patients who were non-responders ie 25%. O'Donoghue and Wivott (2006) reported that between 4% and 34% of patients had been deemed to respond inadequately to clopidogrel depending on the method of testing and the definition of 'resistance' or 'hyporesponsiveness' used. The Panel noted that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, the Code required special care to be taken to ensure that the issue was treated in a balanced manner. The Panel considered that the statement in the press release 'research has also shown that up to 25% of patients do not respond adequately to clopidogrel' did not adequately reflect the situation and in that regard was misleading; high standards had not been maintained. Breaches of the Code were ruled.

In a section of the press release headed 'Method of action' it was stated that there was a risk of bleeding with all antiplatelet medicines and that prasugrel had an increased risk of bleeding compared with clopidogrel. The common bleeding events were described. It was also stated that treatment should only be prescribed to patients at increased risk of bleeding (>75 year of age, < 60kg body weight or with concomitant medicines that might increase the risk of bleeding) when the benefits were deemed to outweigh the risk of serious bleeding. Readers were informed that when the efficacy benefits were compared with the risk of serious bleeding events, for every 1,000 patients treated with prasugrel instead of clopidogrel, there were six more major bleeding events but 23 fewer heart attacks. The Panel noted that the press release referred to serious and major bleeding events and that prasugrel had an increased risk of bleeding compared with clopidogrel. In that regard the Panel did not consider that the comparison with clopidogrel was misleading as alleged. No breach of the Code was ruled.

The Panel considered it was very important that press releases, particularly those made available to consumer journalists, were fair, factual and not misleading. Although the Panel was concerned about the content of the press release it considered that, on balance, the circumstances did not warrant a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.

An anonymous Lilly employee complained about a consumer press release (ref UKEFF00062/March 2009) issued by Eli Lilly and Company Limited and Daiichi-Sankyo UK Ltd to mark the launch of Efient (prasugrel) in the UK.

COMPLAINT

The complainant stated that he was increasingly frustrated at his company and had reached his limit with this press release. Prasugrel was a good medicine but needed to be used with caution. There could be significant issues with bleeding but these could be minimised by carefully considering the patient. Indeed, it was part of the marketing authorization that a risk minimisation programme was carried out. The consumer press release, made a lot of the deserved superior efficacy of prasugrel over clopidogrel [Plavix, marketed by Sanofi-Aventis]. But then it went further and made a cheap point about 25% resistance when it was well known that this study was from a 60 patient study in primary percutaneous coronary intervention (PCI). The safety section described bleeding as epistaxis, haematuria when actually there were significant higher fatal and life threatening and minor and major bleeds. In an attempt to dislodge clopidogrel from its pedestal, Lilly appeared ready to sacrifice safety, pushing the use of this medicine beyond its PCI indication.

When writing to Lilly, the Authority asked it to respond in relation to Clauses 2, 9.1 22.1 and 22.2 of the Code. Lilly noted that the product was co-promoted with Daiichi-Sankyo in the UK and the two companies submitted a joint response.

RESPONSE

Lilly and Daiichi-Sankyo explained that Efient was indicated to prevent atherothrombotic events, when co-administered with acetylsalicylic acid, in patients with acute coronary syndrome (ACS) (ie unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI]) or ST segment elevation myocardial infarction [STEMI] undergoing primary or delayed PCI.

The grant of the European marketing authorization for Efient required Lilly and Daiichi-Sankyo to provide health professionals with important educational information regarding the safe and effective use of the medicine, as part of a broader risk minimisation programme. This educational information was appropriately incorporated in all Efient promotional materials and the launch consumer press release in question. Aligned to this requirement, this press release, in addition to Lilly/Daiichi-Sankyo's procedure for reviewing and certifying materials, had been pre-vetted and approved by the Medicines and Healthcare products Regulatory Agency (MHRA). This ensured compliance with the regulatory requirement that the following key educational information regarding safety was appropriately represented in Efient materials:

- Severe, including fatal, haemorrhagic events were more frequent in patients ≥ 75 years of age or those weighing < 60kg.
- Treatment was generally not recommended for patients of ≥ 75 years of age.
- If, after a careful individual benefit/risk evaluation by the prescriber, treatment was deemed necessary in the ≥ 75 years of age group then following a loading dose of 60mg, a reduced maintenance dose of 5mg should be prescribed.
- Patients weighing < 60kg should have a reduced maintenance dose of 5mg.
- The evidence for a 5mg dose was based only on pharmacokinetic/dynamic analyses and no clinical data currently existed on the safety of this dose in the at risk sub groups.

Accordingly, there was no basis to support the allegation in the press release. The companies stated that patient care and safety was at the heart of what they did and they rejected the allegation.

Lilly and Daiichi-Sankyo noted that the complainant had stated that the press release made a lot of the superior efficacy of prasugrel over clopidogrel but made a cheap point about 25% resistance when this study was from a 60 patient study in primary PCI. The allegation was factually and contextually misleading. The sentence in the press release to which the complainant referred stated:

> 'However, research has also shown that up to 25% of patients do not respond adequately to clopidogrel.'

This statement in the press release was substantiated by reference to two peer-reviewed publications Matetzky *et al* (2008) and Matetzky *et al* (2004); Matetzky *et al* (2004) related to a 60 patient study as suggested and the other related to a 200 patient study. Matetzky *et al* (2008) included 200 patients with acute myocardial infarction, presenting within 12 hours of symptom onset. The study authors stated – 'Previous studies have shown significant variability in platelet response to clopidogrel therapy in patients with coronary artery disease, with up to 25% of patients classified as nonresponders to a conventional dose of clopidogrel.' Further, there existed a considerable body of published evidence which demonstrated that resistance to clodpidogrel varied amongst patients; a matter of some considerable therapeutic importance. Serabruany *et al* (2005) stated that 'Clopidogrel "non-responsiveness" has been reported to be present in as little as 5% to as many as 56% of patients who are undergoing coronary stenting.'

The relevance of this information was clearly established and presented in the context of the under-use of heart medicines, the longstanding availability of clopidogrel and the National Institute for health and Clinical Excellence (NICE) recommendation of the use of clopidogrel in the treatment of ACS; this was evidenced by the text which preceded the above statement:

> 'Despite current guidelines, heart medications for ACS PCI patients are underused. When anti-platelet drugs are used, the risk of heart attack, stroke or death

> is reduced significantly. The National Institute of [sic] Health and Clinical Excellence (NICE) recommends aspirin with clopidogrel in ACS treatment.'

Leading up to this section, the press release highlighted that Efient offered an alternative therapeutic option in the management of ACS PCI, which to date had centred mainly on the use of clopidogrel. In this regard the discussion of clopidogrel treatment, the issue of resistance to it in some patients and the implication of this for patients was pertinent and reasonable. Indeed in this regard the press release did not raise unfounded hopes for successful treatment as implied by the complainant. This information was presented in a factual and balanced manner and could not be considered to be 'making a cheap point' or to be misleading. Accordingly, the companies rejected the allegation.

The safety profile of Efient was evaluated in the key clopidogrel-controlled study; TRITION TIMI.38. In the latter, patients with ACS undergoing PCI were treated with Efient and showed an increased risk of major and minor bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) classification system. As a result the Committee for Medicinal Products for Human Use (CHMP) recommended that the use of Efient in patients at increased risk of bleeding should only be considered when the benefits in terms of prevention of ischaemic events were deemed to outweigh the risk of serious bleedings.

It was this background that guided the detail and context in which the risk of haemorrhagic events was discussed both in general and with particular regards to certain patient types and the risk/benefit associated with Efient treatment compared with clopidogrel. Lilly and Daiichi-Sankyo categorically refuted the complainant's assertion that they had intentionally misled the audience regarding the haemorrhagic safety profile of Efient. To support the allegation, the complainant had misrepresented the precise wording of the press release which stated the following:

> 'The most common bleeding events seen with prasugrel in clinical trials were haematoma (a collection of blood under the skin or in a muscle), epistaxis (nosebleeds), gastrointestinal haemorrhage (bleeding in the stomach or gut), haematuria (blood in the urine) and bleeding from needle puncture sites.'

These bleeding events were qualified in the press release as being 'the most common' which was consistent with the Efient summary of product characteristics (SPC) (reference to which was provided with the press release).

Given the intended consumer audience, Lilly and Daiichi-Sankyo believed that it was not unreasonable that the press release, in order to give balance, referred to undesirable effects, including haemorrhagic events, and that the commonest of these were named. The companies noted that the discussion of the commonly occurring haemorrhagic events was preceded by the following explicit statement regarding the increased risk of bleeding associated with Efient relative to clopidogrel the current mainstay of ACS PCI treatment:

> 'All antiplatlet drugs come with a risk of bleeding. Treatment with prasugrel had an increased risk of bleeding relative to treatment with clopidogrel.'

This statement also related to the last paragraph on this particular page of the press release where the increased propensity of 'major bleeding events' associated with Efient compared with clopidogrel was referred to. Given the latter, the companies failed to comprehend the complainant's assertion that they had intentionally compromised patient safety by minimising the extent and nature of the haemorrhagic events associated with Efient treatment or the implication that by doing so they gained an unfair advantage over clopidogrel.

On the basis of the above, the companies' view was that the consumer press release was factual, balanced and did not mislead with respect to the safety of Efient. Accordingly the companies rejected the allegation.

With regard to the complainant's assertion that, in an attempt to dislodge clopidogrel from its pedestal, Lilly and Daiichi-Sankyo were ready to sacrifice safety, pushing the use of this medicine beyond its PCI indication, the companies repeated their statement with respect to the previous allegation.

The companies noted that the Efient indication was stated explicitly and without ambiguity within the press release. There was no direct or indirect discussion of any unlicensed indication(s) of Efient as asserted by the complainant. The companies therefore rejected any suggestion that the press release misled with respect to the efficacy and safety of Efient in comparison with clopidogrel, or at all.

The companies also categorically refuted any suggestion that the press release advertised Efient directly to the public or would encourage members of the public to ask their health professional to prescribe Efient, a prescription only medicine, in preference to clopidogrel.

In conclusion, Lilly and Daiichi-Sankyo were cogniscent of their responsibilities with respect to the Code and had ensured that all Efient press materials were consistent with this (including, without limitation, Clause 2, 9.1, 22.1, and 22.2) and of the highest standard and quality.

In response to a request for further information Lilly

and Daiichi-Sankyo explained that activated platelets played a central role in the pathogenesis of atherothrombosis and in the formation of thrombi following coronary angioplasty, with and without stent implantation. Although platelets were activated by a variety of endogenous agonists, adenosine diphosate (ADP) played a key role in initiating platelet aggregation. Efient and clopidogrel inhibited ADP-induced platelet aggregation and, in combination with aspirin, helped improve clinical outcomes inpatients with ACS and those undergoing PCI, in both the acute and chronic phases of treatment.

Several potential limitations of clopidogrel therapy had been reported including its variable anti-platelet effect. Studies had demonstrated that even with higher doses, clopidogrel response variability (ie poor response or no response to treatment) was associated with a significant risk of thrombotic complications following PCI. This topic was discussed by the British Cardiovascular Intervention Society in January 2009. It was evident that the subject of the variability of response to clopidogrel in patients and the putative mechanisms for this were widely reported and a matter of considerable therapeutic importance, particularly given the increased risk of recurrent cardiovascular events in patients with ACS-PCI.

Whilst the body of evidence clearly supported the variability of response to clopidogrel in patients, as measured by platelet inhibition/aggregation, it was also apparent that the percentage variability reported varied widely. This was primarily because there was as yet no agreed threshold of platelet inhibition below which a patient would be considered a non-responder to treatment or standardised methodology employed to detect platelet inhibition. Given the latter, the press release cited a relatively conservative estimate with regard to the inter-individual variability in response to clopidogrel treatment; this helped to ensure a fair and balanced approach to representing the variable response of clopidogrel. Lilly and Daiichi-Sankyo considered that the balance of evidence supported the statement '… research has also shown that up to 25% of patients do not respond adequately to clopidogrel'.

The companies noted that whilst the data often measured non-response to clopidogrel treatment, the wording of the press release did not actually assert that clopidogrel did not work at all; in fact the statement 'The National Institute of [sic] Health and Clinical Excellence (NICE) recommends aspirin with clopidogrel in ACS treatment' helped avoid any such misinterpretation.

PANEL RULING

The Panel noted that the consumer press release marked the launch of Efient in the UK. The press release briefly described the indications for Efient and the efficacy data which had led to the approval of the medicine by the regulatory authorities. Some background information was given as to the prevalence of ACS and the economic impact of heart disease. The press release was not an advertisement per se for Efient and so in that regard the Panel ruled no breach of Clause 22.1.

Readers were informed that despite current guidelines, and evidence of efficacy, therapy was underused. NICE had recommended that patients with ACS be treated with aspirin and clopidogrel. It was noted, however, that up to 25% of patients did not respond adequately to clopidogrel. Although the latter statement was referenced to Matetzky *et al* (2008) and Matetzky *et al* (2004) it was the 2004 study which demonstrated that upto 25% patients with ST segment-elevation myocardial infarction (STEMI) were resistant to clopidogrel. The authors noted that the study was an observational one with a relatively small sample size (n=60) and so it did not allow for definitive conclusions. Nevertheless, clopidogrel resistance occurred in a significant percentage of STEMI patients and was associated with a higher risk of recurrent cardiovascular events. Matezky *et al* (2008) examined the effectiveness of reloading to overcome clopidogrel resistance in patients with acute myocardial infarction reporting in the introduction that upto 25% of patients were classified as non-responders to a conventional dose; ten studies were cited in support of this statement including Matetzky *et al* (2004) which the Panel presumed substantiated the higher incidence of 25%. Serebruany *et al* reported that clopidogrel non-responsiveness had been reported in as little as 5% and as many as 56% of patients undergoing coronary stenting. It was unclear from the published paper which of the cited studies supported the higher incidence.

The Panel noted that in response to a request for further information, Lilly and Daiichi-Sankyo had submitted that although it was clear that there was a variability of response to clopidogrel, the percentage variability varied widely because there was no agreed threshold of platelet inhibition below which a patient would be considered a non-responder and no one standardized method by which to measure platelet inhibition. The companies had cited what they considered to be a relatively conservative estimate with regard to the percentage of patients who were non-responders ie 25%. O'Donoghue and Wivott (2006) reported that between 4% and 34% of patients had been deemed to respond inadequately to clopidogrel depending on the method of testing and the definition of 'resistance' or 'hyporesponsiveness' used. The authors stated that there was confusion about the true prevalence of resistance/hypo-responsiveness and no clear consensus on the definition of clopidogrel resistance. The Panel noted that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, the Code required special care to be taken to ensure that the issue was treated in a balanced manner (the supplementary information to Clause 7.2 referred). The Panel considered that the statement in the press release 'research has also

shown that up to 25% of patients do not respond adequately to clopidogrel' did not adequately reflect the situation and in that regard was misleading; a breach of Clause 22.2 was ruled. High standards had not been maintained. The Panel ruled a breach of Clause 9.1.

In a section of the press release headed 'Method of action' it was stated that all antiplatelet medicines came with a risk of bleeding and that treatment with prasugrel had an increased risk of bleeding compared with clopidogrel. The common bleeding events were described. It was also stated that treatment should only be prescribed to patients at increased risk of bleeding (>75 year of age, < 60kg body weight or with concomitant medicines that might increase the risk of bleeding) when the benefits were deemed to outweigh the risk of serious bleeding. Readers were informed that when the efficacy benefits were compared with the risk of serious bleeding events, for every 1,000 patients treated with prasugrel instead of clopidogrel, there were six more major bleeding events but 23 fewer heart attacks. The Panel noted that the press release referred to serious and major bleeding events and that prasugrel had an increased risk of bleeding compared with clopidogrel. In that regard the Panel did not consider that the comparison with clopidogrel was misleading as alleged. No breach of Clause 22.2 was ruled.

With regard to the alleged breach of Clause 2 the Panel considered it was very important that press releases, particularly those that were made available to consumer journalists, were fair, factual and not misleading. Clause 2 was used as a sign of particular censure and reserved for such use. Although the Panel was concerned about the content of the press release it considered that, on balance, the circumstances did not warrant a ruling of a breach of Clause 2.

Complaint received	**10 April 2009**
Case AUTH/2227/4/09 completed	**10 June 2009**
Case AUTH/2222/4/09 completed	**11 June 2009**

PROFESSOR OF CARDIOLOGY v MERCK SHARP & DOHME

Promotion of Cozaar

A professor of cardiology complained that a Cozaar (losartan) journal advertisement, issued by Merck Sharp & Dohme and headed 'Cozaar: The facts', did not refer to the warning regarding the use of losartan in patients with heart failure who were on a beta-blocker and strongly implied that losartan was widely indicated for patients aged 60 years and over with chronic heart failure where acetylcholine esterase (ACE) inhibitors were unsuitable. The advertisement did not refer to the specific warnings in the summary of product characteristics (SPC) for losartan: ie that 'The combination of losartan with a beta-blocker should be used with caution' (Section 4.4) and 'An increased mortality was observed in ELITE II in the small subgroup (22% of all HF [heart failure] patients) taking beta-blockers at baseline' (Section 5.1).

The complainant did not consider that prescribers reading the advertisement would be aware of this important caution. This was particularly important given that professional bodies and the Department of Health strongly encouraged increased prescribing of beta-blockers for this patient group.

The complainant considered it highly likely that the advertisement could lead to increased use of losartan specifically in the group for which there was a caution and increase mortality in this patient group. This was irresponsible and should be condemned. The advertisement was not only misleading but dangerous and should be withdrawn before it caused further damage.

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

The Panel noted that the aim of the advertisement was to compare the licensed indications of Cozaar with those of six other AII-antagonists (AIIAs). Above a table of data it was claimed that 'Cozaar is the only AIIA with four indications'. The table listed one of Cozaar's indications, not held by any of the other medicines, as 'Chronic heart failure in patients ≥ 60 years with an LVF ≤ 40% and where ACE inhibitors are unsuitable due to incompatability or contraindication'. This was a new indication. The Cozaar SPC (Section 4.1) did not qualify the indication in any way or refer the reader to any precautions or warnings about the concomitant use of Cozaar with beta-blockers. The Panel noted that the prescribing information in the advertisement at issue stated, under a heading of heart failure, 'Use with caution in… combination with a beta-blocker'.

The Panel considered that the advertisement was not inconsistent with the particulars listed in the Cozaar SPC and in that regard no breach of the Code was ruled. The Panel further did not consider that the advertisement was dangerous or misleading as alleged.

A professor of cardiology complained about the promotion of Cozaar (losartan) by Merck Sharp & Dohme Limited. The material at issue was an advertisement (ref 03-10CZR.09.GB.10159.Jc) which had appeared in, *inter alia*, the BMJ and was headed 'Cozaar: The facts'.

COMPLAINT

The complainant was concerned that the advertisement did not refer to the warning regarding the use of losartan in patients with heart failure who were on a beta-blocker. In fact the advertisement strongly implied that losartan was widely indicated for patients aged 60 years and over with chronic heart failure where acetylcholine esterase (ACE) inhibitors were unsuitable (due to incompatibility or contraindication). The advertisement did not refer to the specific warnings in the summary of product characteristics (SPC) for losartan:

- 'The combination of losartan with a beta-blocker should be used with caution' (Section 4.4)
- 'An increased mortality was observed in ELITE II in the small subgroup (22% of all HF [heart failure] patients) taking beta-blockers at baseline' (Section 5.1).

The complainant did not consider that prescribers reading the advertisement would be aware of this important caution. This was particularly important given that the professional bodies (including the British Society for Heart Failure, and the European Society of Cardiology) and the Department of Health (through the new quality outcome framework (QOF) target for beta-blockers for patients with heart failure) strongly encouraged increased prescribing of beta-blockers for this patient group.

The complainant considered it highly likely that the advertisement could lead to increased use of losartan specifically in the group for which there was a caution, and in fact could cause increased mortality in this patient group. This was irresponsible and should be condemned. The advertisement was not only misleading but dangerous, and might cost lives. It was very important that it was withdrawn before it caused further damage.

When writing to Merck Sharp & Dohme, the

Authority asked it to respond in relation to Clauses 2, 3.2, 7.2 and 9.1 of the Code.

RESPONSE

Merck Sharp & Dohme denied any breach of the Code. Section 4.1, Indications, of the Cozaar SPC included the following:

> 'Treatment of chronic heart failure (in patients ≥60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤40% and should be stabilised under the treatment of the chronic heart failure.'

There was no qualification on the use of Cozaar in heart failure in Section 4.3 Contraindications. Section 4.4, Special warnings and precautions for use, included the following statement:

> 'The combination of losartan with a beta-blocker should be used with caution (see section 5.1).'

In Section 5.1, Pharmacodynamic properties, it stated:

> 'An increased mortality was observed in ELITE II in the small subgroup (22% of all HF patients) taking beta-blockers at baseline.'

The ELITE II report (Pitt *et al*, 2000) referred to a difference in mortality found in patients receiving losartan and beta-blockers, one of many subsets of several endpoints analysed. In the small numbers involved it was not possible to assess the statistical significance of this finding and the authors commented in the discussion section of the report:

> 'The results on total mortality in ELITE II were generally consistent across subsets, based on predefined baseline characteristics. The on-treatment analysis gave similar results to that by intention to treat. The subsets of patients did not generally differ significantly in effect of losartan and captopril apart from those who were taking beta-blockers at randomisation (22% of the population). This difference was not seen if use was based on concomitant treatment with beta-blockers during the study. Patients on losartan and captopril also taking beta-blockers did better than most patients not on such treatment at randomisation, which is consistent with data from studies supporting a benefit of beta-blockers in such a population. The interaction between treatment effect and baseline beta-blocker use should be interpreted with caution given the small number of patients receiving these drugs and potential bias related to the reasons for administering these agents.'

Merck Sharp & Dohme submitted that in the context of the Cozaar licence in heart failure, it interpreted these findings as follows:

- All patients in the study were randomised to captopril, an ACE-inhibitor, or Cozaar
- A small number of these patients were already on a beta-blocker at the time of study randomisation
- In this subset of patients there was an apparent increase in survival rate in those randomised to captopril
- This was not assessable statistically because of the small numbers involved
- The licensed heart failure indication for Cozaar was restricted to use in those patients in whom treatment with ACE inhibitors is not considered suitable due to incompatibility… or contraindication, ie where ACE-inhibitors were no longer a treatment option
- Therefore these results need to be interpreted cautiously in relation to use in this indication

In the light of the overall study results and the authors' comments the regulatory authorities decided, during the pan-European harmonisation of the SPC that led to the granting of a congestive heart failure indication, to include a warning to use losartan with caution with concomitant beta-blockers in Section 4.4 of the SPC and that a more prominent site within the SPC was not necessary. For similar reasons the company also considered that this warning was appropriately covered by a mention in the prescribing information in advertisements of this sort and that a more prominent position was unnecessary.

Following the grant of the heart failure indication, the advertisement at issue was produced as a summary of the product's indications in a general-interest journal.

In this context, Merck Sharp & Dohme did not consider it either normal or necessary to include precautions from Section 4.4 of the SPC in the main body of promotional material. The company was certain that there was no precedent for a demand that it should give more prominence to the beta-blocker caution on use in heart failure. Proper reference was included in the prescribing information in accordance with the requirements of the Code.

Looking at other SPCs for angiotensin-II antagonists (AIIAs), Merck Sharp & Dohme noted that Section 4.4 of the Amias SPC included a warning on use in heart failure with concomitant ACE-inhibitors; Section 4.4 of the Diovan SPC cautioned careful monitoring in post-myocardial infarction patients; close monitoring of patients at risk from hyperkalaemia was recommended in Section 4.4 of the SPCs for Approvel, Olmetec and Micardis. As far

as Merck Sharp & Dohme knew, none of these warnings were mentioned in promotional copy for these medicines other than in the prescribing information.

To summarise, Merck Sharp & Dohme considered that there was no reason for it to feature the warning to use losartan with care in patients receiving concomitant beta-blockers more prominently than it currently did because:

- The warning on use in heart failure was already mentioned in the prescribing information and the user advised to consult the SPC before use
- There was no precedent for a suggestion that warnings of this sort should be given more prominence in promotional material than their current site in the prescribing information

For the above reasons Merck Sharp & Dohme concluded that the advertisement at issue was neither misleading nor unsafe and that it complied with the Code and the company denied breaches of Clauses 2, 3.2, 7.2 and 9.1.

PANEL RULING

The Panel noted that the aim of the advertisement was to compare the licensed indications of Cozaar with those of six other AIIAs. Above a table of data it was claimed that 'Cozaar is the only AIIA with four indications'. The table listed one of Cozaar's indications, not held by any of the other medicines, as 'Chronic heart failure in patients ≥ 60 years with an LVF ≤ 40% and where ACE inhibitors are unsuitable due to incompatability or contraindication'. This was a new indication. Section 4.1, Therapeutic indications, in the Cozaar SPC did not qualify the indication in any way or refer the reader to any precautions or warnings about the concomitant use of Cozaar with beta-blockers. The Panel noted that the prescribing information in the advertisement at issue stated, under a heading of heart failure, 'Use with caution in… combination with a beta-blocker'.

The Panel considered that the advertisement was not inconsistent with the particulars listed in the Cozaar SPC and in that regard no breach of Clause 3.2 was ruled. The Panel further did not consider that the advertisement was dangerous or misleading as alleged. No breach of Clause 7.2 was ruled. Given these rulings the Panel also ruled no breach of Clauses 9.1 and 2 as it considered that high standards had been maintained and the industry had not been brought into disrepute.

Complaint received **15 April 2009**

Case completed **22 May 2009**

ANONYMOUS DOCTOR v ASTELLAS

Arrangements for a meeting

An anonymous doctor complained that the Astellas summer school for medical professionals had become associated with lavish venues. Astellas had insisted that invitations to such venues should only be accepted on the understanding that all session were attended. This year's venue had a gourmet restaurant and extensive spa.

The complainant noted that Astellas' aggressive marketing style had been of concern for some time and particularly now with its Prograf patent expiring soon and its need to get doctors to transfer to Advagraf.

The detailed response from Astellas is set out below.

The Panel noted Astellas' submission that delegates had initially been invited to the meeting on the basis of its educational reputation; delegates had not been told where the meeting would be held and so could not have been attracted by the venue. In the Panel's view, however, invitees were likely to know what type of venue had been chosen in the past. The Panel noted that this year's venue was conveniently placed for road and air travel and was away from the potential distractions of a city centre. On its website the venue was described as a 'country house hotel'. It did not have a star rating and although its main restaurant played host to 'gourmet meals' it did not have any Michelin stars or similar. In the Panel's view, the impression was that Astellas' guests were being accommodated in a good quality hotel. The draft breakdown of costs showed that the day delegate rate, to include all meals plus coffee and soft drinks throughout the day, was £348.98 per person. The full cost of the meeting, to include transfers but excluding agency fees, was approximately £1,762 per delegate for the three days.

The Panel noted that the majority of the anticipated attendees were doctors; one fifth of those expected to attend were nurses/transplant co-ordinators. The Panel further noted that over three days the summer school provided seventeen and a half hours of education. The Panel considered that although the cost of the hospitality provided was on the limits of acceptability it was nonetheless, secondary to the main purpose of the meeting, not out of proportion to the occasion and at a level that many of the attendees might be expected to pay if doing so for themselves. No breach of the Code was ruled.

The Panel noted Astellas' submission that the meeting was free from any product promotion and that the company had no input into the agenda. In that regard the Panel did not consider that the meeting was associated with the aggressive promotion of Advagraf as alleged. There was no evidence that high standards had not been maintained in this regard and no breach of the Code was ruled including no breach of Clause 2.

An anonymous, non-contactable doctor who stated that he worked in the field of transplantation, complained about the arrangements for a meeting to be held by Astellas Pharma Ltd.

COMPLAINT

The complainant explained that for some time the Astellas school for medical professionals in transplantation had become associated with lavish venues in places where it was generally hard to escape (ie out of city centres). Tied in with this had been an insistence by Astellas that all invitees must attend all sessions and that this was the understanding for accepting the invitation to such a lavish venue.

Once again this year the summer school in June was to be held at a lavish and deluxe venue – in Hampshire. There was no mistaking this for anything other than a lavish and deluxe venue, with a gourmet restaurant and extensive spa. Indeed the opening paragraph in the hotel brochure began '[the hotel] offers its guests quality, style and luxury ...'. Furthermore, the hotel was owned by the a hotel group that described itself as 'Country Hotels of Distinction'. This was clearly a venue that any doctor would expect to be associated with a very special occasion and not one for routine business or meetings. The complainant alleged a breach of Clause 19.1 of the Code.

The complainant noted that the aggressive marketing style of Astellas had concerned many doctors in transplantation for some time particularly currently with its patent of Prograf expiring soon, and a desperate need to persuade doctors to transfer to Advagraf.

When writing to Astellas the Authority asked it to respond in relation to Clauses 2 and 9.1 of the Code, in addition to Clause 19.1 cited by the complainant.

RESPONSE

Astellas explained that its Summer Workshop was an annual, non-promotional, educational meeting in the field of transplantation. The event was wholly sponsored by Astellas and had taken place for the

past 9 years. This year it was scheduled to take place in June. The Summer Workshop provided an open forum which encouraged free discussion through a mixture of sessions including state of the art lectures, case study discussions, workshops and plenary sessions.

An unpaid faculty of respected health professionals from across the range of specialties in the field of transplantation was responsible for the agenda (lectures and workshops) and the final selection of delegates to the meeting. Membership of the faculty was for 2 years with approximately half the faculty changing every year to allow for some continuity. Astellas selected the faculty members but was not officially part of the faculty. Astellas personnel from Head Office attended the faculty meetings as observers but would intervene to ensure the aims of the meeting were achieved and that the meeting arrangements were acceptable and in line with the Code. The Astellas members also ensured that none of the presentations were in an area of commercial interest to Astellas as the very high reputation of this meeting was built on there being no promotional content to any of the sessions. In addition there were no promotional stands and no promotional material (including pens and other brand reminders) anywhere at the meeting. The only signage was corporate and not product related. Finally the presence of company personnel ensured smoother communication with the event management company contracted by Astellas to run the meeting.

The aim of the faculty was to ensure that there was good representation from all specialities and grades within transplantation and therefore consultants, specialist registrars, pharmacists, transplant specialist nurses and donor/recipient co-ordinators were all invited. The faculty, not Astellas, decided the content of the Summer Workshop but traditionally the agenda was usually only finalised at the American Transplant Congress (end of May each year) after the faculty had invited all speakers to present at the meeting and received their confirmations. Astellas noted that, like the faculty, none of the speakers or chairs were paid for their services which highlighted the distance that it maintained from the educational content of the meeting and that speakers genuinely wanted to come to the meeting to discuss topics with their peers. Astellas also noted that all attendees were expected to take a full part in discussions and the faculty decided which attendees should be asked to facilitate workshops and act as scribes for feedback to the main group.

Delegates were asked in November 2008 to register their interest in the 2009 Summer Workshop. The Astellas Key Account Managers (KAMs) nominated a broad list of health professionals within transplantation to the faculty which ratified the list. Once the dates for the meeting were confirmed, a 'Save the date' email was sent to the ratified list of delegates who could then email back to register interest in attending the meeting. At this point no venue was agreed and the agenda was not finalised. From the registered list, a final list of invitees was selected by the faculty and a confirmatory email and invitation was sent via the KAMs to approved invitees to complete and return. This was the first time that delegates knew of the actual venue. Those not initially successful were placed on a waiting list since it was inevitable that some confirmed delegates would drop out nearer the date of the meeting.

Astellas believed, for the reasons outlined above and from feedback from delegates from the past 9 years, that the interest in the Summer Workshop was solely based on the meeting's high educational content, free of promotion, and not the choice of venue.

In summary, Astellas fully sponsored the meeting, organised the logistics including collating expressions of interest from potential delegates and sat as observers on the faculty to ensure the meeting complied with all aspects of the Code. While Astellas selected the faculty, the meeting was free from any product promotion and Astellas had no input into the agenda. The faculty approved lists of potential delegates sent in by Astellas and the faculty confirmed which delegates would attend each year.

For many years Astellas had supported education in the transplant community. The Summer Workshop was a corporate sponsorship and was clearly indicated in materials related to the meeting. It was an educational meeting and none of the materials (agenda, invitations, emails, etc copies of which were provided) promoted Astellas' medicines. The invitations clearly indicated Astellas' sponsorship. Astellas strove to avoid any suggestion of commercial interference by ensuring that none of the topics could be construed as promotional by delegates even if independently suggested by the faculty. The reputation of this four day meeting was so high within the transplant community that many regarded it as the most valuable educational meeting in the whole year. Astellas had certified any communications related to this national meeting and had examined and approved the arrangements as required by the Code.

Astellas believed that high standards had indeed been maintained and that there had been no breach of Clause 9.1.

Astellas firmly believed that the level of subsistence provided at the meeting was consistent with the letter and spirit of Code as it was associated with, and was not disproportional to, the nature of this scientific meeting. Delegates were provided with meals and reimbursed for reasonable, economy travel expenses. It was stated clearly on the invitation that all other incidentals were to be covered by the delegate.

The full cost of the meeting including airport transfers, on-site technical support, four onsite

agency staff throughout the event etc, but excluding agency fees, was approximately £1,762 per delegate (cost breakdown was provided). Specifically looking at the cost of subsistence, which included three nights' accommodation, meals and refreshments for the delegates and Astellas staff, broke down to approximately £1,370 per delegate for the four day meeting. While Astellas understood that this was not an insignificant amount per head, Astellas believed that this compared favourably with any privately provided educational course of such high calibre. Astellas further noted that, in accordance with the Code, no entertainment had been organised.

Astellas disagreed with the complainant's allegation that the hotel was perceived as a luxury hotel and that was why doctors attended the meeting.

When delegates first registered for this meeting they did not know about the venue as it was not yet chosen. An independent agency explored thirty five venues but only two were available on the specific dates, the other venue being in York city centre. The final venue was only selected by the faculty in January 2009 and delegates were told about it in invitations sent at the beginning of February 2009. The agenda was not yet finalised but would be at the American Transplant Congress at the end of May 2009. Workshops, however, had been finalised and delegates would be asked to select the workshops they wished to attend at the beginning of May 2009.

Astellas noted that the complainant had also alleged that the hotel had a gourmet restaurant. While the food would be compatible with that expected of a 4 star hotel, the restaurant did not, to Astellas' knowledge have any Michelin stars or AA rosettes and in this regard Astellas disagreed with the complainant's description of the restaurant. Astellas considered that the arrangements were not incompatible with Clause 19.1 of the Code in that the subsistence provided was secondary to the meeting and not the prime reason for attending.

Astellas acknowledged that the hotel had a leisure complex and spa treatment centre like many larger 4 star hotels throughout the UK. However the hotel was not renowned for being either a deluxe or extravagant venue or for being associated with sporting and leisure facilities; Astellas would be surprised if many of the delegates had actually heard of the venue before they received their confirmation.

The hotel was chosen for its excellent conference facilities and because it was away from any major attraction like a city centre. The faculty believed from its past experiences that delegates should be fully involved in the sessions and therefore it was important to have a venue away from potential distractions like shops. The attendees invested four days of their time, including a whole weekend when travelling back home was included. The transplant community was relatively small compared to some therapeutic areas and it was clear that even a few missing participants could adversely affect the quality of interactivity at a meeting such as this since there was a considerable amount of small group work and discussion. Thus the faculty stipulated that delegates were expected to attend all the educational sessions. Astellas was surprised that the complainant had a problem with that since to accept an invitation to a meeting which was oversubscribed, thereby denying someone else a place, and to not then turn up for parts of the meeting was inconsistent with standards of professional conduct expected by health professionals.

However, for a national meeting, accessibility was also important and the hotel was also with easy reach of the M3, M4 and M25 motorways and was a relatively short transfer from Heathrow and about 45 minutes from Gatwick.

The Summer Workshop was highly regarded as being a genuinely educational meeting with no product promotion and being in its tenth year in a small specialised community, it was not difficult to understand that most, if not all, transplant health professionals would have heard of the meeting even if they had not previously attended. To support this over 100 potential delegates had registered interest in the meeting before knowing the venue or the agenda.

The agenda was developed and finalised by the faculty. The lectures and workshops encompassed a wide variety of current topical research and clinical scientific areas. Any form of therapy, surgery, medicine and other current issues in the field of transplant might be discussed. One of the advantages of confirming the meeting agenda relatively late in the process was that subject matter could be extremely topical.

No agenda item focused on any particular Astellas product and Astellas, by having observers on the faculty, ensured that this was the case. The agenda was therefore purely scientific with no promotional content. To this end Astellas did not review or input into the presentations and workshop content. Throughout the agenda the focus of this meeting was education.

The programme ran from 3pm on Thursday, 11 June to 1pm on Sunday, 14 June. On arrival on the first day delegates participated in a 2.5 hour workshop before dinner. On Friday an intensive programme ran from 9am to 5.30pm with an hour for lunch and on Saturday the programme ran from 9am until 3pm. On Sunday there was a programme till 1pm and delegates left after lunch to travel home. In total, excluding all breaks, there were at least 18 hours of education.

In summary Astellas stated that it strove to maintain high standards and transparency. Astellas had allowed a faculty of health professionals to choose the agenda and to select the delegates while making

it abundantly clear that Astellas sponsored the event. Delegates were not aware of the venue or even the agenda before registering interest in the meeting but would have known about the high academic standing of the faculty and of the meeting's history. Indeed, the fact that the transplant community referred to the meeting as 'Summer School', strongly underpinned Astellas' claim as to the intensive nature and high academic content of the event. Astellas submitted that this year's venue was chosen with careful criteria specifically for the purpose of an interactive, four day educational event as well as availability and location. Astellas did not agree with the complainant that this hotel was a lavish or deluxe venue or that its restaurant was of 'gourmet' standard.

Astellas therefore did not consider any the arrangements to be in breach of Clause 9.1 or Clause 19.1 of the Code.

Astellas did not consider this intense educational programme to be in breach of Clause 2. Rather, it upheld Astellas' commitment to provide high quality education and maintain its established reputation in the transplant community. Astellas believed it was precisely this type of meeting arrangement, where the delegates ran it for themselves and selected their peers to present and attend, that restored trust in the pharmaceutical industry, which was one of the four strategic priorities for the ABPI.

In response to a request for further information, Astellas submitted that it anticipated that the attendees at this year's Summer Workshop would comprise 28 surgeons, 24 physicians, 17 nurses/transplant co-ordinators, 3 pharmacists, 4 paediatricians, 1 anaesthetist, 2 pathologists, 1 islet specialist and 1 non-clinical attendee. Seventeen staff from Astellas would also attend.

PANEL RULING

The Panel noted that the supplementary information to Clause 19.1 stated that a meeting venue must be appropriate and conducive to the main purpose of the meeting; lavish, extravagant or deluxe venues must not be used, companies must not sponsor or organize entertainment and should avoid using venues that were renowned for their entertainment facilities. The supplementary information further stated that it should be the programme that attracted delegates and not the associated hospitality or venue. The impression that was created by the arrangements for any meeting must be kept in mind.

The Panel noted Astellas' submission that delegates had initially been invited to the meeting on the basis of its educational reputation; delegates had not been told where the meeting would be held and so could not have been attracted by the venue. In the Panel's view, however, potential delegates were likely to be aware of the type of venue chosen in the past. The Panel noted that this year's venue was conveniently placed for road and air travel and was away from the potential distractions of a city centre. The hotel's website described it as a 'country house hotel'. It did not have a star rating and although its Restaurant played host to 'gourmet meals' it did not have any Michelin stars or similar. In the Panel's view, the impression was that Astellas' guests were being accommodated in a good quality hotel. The draft breakdown of costs showed that the day delegate rate, to include all meals plus coffee and soft drinks throughout the day, was £348.98 per person. The full cost of the meeting, to include transfers but excluding agency fees, was approximately £1,762 per delegate for the three days.

The Panel noted that the majority of the anticipated attendees were doctors; one fifth of those expected to attend were nurses/transplant co-ordinators. The Panel further noted that over three days the summer school provided seventeen and a half hours of education. The Panel considered that although the cost of the hospitality provided was on the limits of acceptability it was nonetheless, secondary to the main purpose of the meeting, not out of proportion to the occasion and was at a level that many of the attendees might be expected to pay if doing so for themselves. No breach of Clause 19.1 was ruled.

The Panel noted Astellas' submission that the meeting was free from any product promotion and that the company had no input into the agenda. In that regard the Panel did not consider that the meeting was associated with the aggressive promotion of Advagraf as alleged. The Panel noted that the complainant was anonymous and non contactable. The complainant had not provided any material to support their allegation. The complainant had the burden of providing their complaint on the balance of probabilities although in the Panel's view marketing could be 'aggressive' and still comply with the Code. There was no evidence that high standards had not been maintained in this regard and no breach of Clause 9.1 was ruled.

The Panel noted its rulings above and considered that there had also been no breach of Clause 2 of the Code.

Complaint received **21 April 2009**

Case completed **22 May 2009**

CASE AUTH/2226/4/09

MERZ PHARMA v ALLERGAN

Botox product monograph

Merz Pharma alleged that a Botox (botulinum neurotoxin) monograph issued by Allergan, contained unfounded comparisons of Botox with Dysport (Ipsen's product – botulinum toxin Type A – haemaglutinin complex) that would disadvantage its product Xeomin (botulinum neurotoxin).

With regard to the claim 'In summary, the different botulinum formulations differ markedly, this can have a significant impact on clinical performance; Merz knew of no data to support the claim. Allergan had stated that it would not use this claim in future comparisons with Xeomin; however Allergan refused to substantiate the claim against Dysport. Merz alleged that the claim was not an accurate reflection of the clinical evidence and could not be substantiated.

The detailed response from Allergan is given below.

The Panel noted that there were some differences between Botox and Dysport but did not consider that these differences were so marked that they had a significant impact on clinical performance. The implied comparison was misleading and had not been substantiated as alleged. Breaches of the Code were ruled.

With regard to the claim 'Due to differences in the safety profiles, dosing should be based on individual analysis of the safety profile and efficacy of each product for each particular indication' Merz stated there was no evidence that the safety profiles differed between Botox, Xeomin and Dysport. Allergan had again refused to respond to Merz's challenge on this point.

The Panel noted that there were differences in the adverse event profiles. Chapman *et al*, a literature review noted that dysphasia was the primary treatment-related adverse event observed with botulinum toxin type A therapy for cervical dystonia and noted that caution might be warranted with the use of *inter alia*, Dysport at the higher dose range. The Dysport summary of product characteristics (SPC) listed dysphagia as a common (>1/100) adverse event when the patient was treated for arm spasticity and very common (>1/10) in the treatment of spasmodic torticollis. The Botox SPC stated that patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which might be mild but could be severe and listed dysphagia as a very common adverse event in the treatment of blepharospasm or hemifacial spasm. The Panel noted that there were some differences between the safety profiles of Botox and Dysport and thus did not consider that the claim at issue was misleading or incapable of substantiation as alleged. No breaches of the Code were ruled.

Merz alleged that the claim: Botulinum toxins 'act very differently' was not a reflection of the true picture with no clinical evidence that Botox, Xeomin or Dysport acted any differently. The contrary was true with all three being type A toxins. The use of 'very' gave weight to the unsubstantiated and misleading claim.

The Panel considered that its ruling in the first point was relevant here. The Panel noted that there were differences between the products however the claim at issue '… although they are all type A serotypes, they act very differently due to differences in complex size and structure as a consequence of the purification processes' implied fundamental differences in the way the three botulinum neurotoxins acted. The Panel did not consider that any data had been presented in that regard. The claim was misleading and had not been substantiated as alleged. Breaches of the Code were ruled.

Merz did not know of any evidence that supported the claim that 'There are clear differences between these products in terms of potency and migration' for Dysport compared with Botox. Indeed, the SPCs insisted that direct comparisons of potency were not made. Merz, therefore alleged that the claim was misleading and incapable of substantiation.

The Panel noted Allergan's submission that the claim at issue summarized discussions in previous sections. The Panel noted that there were some differences between the products. Section 4.8 of the Botox SPC, Undesirable effects, noted that side effects related to spread of toxin distant from the site of administration had been reported very rarely; exaggerated muscle weakness, dysphagia, aspiration, aspiration pneumonia, with fatal outcome in some cases. A similar reference appeared in the Dysport SPC which referred to fatal outcome in some very rare cases. The Panel noted that Aoki *et al* referred to the lower molecular mass of the Dysport formulation such that it would migrate further from the injection site as a result of fluid based distribution and subsequently reach adjacent tissue or the systemic system.

The Panel noted that the Botox SPC stated that botulinum toxin units were not interchangeable from one product to another. A similar statement appeared in the Dysport SPC. The Panel noted as submitted by Allergan that there were differing opinions about the relative potencies of Dysport and Botox ranging from 1.2 to 1.11.

The Panel considered that there were some differences in relation to both migration and potency but queried whether these could be described as 'clear'. On balance the Panel ruled breaches of the Code.

Merz was particularly concerned that Allergan had refused to provide substantiation for these claims at the request of its medical director.

No data had been provided to Merz and a breach of the Code was ruled.

Merz Pharma complained about a Botox (botulinum neurotoxin) monograph (ref ACA/0343/2007) issued by Allergan. Inter-company correspondence had failed to resolve the matter. Merz supplied Xeomin (botulinum neurotoxin). Merz considered that unfounded comparisons of Botox with Dysport (Ipsen's product – botulinum toxin Type A – haemaglutinin complex) would put the promotion of Xeomin at a disadvantage.

1 Claim: 'In summary, the different botulinum formulations differ markedly, this can have a significant impact on clinical performance'

This claim appeared on page 18 of the product monograph.

COMPLAINT

Merz knew of no data that showed that any variation between Dysport and Botox had any impact upon clinical performance. Allergan had stated in previous correspondence that it would not use this claim in future comparisons with Xeomin; however Allergan refused to substantiate the claim against Dysport. Merz alleged that the claim was not an accurate reflection of the clinical evidence and could not be substantiated in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Allergan stated that the sentence, which immediately followed the claim at issue, 'Due to differences in the safety profiles, dosing should be based on individual analysis of the safety profile and efficacy of each product for each particular indication; gave more context.

Allergan denied a breach of Clause 7.2 or 7.4.

This claim was contained within a section entitled 'Non-Interchangeability'. The fundamental message of this section was that botulinum toxin units were not interchangeable from one product to another, as stated in the summary of product characteristics (SPCs) for Botox, Dysport and Xeomin.

A significant part of this section compared Botox with Dysport.

Regarding Xeomin, context with respect to efficacy and safety was provided with reference to the Merz non-inferiority studies (Benecke *et al* 2005, Roggenkamper *et al* 2006).

Across all three botulinum toxin type A products there were clear differences between the formulations, each preparation was manufactured using unique methods of purification and formulation (Aoki *et al*, 2006). A number of clinical studies had demonstrated differences in the comparative safety profiles of Botox and Dysport. A study investigating Botox and Dysport in the treatment of blepharospasm found a difference in adverse event rates (Nussgens and Roggenkamper, 1997). Ranoux *et al* (2002) compared Botox and Dysport in the treatment of cervical dystonia and found differences in the incidence of treatment-related adverse events between the two products. Chapman *et al* (2007) systematically reviewed and analysed published literature, focusing on cervical dystonia, to compare rates of dysphagia and dry mouth in studies of different botulinum toxin products. The authors concluded that their results indicated differences in adverse event rates between botulinum toxin preparations, suggesting that use of these products should be based on their individual dosing, efficacy and safety profiles. This systematic review also included Myobloc, a botulinum toxin type B.

As confirmed by Aoki *et al*, differences were apparent when considering the clinical application and adverse event profile of the different toxin formulations.

When considering all three botulinum toxin type A products, the doses and injection patterns varied, as well as the range of licensed indications. All this needed to be borne in mind by the clinician treating an individual patient.

PANEL RULING

The Panel noted Allergan's submission about the studies which compared, *inter alia* the safety profiles of Botox and Dysport. The Panel noted that there were some differences between the products but did not consider that these differences were so marked that they had a significant impact on clinical performance. The Panel considered the implied comparison with Dysport was misleading and had not been substantiated as alleged. A breach of Clauses 7.2 and 7.4 was ruled.

2 Claim: 'Due to differences in the safety profiles, dosing should be based on individual analysis of the safety profile and efficacy of each product for each particular indication'

This claim immediately followed the claim at issue at point 1.

COMPLAINT

Merz noted that this claim for a difference in the safety profiles of the products was unreferenced. There was no evidence that the safety profiles differed between Botox, Xeomin and Dysport. Allergan had again refused to respond to Merz's challenge on this point. Merz alleged a breach of Clauses 7.2 and 7.4.

RESPONSE

Allergan stated that in the monograph the claim regarding differing safety profiles related to the entire section on non-interchangeability discussing Botox, Dysport and Xeomin. Across the botulinum toxin type A products on the market this would seem a prudent measure for a clinician to take, in line with the SPCs for the products.

Whilst acknowledging the two non-inferiority studies (Benecke *et al*, Roggenkamper *et al*), there were differences in the safety profiles of botulinum toxin products on the market as outlined in the section above and as stated in the SPCs for Botox, Dysport and Xeomin.

As confirmed by Aoki *et al* (2006), differences were apparent when considering the clinical application and adverse event profile of the different toxin formulations.

When considering all three botulinum toxin type A products, the doses and injection patterns varied, as well as the range of licensed indications. All this needed to be borne in mind by the clinician treating an individual patient.

Allergan denied a breach of Clauses 7.2 or 7.4.

PANEL RULING

The Panel noted that there were differences in the adverse event profiles. Chapman *et al*, a literature review noted that dysphasia was the primary treatment-related adverse event observed with botulinum toxin type A therapy for cervical dystonia and noted that caution might be warranted with the use of *inter alia*, Dysport at the higher dose range. The Dysport SPC listed dysphagia as a common (>1/100) adverse event when the patient was treated for arm spasticity and very common (>1/10) in the treatment of spasmodic torticollis. Section 4.4 of the Botox SPC stated that patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which might be mild but could be severe and listed dysphagia as a very common adverse event in the treatment of blepharospasm or hemifacial spasm. The Panel noted that there were some differences between the safety profiles of Botox and Dysport and thus did not consider that the claim at issue was misleading or incapable of substantiation as alleged. No breach of Clauses 7.2 and 7.4 was ruled.

3 Claim: Botulinum toxins 'act very differently'

This claim appeared on page 22 of the monograph.

COMPLAINT

Merz submitted that again this was not a reflection of the true picture with no clinical evidence that Botox, Xeomin or Dysport acted any differently. The contrary was true with all three being type A toxins. The use of 'very' gave weight to the unsubstantiated and misleading claim. The fact that it appeared in the conclusion of a much larger document was not only irrelevant (as all sections must be capable of standing alone) but compounded the problem as readers might only read the conclusion section of a large document. Whilst Allergan had agreed in previous correspondence to withdraw the claim in comparison with Xeomin it refused to withdraw the claim in comparison with Dysport. Merz alleged breaches of Clauses 7.2 and 7.4.

RESPONSE

Allergan stated that the words at issue, 'act very differently' were part of a larger paragraph on page 22 of the monograph:

> 'There are currently three available preparations of botulinum toxin type A (Botox, Dysport and Xeomin (which was recently made available in some countries in Europe) and although they are all type-A serotypes, they act very differently due to differences in complex size and structure as a consequence of the purification processes. There are clear differences between these products in terms of potency and migration. As such, there is no comparability between the different preparations and it is not possible to establish a dose ratio conversion since none of the products are interchangeable.'

The context surrounding these words had been missed. This claim was contained in the conclusion of the monograph, summarised the discussions in the previous sections, and related to the three botulinum toxin type A products on the market.

If, as suggested by Merz, readers only read the conclusion of this document there was sufficient information in the sentences immediately following the one at issue, to support the claim. The paragraph concluded that it was not possible to establish a dose ratio conversion for the products, and that the products were not interchangeable as stated in the SPCs for Botox, Dysport and Xeomin.

Allergan did not accept the assertion by Merz that the fact the words at issue were part of the conclusion of a larger document was 'irrelevant'. Here context was important, both in the

surrounding sentences and also the earlier sections, as discussed above.

Allergan denied a breach of Clauses 7.2 or 7.4.

PANEL RULING

The Panel considered that its ruling at point 1 was relevant here. The Panel noted that there were differences between the products however the claim at issue '… although they are all type A serotypes, they act very differently due to differences in complex size and structure as a consequence of the purification processes.' implied fundamental differences in the way the three botulinum neurotoxins acted. The Panel did not consider that any data had been presented in that regard. The claim was misleading and had not been substantiated as alleged. A breach of Clauses 7.2 and 7.4 was ruled.

4 Claim: 'There are clear differences between these products in terms of potency and migration'

This claim immediately followed the one at issue at point 3.

COMPLAINT

Merz stated that it did not know of any evidence that supported the claim that there were differences in potency and/or migration for Dysport compared with Botox. Indeed, the SPCs insisted that direct comparisons of potency were not made. Allergan had refused to engage in any dialogue on this point or attempted to justify it. Merz, therefore alleged, without any evidence to the contrary from Allergan, that the claim was misleading and incapable of substantiation in breach of Clauses 7.2 and 7.4.

RESPONSE

Allergan stated that the claim at issue 'There are clear differences between the products in terms of potency and migration' was part of the following paragraph:

> 'There are currently three available preparations of botulinum toxin type A (BOTOX®, Dysport and Xeomin (which was recently made available in some countries in Europe) and although they are all type-A serotypes, they act very differently due to differences in complex size and structure as a consequence of the purification processes. There are clear differences between these products in terms of potency and migration. As such, there is no comparability between the different preparations and it is not possible to establish a dose ratio conversion since none of the products are interchangeable.'

The context surrounding this claim had been missed. This claim was contained in the conclusion of the monograph, summarised the discussions in the previous sections, and related to the three botulinum toxin type A products on the market.

As discussed in the section on non-interchangeability (page 17 of the monograph) there were differing opinions as to the relative potencies of Botox and Dysport. These had ranged from 1:2 to 1:11 (Marchetti *et al*, 2005). The published data therefore supported the assertion that a fixed dose ratio could not be used when comparing the two toxins and that there was a range of ratios dependent on patient populations and indications. Regarding botulinum toxin diffusion/migration, full dose-response curves could not be generated with botulinum toxins in humans for obvious ethical reasons and thus preclinical models were useful in this regard. Differences in safety margins seen in animal models might result from differences in formulation and molecular size (Aoki *et al*). The claim at issue did not suggest that this matter had been resolved in favour of one generally accepted viewpoint. It merely summarised the presented data and the fact that between all three botulinum toxin type A products there were differences.

Allergan could not agree to Merz's broad request not to make any claims suggesting differences in potency and/or migration between any of the botulinum toxin type A products on the market. This very broad request, seemed inappropriate, and Allergan believed should not be part of the complaint process. Again, the suitability of such a claim would depend on the context and the supporting evidence provided.

Allegan denied breaches of Clauses 7.2 or 7.4.

PANEL RULING

The Panel noted Allergan's submission that the claim at issue summarized discussions in previous sections. The Panel noted that there were some differences between the products. Section 4.8 of the Botox SPC, Undesirable effects, noted that side effects related to spread of toxin distant from the site of administration had been reported very rarely; exaggerated muscle weakness, dysphagia, aspiration, aspiration pneumonia, with fatal outcome in some cases. A similar reference appeared in the Dysport SPC which referred to fatal outcome in some very rare cases. The Panel noted that Aoki *et al* referred to the lower molecular mass of the Dysport formulation such that it would migrate further from the injection site as a result of fluid based distribution and subsequently reach adjacent tissue or the systemic system.

The Panel noted that the Botox SPC stated that botulinum toxin units were not interchangeable from one product to another. A similar statement appeared at Section 4.2 of the Dysport SPC. The

Panel noted as submitted by Allergan that there were differing opinions about the relative potencies of Dysport and Botox ranging from 1.2 to 1.11.

The Panel considered that there were some differences in relation to both migration and potency but queried whether these could be described as 'clear'. On balance the Panel ruled a breach of Clauses 7.2 and 7.4 of the Code.

5 Request for information

COMPLAINT

Merz was particularly concerned that Allergan had refused to engage with it and provide it with data concerning these claims. If Allergan subsequently provided data to the Panel that it refused to provide to Merz this would clearly be a deliberate ploy to put Merz at a disadvantage in front of the Panel. Merz alleged a breach of Clause 7.5 of the Code as Allergan had refused to provide substantiation for these claims at the request of the Merz medical director (a member of the health professions).

RESPONSE

Allergan did not believe that complaints about possible theoretical future use of claims could be considered by the Authority. Hence Allergan's response to Merz regarding the open-ended nature of its request.

Allergan had entered into extensive and protracted correspondence and two Code cases around claims, taken out of context, from a withdrawn item.

Merz appeared to be anticipating the way Allergan might use potential claims in the future – which Allergan did not believe was the role of the complaints process.

PANEL RULING

The Panel noted Merz's letter dated 2 April wherein it requested substantiation for certain claims. The Panel did not consider, as stated by Allergan, that this was a speculative request requiring Allergan to justify how it might use such claims in the future. The request related, *inter alia*, to comparative claims in the product monograph in relation to Dysport and Botox. No data had been provided to Merz. A breach of Clause 7.5 was ruled.

Complaint received **23 April 2009**

Case completed **26 June 2009**

CASE AUTH/2229/5/09

VOLUNTARY ADMISSION BY ASTRAZENECA

Arrangements for a meeting

AstraZeneca voluntarily admitted a breach of the Code arising from an internal email to a group of the company's representatives. The email linked the offer of sponsorship to attend an American Urological Association (AUA) meeting to the protection and growth of AstraZeneca's Zoladex (goserelin) business.

The Authority's Constitution and Procedure provided that the Director should treat an admission as a complaint if, *inter alia*, it related to a potentially serious breach of the Code. Linking sponsorship to attend a meeting to the prescription of a medicine was a serious matter and the admission was accordingly treated as a complaint.

AstraZeneca referred to an internal email to representatives which read:

'Finally I can share the outcome from the director's meeting where the business cases for the AUA delegates were reviewed …. In your case the directors felt that taking your customers to the AUA as part of the AZ group would help protect our Zoladex business and in many cases help grow it'. Representatives were asked to pass on an attached invitation although one representative forwarded the whole email to a doctor.

AstraZeneca noted that no meeting of the directors took place for the AUA delegate selection and no director endorsed this method of delegate selection. The directors were not involved in the selection process at all. However, the email clearly implied that the selection criteria for delegates were previous and/or future prescriptions of Zoladex.

The email was certified by two registered signatories who failed to validate the claims therein or question the nature of delegate selection.

The detailed response from AstraZeneca is given below.

The Panel noted with concern that the directors' meeting referred to in the email had not taken place. The email had been certified by two signatories who, according to AstraZeneca, failed to validate the claims therein or query the nature of delegate selection. The email had been sent to representatives one of whom, despite no instructions to do so, had forwarded it to a potential delegate.

The Panel considered that the email inappropriately linked the offer of sponsorship to attend an overseas meeting with past or future prescriptions of Zoledex. This would certainly be the impression given to representatives and the potential delegate who had received the email. Such an impression was unacceptable. A breach of the Code was ruled. The Panel considered that the provision of the email at issue to a health professional amounted to an inducement to prescribe contrary to the Code; a breach of the Code was thus ruled.

The Panel was extremely concerned that the content of the email demonstrated a lack of awareness of the requirements of the Code by those involved. High standards had not been maintained. A breach of the Code was ruled. The Panel did not consider that overall the email warranted a ruling of a breach of Clause 2 which indicated particular censure and was reserved for such use. No breach of Clause 2 was ruled.

AstraZeneca UK Limited voluntarily admitted a breach of Clause 18.1 of the Code arising from an internal email to a group of the company's representatives. The email linked the offer of sponsorship to attend an American Urological Association (AUA) meeting in the US to the protection and growth of AstraZeneca's Zoladex (goserelin) business.

The action to be taken in relation to a voluntary admission by a company is set out in Paragraph 5.4 of the Constitution and Procedure which states, *inter alia*, that the Director shall treat the matter as a complaint if it relates to a potentially serious breach of the Code. Linking sponsorship to attend a meeting to the prescription of a medicine was a serious matter and the admission was accordingly treated as a complaint.

COMPLAINT

AstraZeneca stated that the internal email informed the representatives that the company was to invite some of their customers to the AUA meeting; representatives were asked to pass on an attached invitation. The email contained the following: 'Finally I can share the outcome from the director's meeting where the business cases for the AUA delegates were reviewed …. In your case the directors felt that taking your customers to the AUA as part of the AZ group would help protect our Zoladex business and in many cases help grow it'.

This was an erroneous and untrue statement as no meeting of the directors took place for the AUA delegate selection and no director endorsed this method of delegate selection. Indeed, the directors

were not involved in the selection process at all. However, the email clearly implied that the selection criteria for delegates were previous and/or future prescriptions of Zoladex.

Internal investigations established that the following specific selection criteria were applied by the head office brand team:

- Whether the health professional worked in the field of prostate cancer.
- Whether they had an interest in the latest developments in prostate cancer, were likely to apply evidence based logic to their treatment approaches and whether this was relevant to their work.
- Whether they would be interested in an evening session during the conference for AstraZeneca to share its latest survival data.

AstraZeneca explained that on 12 February 2009, a member of staff composed an email for internal use only, to be sent to representatives designed to expedite the delivery of invitations to potential delegates to the meeting. As was evident from the content of the email, the author was keen to get the invites out and replies returned quickly.

The email was certified by two registered signatories who failed to validate the claims in the email or question the nature of delegate selection.

One representative, despite receiving no instruction to do so, forwarded the email to a doctor and potential delegate. The representative then asked the customer to delete the email on instruction from his manager, who had given this instruction on his own initiative.

The email was brought to the attention of AstraZeneca's compliance team, through AstraZeneca's internal reporting system, on 17 February. An internal investigation then began and the following actions taken:

- Individuals involved were managed according to AstraZeneca internal policies.
- It was explained to the health professional who received the email that it was sent in error and was inaccurate and misleading.
- All delegates were told about this mistake and that AstraZeneca would be making a voluntary admission to its regulatory authority.
- Only medical staff from AstraZeneca UK marketing company attended the conference
- Relevant staff were reminded on the content of Clause 18 when arranging such events and that the focus for choosing appropriate delegates must be based upon maximizing patient benefit.

AstraZeneca strove to set the highest of standards and emphasised how seriously it took this failing of its internal procedures and that it considered the contents of the email fell far short of its own high standards as well as those expected by the Code. AstraZeneca was reinforcing the necessary high standards in undertaking any such educational programmes in the future.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 2, 9.1, 15.9 and 18.1 of the Code.

RESPONSE

AstraZeneca reiterated that the email at issue contained erroneous information about the basis for delegate selection and the involvement of the directors. None of the directors were involved in this matter.

The email implied that the selection of delegates to attend the AUA meeting was based upon 'our Zoladex business'. AstraZeneca noted that if this were true it would have been a breach of Clause 18.1. In reality, selection criteria for delegates were legitimately related to the appropriateness of the meeting to the delegates' area of therapeutic interest except for one, which was their interest in attending an evening meeting at which data on AstraZeneca's product was to be shared. AstraZeneca ensured that this evening meeting did not take place. However, it accepted that delegate selection criteria had already been linked to an interest in its product data and it therefore accepted that there was a breach of Clause 18.1, for which it sincerely apologised.

The email constituted a representative briefing. While technically, the email did not instruct representatives to act directly or indirectly in breach of the Code, AstraZeneca accepted that the briefing implied that AstraZeneca had selected delegates in breach of Clause 18.1. AstraZeneca, therefore, accepted that the email was in breach of Clause 15.9 and apologized for this. Corrective action was taken to ensure that this miscommunication was addressed and all of the representatives involved were contacted to explain the error.

While AstraZeneca admitted breaches of Clauses 18.1 and 15.9 in this instance following the spirit of the Code, it did not consider that it had either failed to maintain high standards or brought discredit upon or reduced confidence in the industry because:

- The email itself was erroneous and did not reflect the actual situation and therefore there was no underlying activity justifying a breach of Clauses 9.1 or 2.
- AstraZeneca had demonstrated that it had effective systems to ensure that employees brought instances of potential Code breaches to the attention of managers and its compliance team and that it would take effective action to deal with those breaches; it was this robust approach that brought the matter to the Authority's attention.
- Immediate and appropriate action was taken, including informing all the delegates involved in

this meeting of AstraZeneca's evaluation of this matter in relation to the Code and the action that it was taking. The delegates were impressed by the high standards and honesty that this demonstrated.
- Only one delegate was sent the email intended for the representatives and there had been no external complaint in relation to it.

These facts, together with the corrective action taken, meant that there was no question that the reputation of the industry had been damaged nor had there been any reduction of confidence in the industry.

AstraZeneca took the Code extremely seriously and undertook every effort to comply with it in both letter and spirit.

PANEL RULING

The Panel noted that the email referred to a directors' meeting at which the business cases for AUA delegates were reviewed and stated that 'the directors felt that taking your customers to the AUA as part of the AstraZeneca group would help protect our Zoladex business and in many cases help grow it'. The Panel noted with concern that the directors' meeting referred to had not taken place. The email had been certified by two signatories who, according to AstraZeneca, failed to validate the claims therein or query the nature of delegate selection. The email had been sent to representatives one of whom, despite no instructions to do so, had forwarded it to a potential delegate.

Clause 15.9 required that briefing material must not advocate directly or indirectly a course of action which would be likely to lead to a breach of the Code. The Panel considered that the email inappropriately linked the offer of sponsorship to attend an overseas meeting with past or future prescriptions of Zoladex. This would certainly be the impression given to representatives and the potential delegate who had received the email. Such an impression was unacceptable. A breach of Clause 15.9 was ruled. The Panel considered that the provision of the email at issue to a health professional amounted to an inducement to prescribe contrary to Clause 18.1 of the Code; a breach of Clause 18.1 was thus ruled.

The Panel was extremely concerned that the content of the email demonstrated a lack of awareness of the requirements of the Code by those involved. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that overall the email warranted a ruling of a breach of Clause 2 which indicated particular censure and was reserved for such use. No breach of Clause 2 was ruled.

Complaint received **6 May 2009**

Case completed **12 June 2009**

ANONYMOUS v ASTRAZENECA

Conduct of representative

An anonymous and uncontactable complainant, who described himself as a local general practitioner, alleged that an AstraZeneca representative had told the practice manager that the surgery could make a great saving if it ordered certain products from his own private company that supplied consumable and disposable products. The complainant noted that the surgery used AstraZeneca's products but if the local health board thought that the surgery was using them because of the discount it received from the representative's own private company it could question the surgery's impartiality when choosing a medicine for its patients.

The complainant alleged that there was a real conflict of interest with this representative, not only with his surgery but others.

The detailed response from AstraZeneca is given.

The Panel noted that in the anonymous allegations about a representative's conduct in this case neither the surgery nor the practice manager had been identified and there was no way to ask the complainant for more information. AstraZeneca submitted that its representative had not offered unusual discounts to health practices from his supplies company and no discounts had been offered in return for prescriptions of AstraZeneca products.

Companies had to be vigilant when a representative's personal business interests involved dealing with health professionals. The contractual relationship between AstraZeneca and its employees was not a matter for the Code. The Panel considered that whilst the company might be clear about the representative's distinct and separate roles such a distinction might not be clear to third parties. The company should be mindful of the impression created and ensure that the representative's private business activities did not compromise his compliance with the Code when he acted on behalf of AstraZeneca.

The Panel considered that the representative's ownership of a consumable supplies company was not a matter covered by the Code *per se*. Nonetheless, the Panel was concerned about the impression created by the arrangements; the representative might be seen as personally benefiting from interactions with health professionals. It was difficult for medical representatives to have two different types of professional relationships with health professionals without there being a perceived conflict of interest.

The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. Although the allegation was a serious one the Panel did not consider that the complainant had provided evidence to show that on the balance of probabilities the representative had offered discounts from his company when promoting AstraZeneca products such that the arrangements amounted to an inducement to prescribe AstraZeneca products. No breach of the Code was ruled including a ruling of no breach of Clause 2.

An anonymous and uncontactable complainant who described himself as a local general practitioner complained about the conduct of an AstraZeneca representative. The complaint was copied to the local health board.

COMPLAINT

The complainant alleged that when the representative was in his surgery recently, he had told the practice manager that the surgery could make a great saving if it ordered certain products from his own private company that supplied consumable and disposable products.

The complainant stated that whilst this might not sound like a major issue he was concerned that this could be connected to the use of AstraZeneca's product in the surgery. The surgery already used AstraZeneca's products but if the local health board thought that it used them because of the discount it received from the representative's own private company it could question the surgery's impartiality when choosing a medicine for its patients.

The complaint was sent anonymously because of the standing that the representative had with local doctors and the complainant did not want to be seen as the one to criticise him.

The complainant alleged that there was a real conflict of interest with this representative, not only with his surgery but others.

The Authority asked AstraZeneca to respond in relation to Clauses 2, 9.1, 15.2 and 18.1 of the Code.

RESPONSE

AstraZeneca noted that this complaint was similar to a previous case, Case AUTH/2210/3/09. However, the complainant this time referred to a specific occasion when its representative was alleged to

have offered a discount from his supplies company during a discussion with a practice manager. The complainant stated that he was, '….concerned that this could be connected to the use of AstraZeneca products in the surgery' and furthermore that the local health board could '.... call into question the surgery's impartiality when choosing a medicine for its patients'. Clearly, the complainant had alleged at least a *perceived* inducement to prescribe.

The complainant did not provide any dates, locations or names that would allow AstraZeneca to more specifically investigate this alleged discussion. However, AstraZeneca had re-interviewed its representative and established the following:

- As stated in its response to Case AUTH2210/3/09, the representative part owned a consumable supplies company that provided a range of supplies for the catering and licensing trades including specialist washroom supplies. The majority of customers for this business were therefore non-medical organisations.
- The representative had confirmed that only two health care practices had ever been supplied by his company, on terms comparable to all other customers.
- The representative had confirmed that he had identified all the practices where he had most successfully promoted AstraZeneca products and in no case did any of these practices procure any products from the representative's company.
- The representative had categorically denied that there was ever a specific occasion when he had discussed discounts from his consumable supplies company with a practice manager.
- The representative had confirmed explicitly that he had never pro-actively initiated any conversations relating to his company during the course of his AstraZeneca work.

The representative had confirmed (and AstraZeneca could find no evidence to the contrary) that no unusual discounts were given to health practices from his consumable supplies company and that no discounts had been offered in return for the prescription of AstraZeneca products. Therefore AstraZeneca denied a breach of Clause 18.1.

The representative had confirmed that any queries received in relation to his supplies company had always been redirected to his business partner. He had also in the past openly declared his conflicts of interest internally to AstraZeneca, as stated in Case AUTH/2210/3/09. AstraZeneca therefore denied a breach of Clauses 9.1 or 15.2.

AstraZeneca submitted that these complaints were an isolated instance in the many years that its reputable representative had worked for AstraZeneca whilst conducting his businesses locally and no specific evidence had been supplied to substantiate the allegations. AstraZeneca therefore denied a breach of Clause 2.

AstraZeneca continued to take this matter seriously. AstraZeneca had issued a company bulletin to remind employees of the company's conflict of interest policy. In addition, AstraZeneca had noted the concerns expressed by the Panel in its ruling to the earlier case and would implement processes to ensure that employees were not engaged in businesses that specifically targeted health professionals or administrators.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. When an allegation had been made about a representative's conduct it was difficult in the absence of corroborating evidence to determine precisely what had occurred. In this instance the surgery and practice manager had not been identified and there was no way to ask the complainant for more information. AstraZeneca submitted that its representative had confirmed that no unusual discounts were given to health practices from his supplies company and no discounts offered in return for prescriptions of AstraZeneca products.

Companies had to be vigilant when a representative's personal business interests involved dealing with health professionals. Although the contractual relationship between AstraZeneca and its employees was not a matter for the Code, the Panel noted that the representative had declared his interests to AstraZeneca in line with company policy. The Panel considered that whilst the company might be clear about the representative's distinct and separate roles such a distinction might not be clear to third parties. The company should thus be mindful of the impression created by such activities and ensure that the representative's personal business activities did not compromise his compliance with the Code when he acted on behalf of AstraZeneca.

The Panel considered that the fact that the representative owned a consumable supplies company was not matter covered by the Code per se. Nonetheless, the Panel was concerned about the impression created by the arrangements; the representative might be seen as inevitably personally benefiting from interactions with health professionals. The Panel noted that AstraZeneca would implement processes to ensure that its employees were not engaged in business that specifically targeted health professionals. In the Panel's view it was difficult for medical representatives to have two different types of professional relationships with health professionals without there being the perception of a conflict of interest.

The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. The Panel had some concerns about a possible conflict of interest and the impression created by the arrangements. The Panel considered that the allegation was a serious one but it did not consider that evidence had been provided by the complainant to show that on the balance of probabilities the representative had offered discounts on consumables from his company when promoting AstraZeneca products such that the arrangements amounted to an inducement to prescribe AstraZeneca products. No breach of Clauses 9.1, 15.2, 18.1 and consequently no breach of Clause 2 were ruled.

Complaint received **12 May 2009**

Case completed **9 June 2009**

CASE AUTH/2232/5/09

ANONYMOUS FORMER REPRESENTATIVE v CEPHALON

Training of representatives promoting Effentora

An anonymous former representative from Cephalon complained about the company's training of its representatives with regard to the promotion of Effentora (fentanyl buccal tablet).

The complainant alleged that he had received the first and only face to face training on the Code at the Effentora launch meeting from 12-15 January 2009. Afterwards the complainant's line manager told staff not to change what they did but just to be more careful what information they put in the customer database and another manager suggested telephoning off-label targets to avoid being seen and thus reported by competitor companies.

At the launch meeting none of the training materials appeared to have been copy approved. The complainant had provided copies of some of the material at issue and queried whether they should also have the black triangle.

The complainant noted that staff were trained on an audio visual (AV) presentation which was intended for use with customers but were told that it had not been copy approved so there could be some changes in the final version.

As part of the Effentora Risk Management Plan, agreed with the European Medicines Evaluation Agency (EMEA), representatives had to give customers an Effentora Prescription Guide during the first Effentora call. The sales manager did not realise that staff needed to be trained on this document so they were trained on a copy that was not copy approved. None of the materials trained staff on when to use the Effentora Prescription Guide.

At the complainant's previous company staff were trained on written guidance on how much could be spent on speaker fees, lunches, dinners and other hospitality. The complainant had never been trained on this at Cephalon and nor had his colleagues. At the complainant's previous company staff were also trained on grants and donations, medical and educational goods and services and on how their expenses would be audited. The complainant was not aware that Cephalon had policies on these activities. It was difficult to see how senior managers thought that representatives could comply with the Code if they did not train them on Cephalon ABPI policies and procedures.

At the meeting in January, staff were trained mainly on promoting Cephalon's products in line with the summary of product characteristics (SPC). Staff were told that the targets lists were to be changed and more tightly controlled by head office in future. One of the other representatives had told the complainant that one of his children's hospital's targets was being deleted from the Actiq customer database because it was not licensed for use in children.

The detailed response from Cephalon is given below.

The Panel noted that a list of materials and certification status provided by Cephalon showed that some of material used to train the representatives at the Effentora launch meeting had not been certified including some of the materials specifically referred to by the complainant. The complainant had referred to an AV presentation. The Panel noted Cephalon's submission that an AV presentation had been presented at the meeting as a concept before final sign off. The Panel queried whether concept material should be used at a product launch/training meeting for representatives. In any event it was likely to be viewed as briefing material and should have been certified. Given that uncertified materials were used breaches of the Code were ruled as acknowledged by Cephalon. It was unclear as to whether the Effentora Script Detail Aid as referred to by the complainant had been certified before the meeting. Information provided by Cephalon in response to a request for a comprehensive list of materials and presentations used at the Effentora launch meeting showed that several items were certified after the event. The Panel agreed with Cephalon that the meeting agenda, as referred to by the complainant, did not need to be certified and no breach of the Code was ruled in that regard.

The Panel considered that the failure to certify much of the representatives' training material before it was used was unacceptable. The Panel noted Cephalon's submission that the circumstances leading up to the launch meeting had been exceptional. Nonetheless high standards had not been maintained and a breach of the Code was ruled.

The Panel considered that it was good practice to include the inverted black triangle on representatives' training materials. However, there was no evidence that the materials used at the training meeting had been used with health professionals and thus no breach of the Code was ruled.

The Panel noted Cephalon's submission that the representatives had been trained on the Effentora

Prescribing Guide and thus no breach of the Code was ruled.

The Panel noted that Cephalon had issued guidance on the allowable costs for meetings and other activities etc in addition to six standard operating procedures (SOPs). The guidance document was not dated.

Training was provided on the 2008 Code although the Panel queried why this was not completed until November of that year; the 2008 Code came into operation on 1 July with a three month grace period for newly introduced requirements. Materials relating to the Code were provided for representatives to read. The Panel noted that no training had been provided on medical and educational goods and services; an SOP was being produced. It appeared that Cephalon asked staff to read various documents and policies rather than providing structured training. A Code compliance project was ongoing with the aim of establishing policies and procedures to ensure ongoing compliance with the Code. The Panel was concerned about the arrangements for training the representatives. No evidence was provided documenting the training each representative received nor was documentation supplied with regard to phamacovigilance training.

Overall the Panel considered that although some training had been provided there was a need for more focused and validated training. Thus the Panel ruled breaches of the Code.

A senior employee (the general manager) had been appointed as the person responsible for ensuring Code compliance and so no breach was ruled. The Panel did not consider, on the material before it, that Cephalon had failed to adequately train its representatives such that they did not have sufficient scientific knowledge to enable them to provide full and accurate information about the medicines they promoted. Nor was there information to show that representatives had not maintained a high standard of ethical conduct. No breaches of the Code were ruled.

The Panel noted that no evidence had been provided by the complainant to show that the alleged failure to train representatives on the company policies for hospitality, speaker fees, grants and donations had resulted in breaches of the Code. Thus the Panel ruled no breach of the Code. Such guidance was not necessarily regarded as briefing material and thus no breach of the Code was ruled.

The Panel considered that the inadequacy of the training arrangements at Cephalon meant that high standards had not been maintained and a breach of the Code was ruled.

Overall the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

With regard to the alleged promotion of unlicensed indications the Panel considered it was very important that representatives were given clear instructions regarding potential audiences. It was of concern that the complainant alleged that a manager suggested telephoning off-label targets so that 'the competitor company's representatives would not see Cephalon's representatives visiting them and report them'. The Panel noted Cephalon's explanation that health professionals at children's hospitals could work across several units – including adult units. Cephalon denied there was a policy to promote the use of Actiq in children. Although the Panel was concerned about the arrangements, in particular the lack of clear instructions to representatives, it did not consider that the complainant had proved their complaint on the balance of probabilities and thus no breach of the Code, including Clause 2 was ruled.

An anonymous former representative from Cephalon complained about the company's training of its representatives with regard to the promotion of Effentora (fentanyl buccal tablet) an opiod analgesic..

COMPLAINT

The complainant alleged that he had received the first and only face to face training on the Code at the Effentora launch meeting (12-15 January 2009). Afterwards the complainant's line manager told staff not to change what they did but just to be more careful what information they put in the TEAMS database [customer-relationship management database] and another manager suggested telephoning off-label targets so that the competitor company's representatives would not see Cephalon's representatives visiting them and report them.

The complainant alleged that none of the training materials used at the launch meeting had job bag numbers or a date of preparation which meant that they had not been copy approved (breaches of Clauses 9.1, 15.9 and 14.1). The complainant had provided some examples as proof of this:

- Training agenda for 13 and 14 January 2009.
- Effentora Script Detail Aid.
- Effentora BTcP [breakthrough cancer pain] and Treatment Strategy slide set.
- Practice detail role plays.

The complainant queried whether these materials should also have the black triangle (breach of Clause 4.11).

The complainant noted that staff were trained on an audio visual (AV) presentation intended for use with customers but were told that it had not been copy approved so there could be some changes in the final version (breach of Clause 14.1).

As part of the Effentora Risk Management Plan,

agreed with the European Medicines Evaluation Agency (EMEA), staff were told that all the representatives had to give customers an Effentora Prescription Guide during the first Effentora call. The Effentora sales manager did not realise that staff needed to be trained on this document so they were trained on a copy that was also not copy approved. None of the Effentora training materials trained staff on when to use the Effentora Prescription Guide, for example the practice detail role plays did not mention discussion of the Effentora Prescription Guide (breaches of Clauses 16.2, 7.10, 9.1, 14.1 and 15.9).

The complainant submitted that at his previous company staff were trained on written guidance on how much could be spent on speaker fees, lunches, dinners and other hospitality. The complainant had never been trained on this at Cephalon and nor had his colleagues (breaches of Clauses 19.1, 16.1, 15.2, 15.9 and 9.1). At the complainant's previous company staff were also trained on grants and donations, medical and educational goods and services and on how their expenses would be audited. The complainant was not aware that Cephalon had policies on these activities at all. In fact the complainant was not trained on any Cephalon ABPI Code policies (breaches of Clauses 9.1, 15.2, 15.9, 16.1, 19.1 and 2). The complainant doubted if Cephalon had policies and procedures or evidence of training staff on them (breach of Clause 15.9). It was difficult to see how senior managers thought that representatives could comply with the Code if they did not train them on Cephalon ABPI policies and procedures (breaches of Clauses 9.1, 15.1, 15.2, 15.9, 16.1, 16.2, 1.7, 1.8 and 2).

At the ABPI Code training in January, staff were trained mainly on promoting Cephalon's products in line with the summary of product characteristics (SPC) (Clause 3.2). Staff were told that the targets lists were to be changed and more tightly controlled in future. One of the other representatives had told the complainant that one of his children's hospital's targets was being deleted from TEAMS for Actiq because it was not licensed for use in children (breaches of Clauses 3.2, 9.1 and 2).

Overall the complainant alleged that Cephalon did not take the Code as seriously as other companies that he had worked for and seemed to get away with putting less effort and resources into it. This did not seem fair or ethical when the same standards should be applied.

The complainant noted that he had not felt able to raise these issues when working at Cephalon.

RESPONSE

Cephalon noted that the complaint was from an anonymous former representative; it was unfortunate that such matters had been brought to the Authority's attention without recourse by that employee during their employment.

1 Code training and alleged line manager statements

Cephalon disputed the allegation that any line manager had directed representatives to behave in a manner outside of the requirements of the Code and company policies. No specific clauses of the Code were cited in regard to this aspect of the complaint, so Cephalon only responded to the information provided.

The complainant provided no further information as to what behavior need not change or the nature of the caution over database entries.

With respect to the allegation of telephoning off-label targets, no briefings would direct representatives to take actions that would compromise compliance with the Code. The training delivered at the launch meeting reinforced the importance of promoting within the licence.

In summary, Cephalon refuted the allegation as it knew of no evidence to support it.

2 Effentora launch meeting materials

Cephalon noted that it was alleged that none of the training materials used at the launch meeting had job bag numbers or a date of preparation, implying that they had not been copy approved. A number of materials were submitted as evidence. However Cephalon submitted that the key training manuals on Effentora were certified and materials could be supplied to support this point.

The alleged breach of Clause 9.1 was not applicable to such training materials, as the high standards relevant to this clause related to materials used with health professionals ie promotional.

Cephalon accepted the alleged breaches of Clauses 15.9 and 14.1, relating to the failure to certify materials, and specifically briefing materials. However, the agenda submitted as proof did not contain information that otherwise required certification, hence there was no code number, although it was dated.

Cephalon submitted that, with reference to the alleged breach of Clause 4.11, the requirement to include a black triangle only applied to promotional materials. As training or briefing materials, this clause was not applicable, although Cephalon accepted that it was good practice to include this on internal material.

Cephalon submitted that an AV presentation was presented as a concept, prior to being finally certified, and was not given to representatives. Cephalon refuted the allegation that such use constituted a breach of Clause 14.1.

Cephalon submitted that its representatives were trained on pharmacovigilance responsibilities

during their initial training, and at least annually. A verbal brief was provided to the representatives regarding use of the Prescription Guide during the role play activities. During the initial Effentora product training (17-21 November 2008 and 1-5 December 2008), presentations were made on the Risk Management Plan, at which time the Prescription Guide was referred to verbally and the requirements to provide during a detail. As such, Cephalon refuted the alleged breaches of Clauses 16.2, 7.10, 9.1, 14.1 and 15.9. The certified Prescription Guide was available for use by representatives following the launch meeting and its use within calls had been tracked since launch.

In response to a request for further information Cephalon provided a list of material and presentations used at the launch meeting together with details as to their certification status. Guidance regarding costs of meetings was also provided and this included guidance for honoraria. The company was in the process of producing a standard operating procedure (SOP) on the provision of medical and educational goods and services and grants and donations.

Cephalon submitted that it planned to update all documentation and training relating to requirements of the Code. The circumstances leading up to the internal launch meeting were exceptional, with serious, long-term illness of the responsible product manager. However, Cephalon had already identified the need to review the current policies and procedures and this was ongoing.

3 Cephalon policies and training on the Code

Cephalon submitted that during November 2008 all sales representatives completed the Code 2008 update module available via Wellards. A project was implemented for 2009 to address numerous aspects of policies, procedures and training within Cephalon. Currently, there were SOPs for the following:

- Approvals and certification of promotional material (SOP-0004710)
- Withdrawal of promotional material (SOP-0004713)
- Handling of medical information enquiries (SOP-0004714)
- Meetings approval (SOP-0004718)
- Provision of information regarding unlicenced use (SOP-0004719)
- Direct healthcare professional communications (SOP-0004720)

Cephalon submitted that the Code compliance project was an all-encompassing review and implementation to establish the policies and procedures required to ensure ongoing compliance with the Code and other applicable requirements.

The complainant alleged that no training was provided on meetings and hospitality. Cephalon submitted that all employees could access current policies and procedures, where such a policy existed, on the company intranet. As such, Cephalon refuted the alleged breach of Clause 19.1.

Cephalon's practice was to employ representatives who were familiar with the Code and who had successfully completed the ABPI Representatives Examination.

Cephalon submitted that in addition to completing the Wellards training, there was a training session at the launch meeting which was further evidence of training focused on the requirements of the Code. 'The Code in Practice' and the 'The Code in the Field' books were given to appropriate personnel in February 2009. Therefore, Cephalon refuted the allegation that personnel were not conversant with the requirements of the Code (Clause 16.1).

Cephalon submitted that with regard to the alleged breach of Clause 15.2 that representatives had not maintained high standards, there was nothing in the complaint that identified specific representative activity for this to be considered relevant or for a response to be produced.

Cephalon submitted that the alleged breach of Clause 15.9 related to there being no detailed briefing materials. Again, there was no specific allegation as to what briefing materials. Effentora training manuals had been reviewed and certified on 11 September 2008.

Cephalon submitted that the alleged breach of Clause 9.1 was not applicable here, as the high standards relevant to this clause related to promotional activities and materials used with health professionals. The complainant had made no specific allegation relating to promotional activity.

Cephalon refuted that the alleged breach of Clause 15.1 regarding lack of adequate scientific training on promoted medicines. The training manuals were certified for briefing purposes and two separate training modules were performed for the two business units (17-21 November 2008 and 1-5 December 2008).

Cephalon reiterated that its representatives were trained on pharmacovigilance responsibilities during their initial training, and at least annually. During the initial Effentora product training (17-21 November 2008 and 1-5 December 2008), presentations were made on the Risk Management Plan. As such, Cephalon refuted the alleged breaches of Clause 16.2.

Cephalon refuted that the alleged breach of Clause 1.7, not complying with all applicable codes, laws and regulations. No specific allegations were made. To Cephalon's knowledge it fulfilled these obligations by the explicit expectation that all

personnel complied with the Code.

Cephalon denied the allegation that it had not appointed a senior employee responsible for ensuring the company met the requirements of the Code; the general manager assumed this obligation. Therefore, Cephalon refuted the alleged breach of Clause 1.8.

Cephalon noted that although the complainant had alleged a breach of Clause 2, bringing discredit to, and reducing confidence in the industry, no allegations or examples submitted constituted such a breach.

4 Children's hospital targets

Cephalon submitted that the complainant referred to Code training during the January meeting, and being trained on promoting products in line with the SPC, correctly referring to Clause 3.2. This was a specific aspect of the training session.

The complainant referred to anecdotal information that a target in a children's hospital had been deleted from the TEAMS database because Actiq did not have a licence for children. The alleged breaches of Clauses 3.2, 9.1 and 2 were refuted. In the absence of details relating to a specific health professional, hospital or representative then Cephalon had insufficient information to investigate this matter further.

In response to a request for further information about whether health professionals at children's hospitals had been on target lists for Actiq, Cephalon stated that its customer targeting was a dynamic process with periodic list revisions. In line with data protection legislation it did not hold information that was no longer relevant. It was therefore not possible to give an accurate answer covering all of 2008. However, based on the last two list revisions kept on file, covering the second half of 2008, there were six health professionals with an Actiq target flag co-located in children's hospitals or children's units during 2008. Two of these were flagged as target customers and the remainder as support personnel (such as nursing staff). Two of the six health professionals had not been contacted by Cephalon as far back as records existed. Five of the six health professionals had palliative medicine listed as a prime speciality and would be responsible for adult patients.

The database of health professionals was compiled by a third party. Health professionals were given one address within the database, although they could work across several units (eg in both adult and children's units as palliative medicine specialists). These health professionals could thus be seen at an alternative address (eg the adult unit), although the call record defaulted to the primary address which might be a children's unit. There had been no policy to promote the use of Actiq in children.

PANEL RULING

The Panel noted that Clause 15.9 required that representatives' briefing material was produced and certified. Briefing material consisted both of the training material about the product and the instructions as to how it should be promoted. The requirement to certify applied to printed briefing material and to the transcripts used in presentations to representatives. The Panel noted that a list of materials and certification status provided by Cephalon showed that when the Effentora launch meeting took place (12-15 January) some of material used to train the representatives had not been certified. Of the materials specifically referred to by the complainant the Effentora BTcP and Treatment Strategy slide set, the role play materials and the Effentora Prescribing Guide had not been certified. The complainant had also referred to an AV presentation. The Panel noted Cephalon's submission that an AV presentation had been presented at the meeting as a concept before final sign off. The Panel queried whether concept material should be used at a product launch/training meeting for representatives. In any event it was likely to be viewed as briefing material and should have been certified. Given that uncertified materials were used a breach of Clauses 14.1 and 15.9 was ruled as acknowledged by Cephalon. It was unclear as to whether the Effentora Script Detail Aid had been certified before the meeting. Information provided by Cephalon in response to a request for a comprehensive list of materials and presentations used at the Effentora launch meeting showed that several items were certified after the event. The Panel agreed with Cephalon that the meeting agenda did not need to be certified and no breach of Clauses 14.1 and 15.9 was ruled in that regard.

The Panel considered that the requirement of Clause 9.1 to maintain high standards applied to all activities covered by the Code – it was not limited to promotional activities as submitted by Cephalon. The Panel considered that the failure to certify much of the representatives' training material before it was used was unacceptable. The Panel noted Cephalon's submission that the circumstances leading up to the launch meeting had been exceptional. Nonetheless high standards had not been maintained and a breach of Clause 9.1 was ruled.

As acknowledged by Cephalon the Panel considered that it was good practice to include the inverted black triangle on representatives' training materials. Of the materials specifically referred to in this regard by the complainant the Effentora Script Detail Aid and the practice detail role plays did not incorporate the black triangle symbol. However, the Panel noted that Clause 4.11 only required a black triangle to be included on promotional material. There was no evidence that the materials used at the training meeting had been used with health professionals and thus no breach of Clause 4.11 of the Code was ruled.

The Panel noted Cephalon's submission that the representatives had been trained on the Effentora Prescribing Guide and thus no breach of Clauses 7.10 and 16.2 was ruled.

The Panel noted that Cephalon had issued guidance on the allowable costs for meetings and other activities etc in addition to the six SOPs. The guidance document was not dated.

Training was provided on the 2008 Code via Wellards although the Panel queried why this was not completed until November of that year; the 2008 Code came into operation on 1 July with a three month grace period for newly introduced requirements. Materials relating to the Code were provided for representatives to read. The Panel noted that no training had been provided on medical and educational goods and services; an SOP was being produced. It appeared that Cephalon asked staff to read various documents and policies rather than providing structured training. A Code compliance project was ongoing with the aim of establishing policies and procedures required to ensure ongoing compliance with the Code. The Panel was concerned about the arrangements for training the representatives. No evidence was provided documenting the training each representative received nor was documentation supplied with regard to phamacovigilance training.

Overall the Panel considered that although some training had been provided there was a need for more focused and validated training. Thus the Panel ruled breaches of Clauses 16.1 and 16.2 of the Code.

Cephalon had not complied with the Code and thus a breach of Clause 1.7 was ruled. As required by Clause 1.8 a senior employee (the general manager) had been appointed as the person responsible for ensuring Code compliance and so no breach of that clause was ruled.

The Panel did not consider, on the material before it, that Cephalon had failed to adequately train its representatives such that they did not have sufficient scientific knowledge to enable them to provide full and accurate information about the medicines they promoted. Nor was there information to show that representatives had not maintained a high standard of ethical conduct. No breach of Clauses 15.1 and 15.2 was ruled.

The Panel noted that no evidence had been provided by the complainant to show that the alleged failure to train representatives on the company policies for hospitality, speaker fees, grants and donations had resulted in breaches of the Code. Thus the Panel ruled no breach of Clauses 19.1 and 15.2. Such guidance was not necessarily regarded as briefing material and thus no breach of Clause 15.9 was ruled.

The Panel considered that the inadequacy of the training arrangements at Cephalon meant that high standards had not been maintained and a breach of Clause 9.1 of the Code was ruled.

Overall the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure.

With regard to the alleged promotion of unlicensed indications the Panel considered it was very important that representatives were given clear instructions regarding potential audiences. It was of concern that the complainant alleged that a manager suggested telephoning off-label targets so that 'the competitor company's representatives would not see Cephalon's representatives visiting them and report them'. The Panel noted Cephalon's explanation that health professionals at children's hospitals could work across several units – including adult units. Cephalon denied there was a policy of promoting use of Actiq in children. Although the Panel was concerned about the arrangements, in particular the lack of clear instructions to representatives, it did not consider that the complainant had proved their complaint on the balance of probabilities and thus no breach of Clauses 3.2, 9.1 and consequently Clause 2 were ruled.

Complaint received **22 May 2009**

Case completed **6 July 2009**

ANONYMOUS GENERAL PRACTITIONER v LEO

Meeting arrangements

An anonymous General Practitioner complained that Leo Pharma had invited him to a meeting which he considered was in breach of the Code given that the venue had a 5 star rating and included an exhibition centre. The complainant noted that the venue was 65 miles from his practice.

The detailed response from Leo is given below.

The Panel noted that the meeting 'Early Recognition of Melanoma & Optimal Treatment of Psoriasis' was aimed at GPs. According to the invitation it began at 6.30pm with registration and dinner. The educational programme began at 7pm and comprised two half hour presentations each followed by discussion and questions. There was a 15 minute coffee break and the programme finished at 8.45pm. A reminder letter about the meeting stated that it was fully subscribed at 120 delegates.

The Panel noted Leo's submission that dinner was provided as a buffet at £18 per head. The total cost of food and drinks for 120 GPs was £22.50 per head. The total cost of the meeting was £5,619.25 which was not dissimilar to the estimated total cost quoted by two local hotels.

The Panel noted that the venue, a visitor and learning centre which focussed on health, science and technology, included a science mall, cinema, science and climate change theatres and a planetarium. One of its aims was to develop and enhance awareness of educational opportunities surrounding current and future health, science and technology issues. It had been awarded a 5 star visitor rating. The Panel, however, did not agree with Leo's submission that a distinction must be made between a 5 star rating for a luxury hotel and that for a scientific learning facility; the impression created by the arrangements, whatever the venue, must be borne in mind and venues must be considered on their own merits. The Panel noted that the 120 delegates were drawn from a wide area. The venue was well placed for motorway access and had good car parking facilities. The centre was closed to the public at the time of the meeting and the exhibits were not accessible to the delegates. The venue's facilities were not referred to on the invitation or meeting reminder and there was little time for registration and dinner (30 minutes) before the meeting started. The conference facilities included a 120 seated learning auditorium which Leo submitted had good audio visual facilities particularly suited to dermatology audio visuals. Subsistence was provided as a buffet served during registration at the start of the evening. The Panel did not consider that the venue was lavish, extravagant or deluxe. The Panel thus considered that the venue was not inappropriate for the meeting in question and ruled no breach of the Code including Clause 2.

COMPLAINT

An anonymous GP complained about a meeting to be held in May organised by Leo Pharma. The meeting would be at a 5 star venue, which, as far as the complainant was aware, was not allowed under the Code. It was also an exhibition centre which the complainant also thought was not allowed. The complainant stated that the meeting was 65 miles away from his practice.

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

RESPONSE

Leo explained that the venue at issue rated itself as a '5 star venue for corporate events' but submitted that a distinction must be made between a 5 star luxury hotel or resort and a 5 star scientific learning facility. This venue had no added advantages for the attendees by the way of a spa, gymnasium, golf course, highly regarded restaurant or fashionable bar that most 5 star luxury hotels boasted.

The venue was an independent charity which aimed to:

- develop and enhance awareness of educational opportunities surrounding current and future health, science and technology issues;
- be a socially inclusive and accessible visitor centre of excellence;
- extend all opportunities within the venue to as many people as possible, particularly addressing the needs of people of all ages who were socially, cognitively or physically challenged.

Clause 19.1 stated that 'Meetings must be held in appropriate venues conducive to the main purpose of the event'. Leo submitted that the venue was appropriate because it had a 120 seated learning auditorium with excellent audio visual facilities, a vital component especially at a skin meeting where skin cancer and psoriasis visuals were a vital part of differential diagnosis. A hotel or similar venue would not be able to offer such appropriate audio visual facilities.

Leo noted that as the venue was closed during the time of the meeting, promotional materials could be exhibited without the public viewing them. As the

venue exhibits were also roped off throughout the meeting these attractions played no role in the evening and were not advertised or used as any form of enticement for the meeting.

The venue was a well known, centrally located, price equivalent venue offering reasonable catering facilities, free parking and good access to local motorway routes. Indeed Leo submitted that the cost of the event at this venue was cheaper than many local hotels.

The purpose of the GP dermatology meeting was to offer educational advice on skin cancer and psoriasis. It comprised two half hour talks by highly respected local consultants with 15 minutes of questions. A buffet was included in the 30 minute registration period as it was expected that most GPs would attend immediately after their evening surgery. The meeting was organised by local representatives in conjunction with head office administrative and marketing staff.

Invitations were sent out in two simultaneous mailings from an agency which was outsourced to provide this service. Invites were sent throughout the Scottish central belt and acceptances were received from most areas. Local representatives also individually dropped off invites in some areas by way of a reminder. A list of invitees could be made available if appropriate. Reminders were also dropped by local representatives to doctors who agreed to attend. Therefore Leo submitted that this venue did not contravene Clauses 19.1, 9.1 or 2 of the Code as it would not, in any way, be considered 'lavish, extravagant or deluxe' and would not be an enticement to attend the meeting. Leo was convinced that this was an excellent educational facility and wished to use it for future meetings.

In response to a request for further information Leo provided a list of all invitees and delegates together with details of the costs for venue hire and hospitality. A quotation obtained from a local hotel was provided which had inferior audio visual equipment and cost over £300 more demonstrating the value for money for the venue.

PANEL RULING

The Panel noted that Clause 19.1 of the Code permitted companies to provide hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings. Hospitality must be strictly limited to the main purpose of the meeting ie subsistence only and the level of subsistence offered must be appropriate and not out of proportion to the occasion. The costs incurred must not exceed the level which recipients would normally adopt if paying for themselves. It must not extend beyond members of the health professions or appropriate administrative staff. The supplementary information stated that the impression created by the arrangements must be borne in mind and provided helpful advice about the venue. The venue must be appropriate and conducive to the main purpose of the meeting; lavish, extravagant or deluxe venues must not be used. Companies must not sponsor or organise entertainment and should avoid using venues renowned for their entertainment facilities.

The Panel noted that the meeting 'Early Recognition of Melanoma & Optimal Treatment of Psoriasis' was aimed at GPs. According to the invitation it began at 6.30pm with registration and dinner. The educational programme began at 7pm and comprised two half hour presentations each followed by 15 minutes of discussion and questions. There was a 15 minute coffee break and the programme finished at 8.45pm. A reminder letter about the meeting stated that it was fully subscribed at 120 delegates.

The Panel noted Leo's submission that dinner was provided as a buffet at £18 per head. The total cost of food and drinks for 120 GPs was £2,700 (£22.50 per head). The total cost of the meeting was £5,619.25 which was not dissimilar to the estimated total cost quoted by two local hotels.

The Panel noted that the venue was a visitor and learning centre which focussed on health, science and technology. The centre included a science mall, cinema, science and climate change theatres and a planetarium. One of its aims was to develop and enhance awareness of educational opportunities surrounding current and future health, science and technology issues. It had been awarded a 5 star visitor rating. The Panel, however, did not agree with Leo's submission that a distinction must be made between a 5 star rating for a luxury hotel and that for a scientific learning facility; the impression created by the arrangements, whatever the venue, must be borne in mind and venues must be considered on their own merits. The Panel noted that the 120 delegates to the meeting were drawn from a wide area. The venue was well placed for motorway access and had good car parking facilities. The centre was closed to the public at the time of the meeting and the exhibits were not accessible to the delegates. No mention was made about the venue's facilities on the invitation or meeting reminder and there was little time for registration and dinner (30 minutes) prior to commencement of the meeting. The conference facilities available included a 120 seated learning auditorium which Leo submitted had good audio visual facilities particularly suited to dermatology audio visuals. Subsistence was provided as a buffet served during the registration period at the start of the evening. The Panel did not consider that the venue was lavish, extravagant or deluxe. The Panel thus considered that the venue was not inappropriate for the meeting in question and ruled no breach of Clauses 19.1, 9.1 and consequently Clause 2 of the Code.

Complaint received **26 May 2009**

Case completed **9 July 2009**

CASE AUTH/2236/6/09

PHARMACIST v SANOFI-AVENTIS

Conduct of representatives

A pharmacist complained that a representative from Sanofi-Aventis had taken members of the local oncology team (2 doctors and 5 nurses) to dinner in a restaurant on 17 June, 2008. Those involved had told the complainant that the evening was purely social. A sales/educational event had been held earlier in the day.

The detailed response from Sanofi-Aventis is given below. It became clear that two representatives had been involved.

The Panel noted that the parties' accounts differed; it was extremely difficult in such cases to know exactly what had transpired. In that regard it was unfortunate that the meeting at issue had taken place almost a year ago, that the complainant had not attended the meeting, that one of the representatives no longer worked for Sanofi-Aventis and that the representatives' meeting records were not wholly consistent. A judgement had to be made on the available evidence and the balance of probability bearing in mind the extreme dissatisfaction usually required before an individual was moved to complain.

The Panel noted that the first representative's meeting log recorded a small audio-visual meeting which started at 7.30pm and would last an hour and a half; the meeting venue was to be confirmed. The second representative's meeting log recorded a round table meeting which started at 6pm at the chemotherapy unit followed by the restaurant. The meeting was to last four hours. Five of the delegates were hospital nurses, one was a hospital doctor and one GP also attended. Sanofi-Aventis had submitted that the first representative had presented on early breast cancer for approximately one hour. The second representative had then presented on prostate cancer. No formal agenda for the meeting was produced.

Sanofi-Aventis had submitted that, following the meeting at the hospital, the representatives had taken the attendees to a restaurant because no on-site catering facilities were available at the time of the meeting. This was disputed by the complainant. The Panel was concerned to note that in choosing the restaurant the representatives had consulted the delegates and their preferences appeared to have been considered. Sanofi-Aventis had submitted that non-product related discussions continued at the restaurant. The complainant had been assured that the evening was entirely social in purpose and that most of the educational event had occurred earlier in the day.

The Panel noted all the discrepancies particularly those of the representatives' meeting logs. The timing and venue for the meeting were not clear. It would be a breach of the Code for a company to delay the provision of hospitality eg to hold a meeting at lunchtime and provide dinner in the evening. It would also be a breach of the Code to hold the meeting in a restaurant unless a private room was used or the restaurant closed to the public. Hospitality had to be secondary to the main purpose of a meeting. The level must be reasonable and not out of proportion to the occasion.

The Panel noted that a three course meal with wine had been provided. The cost per head was £36.20 of which £9.83 per head was wine. The Panel was concerned to note that one liqueur had also been paid for. The Panel considered that the hospitality provided was not limited to subsistence only and was out of proportion to the occasion. The Panel also considered that for some of the attendees the hospitality provided might have exceeded the level which they would normally adopt when paying for themselves. A breach of the Code was ruled. The representatives had not maintained a high standard of ethical conduct and a further breach was ruled.

A pharmacist complained about the conduct of a representative from Sanofi-Aventis.

COMPLAINT

The complainant stated that the representative had entertained members of the local oncology team (2 doctors and 5 nurses) at a dinner in a restaurant on one of the Channel Islands on 17 June, 2008. Those involved had told the complainant that there was no educational content to the dinner, it was purely social. The representative had held a sales/educational event earlier in the day for the staff involved.

The complainant alleged that the arrangements were in breach of the Code.

When writing to Sanofi-Aventis the Authority asked it to consider the requirements of Clauses 2, 15.2 and 19.1 of the 2006 edition of the Code. The case was considered under the Constitution and Procedure as set out in the 2008 edition of the Code.

RESPONSE

Sanofi-Aventis explained that the representative in question, from the company's oncology sales team, promoted Taxotere for breast cancer; she had since

joined another pharmaceutical company.

The representative had passed the ABPI Representatives Examination, with distinction. She had been trained on Taxotere and on the Code, in particular the revised 2006 Code and the provisions on meetings and hospitality, including the company standard operating procedure (SOP) on meetings and hospitality.

The meeting in question took place during a visit by the representative to the oncology centre; another Sanofi-Aventis oncology representative who promoted Taxotere in metastatic hormone-resistant prostate cancer, accompanied her. The meeting was arranged with the local oncology unit and involved both representatives.

Sanofi-Aventis explained that it required details of all meetings to be held on a central salesforce activity database. The details of the meeting logged by the representative were provided. These did not provide enough detail to adequately account for the activity; however the other representative at the meeting kept more appropriately detailed records and her summary of the meeting was also provided. From this, the meeting started at the oncology centre at 6pm (once all patients had left) and carried on at the restaurant, finishing at approximately 10pm that evening.

The representative who jointly held the meeting with the representative at issue recalled that her colleague presented on early breast cancer for approximately an hour using her detail aid and support materials. Copies of the relevant materials were provided; unfortunately there was no confirmation as to which specific materials were used. The discussion focussed on the issues with side effects and their management and also problems posed by cases the unit had seen. The second representative then presented on prostate cancer, discussing urology referral and its importance, the patient pathway and the National Institute for health and Clinical Excellence (NICE) guidance in depth. She used the current detail aid and support materials to do this, copies of which were provided. No formal agenda was produced for the meeting.

The discussion at the restaurant was non product-related, and focussed on environmental and service-related issues, including oncology services on the mainland and progress with the new oncology centre.

There were no refreshment facilities available at the oncology centre at the time of the meeting. Cognisant of the requirements of the Code and Sanofi-Aventis' policies, the representatives requested advice from the oncology unit approximately a week before their visit to identify a suitable venue for refreshments. Criteria discussed were that the venue be not lavish, nor have an international reputation or be linked to a spa or golf course. The restaurant used was suggested by the oncology unit as being appropriate and convenient for the attendees; as part of a bistro franchise known to the representatives on the mainland, it was considered to be of the standard that the attendees might normally frequent themselves.

A full breakdown of the costs for the meal was provided. The bill of £350, including tax, was divided between the two representatives. Nine people attended, the two representatives and seven health professionals consisting of one hospital consultant, one GP with a special interest in oncology, and five oncology nurses. Details of the attendees were provided.

Sanofi-Aventis regretted that the detail recorded in the sales activity system was not sufficient to provide a fully comprehensive response on all aspects of this meeting and impaired recall due to the passage of time also hindered the supply of a fully detailed account. It was not possible therefore to completely refute the allegation of breaches of Clauses 15.2 and 19.1. The company was currently taking steps to re-brief its sales team on the requirements of the Code regarding meetings and hospitality, with particular emphasis on accurate and diligent record keeping. Sanofi-Aventis considered that the representative concerned acted in good faith but in retrospect, greater control over the costs of refreshments, and an agenda setting out the educational content of the meeting should have been evident. The company submitted, however, that this isolated specific occasion did not represent a breach of Clause 2.

FURTHER COMMENTS FROM THE COMPLAINANT

In response to a request for her comments upon Sanofi-Aventis' response, the complainant noted that the background on the representative's training was irrelevant; one would expect this to have taken place given that she promoted oncology medicines.

The complainant had been told by the individuals involved that the representatives met the oncology staff earlier in the day when the sales information was presented. They might have met again at 6pm after clinic, regrouped and held brief discussions before moving on. It was incorrect to give the impression that the meal was an extension of the meeting. The complainant had been assured that the evening was entirely social in purpose and that the bulk of the event was earlier in the day.

The complainant noted that it was wrong to state that there were no refreshment facilities available at the oncology centre. This was a unit directly attached to a hospital and the catering department, frequently supplied good quality buffets on request. There was also a meeting room available with modern presentation facilities.

The complainant further noted that the restaurant was at least a taxi ride away from the hospital. The

complainant considered that £350 for nine people (ie £39 per head) was a very large bill on territory where VAT was not payable and the individuals involved presumably had to attend work the following morning.

The complainant's comments were sent to Sanofi-Aventis for its comments.

FURTHER COMMENTS FROM SANOFI-AVENTIS

Sanofi-Aventis submitted that to address the specific questions about the meeting which was held over a year ago it had to rely on the records of the representatives involved. These revealed some discrepancies. Notwithstanding, the company acknowledged that the standard of record keeping was not acceptable and measures were in place to address this matter.

Sanofi-Aventis provided the complete records of the second representative which detailed the interactions between the representatives and the health professionals on 17 June. The record of both representatives had shown that seven health professionals had attended the meeting. The one discrepancy in an attendee's name was assumed to be an inputting error.

With regard to the duration of the meeting Sanofi-Aventis did not have further details to explain the anomaly between the two representatives' records. The records of the second representative were more detailed. Similarly the company did not have any further details regarding the meeting description; it was possible that the difference was indicative of the presentation styles that the two representatives might have used to convey their product-related messages on the two different tumour types.

Sanofi-Aventis noted that company policy required representatives to have meeting arrangements approved in advance. However, circumstances sometimes prevented this. On this occasion, whilst not ideal, the second representative was on two weeks' annual leave prior to the meeting (30 May – 16 June) and again on 19 June. Sanofi-Aventis gave its assurance that both meetings logs referred to the meeting in question on 17 June.

Sanofi-Aventis submitted that the receipt for the meal showed the purchase of five bottles of wine which equated to approximately half a bottle of wine per attendee, which was in line with the company's internal guidance. Sanofi-Aventis had reviewed the restaurant and stated that it appeared that it was not part of the franchise of the same name on the mainland, which was the belief of the representative.

The company believed that discussions were held at both the oncology centre and the restaurant.

With regard to the choice of venue, the representatives worked with the attendees to find a suitable venue for the evening part of the meeting. The appropriate choice of venue, together with individual preferences would have dictated the mode of transport to the restaurant.

Over the course of the evening, until the bill was settled at 10.10pm, three courses were served and the cost reflected this.

Sanofi-Aventis reiterated that it regretted the paucity of details in the sales activity system. It was not possible to refute allegations of Clauses 15.2 and 19.1. The company still considered that this case did not represent a breach of Clause 2.

Sanofi-Aventis stated that it was currently taking steps to re-brief its sales team on the requirements of the Code with regard to meetings and hospitality, with particular emphasis on accurate and diligent record keeping.

PANEL RULING

The Panel noted that the parties' accounts differed; it was extremely difficult in such cases to know exactly what had transpired. In that regard it was unfortunate that the meeting at issue had taken place almost a year ago, that the complainant had not attended the meeting, that one of the representatives no longer worked for Sanofi-Aventis and that the representatives' meeting logs where not wholly consistent. A judgement had to be made on the available evidence and the balance of probability bearing in mind that extreme dissatisfaction was usually required on the part of an individual before he or she was moved to complain.

The Panel noted that the first representative's meeting log recorded a small audio-visual meeting which started at 7.30pm and would last an hour and a half; the meeting venue was to be confirmed. The second representative's meeting log recorded a round table meeting which started at 6pm at the chemotherapy unit followed by the restaurant. The meeting was to last four hours. Five of the delegates were hospital nurses, one was a hospital doctor and one GP also attended. Sanofi-Aventis had submitted that the first representative had presented on early breast cancer for approximately one hour. The second representative had then presented on prostate cancer. No formal agenda for the meeting was produced.

Sanofi-Aventis had submitted that, following the meeting at the hospital, the representatives had taken the attendees to a restaurant because no on-site catering facilities were available at the time of the meeting. This was disputed by the complainant. The Panel was concerned to note that in choosing the restaurant the representatives had consulted the delegates and their preferences appeared to have been considered. The representatives had reported that the restaurant was part of the

mainland franchise of the same name which was not so. The restaurant was two miles from the meeting venue. Sanofi-Aventis had submitted that non-product related discussions continued at the restaurant. The complainant had been assured that the evening was entirely social in purpose and that most of the educational event had occurred earlier in the day.

The Panel noted all the discrepancies, particularly those of the representatives' meeting logs. The timing and venue for the meeting were not clear. It would be a breach of the Code for a company to delay the provision of hospitality eg to hold a meeting at lunchtime and provide dinner in the evening. It would also be a breach of the Code to hold the meeting in a restaurant unless a private room was used or the restaurant closed to the public. Hospitality had to be secondary to the main purpose of a meeting. The level must be reasonable and not out of proportion to the occasion.

The Panel noted that a three course meal, with wine had been provided. The cost per head was £36.20 of which £9.83 per head was wine (excluding tip). The Panel was concerned to note that one liqueur had also been paid for. The Panel considered that the hospitality provided was not limited to subsistence only and was out of proportion to the occasion. The Panel also considered that for some of the attendees the hospitality provided might have exceeded the level which they would normally adopt when paying for themselves. A breach of Clause 19.1 was ruled. The representatives had not maintained a high standard of ethical conduct. A breach of Clause 15.2 was ruled. On balance the Panel did not consider that the matter warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such.

Complaint received **1 June 2009**

Case completed **22 July 2009**

CASE AUTH/2238/6/09

PROCTER & GAMBLE v SHIRE

Promotion of Mezavant XL

Procter & Gamble Pharmaceuticals alleged that maintenance of remission claims for Mezavant XL (mesalazine prolonged release) by Shire Pharmaceuticals Limited were misleading. In two leavepieces Shire presented data for patients who were maintained in remission whilst taking Mezavant XL.

Procter & Gamble alleged that the leavepieces did not explain that 68% of patients who maintained 'complete remission' represented 68% of the approximately 40% or less of patients who achieved remission in the original trials (Kamm *et al* 2007 and Lichtenstein *et al*) and which included the placebo and comparator groups also in remission.

Procter & Gamble noted that page 1 of one of the leavepieces stated that 'Mezavant XL once-daily maintained clinical and endoscopic remission over 12 months' followed by 'Efficacy to induce complete remission'. Procter & Gamble alleged that these were separate endpoints in separate trials. Page 2 stated, 'Patients maintained the stringent endpoints of complete remission' and was followed by the claim, '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12'. There was no indication of how many patients achieved remission and the reader could be mistaken for thinking that the 68% referred to patients who achieved and maintained remission.

Similarly in the second leavepiece, Procter & Gamble acknowledged that Shire had presented the percentage of patients reported by Kamm *et al* (2007) who achieved remission. However, whilst a footnote explained that the figures were from those patients who achieved remission in parent trials, it did not clearly connect the reader to the number of patients who achieved remission to put the figures into context.

The detailed response from Shire is given below.

The Panel noted that each leavepiece included on its front page 'Efficacy to induce complete remission' together with the tag line 'Discover complete remission'. Each included the claim '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12' followed by an asterisk which directed readers to the footnote 'Results in patients who achieved clinical and endoscopic remission in parent trials. These patients then entered into a 12 month maintenance study'. The claim was referenced to Kamm *et al* (2008).

In the parent studies (Lichtenstein *et al* and Kamm *et al* 2007) patients were treated for acute disease for up to 8 weeks. In the per-protocol group 100% of patients met the strict remission criteria at month 0 and these were maintained at month 12 in 67.8% of patients in the once daily group. At 12 months 88.7% of patients in the per-protocol population had not relapsed.

One of the leavepieces included the data from one of the parent studies (Kamm *et al* 2007) showing that 40.5% of patients taking 2.4g/day once daily, n=84, achieved complete remission defined by clinical and endoscopic endpoints at week 8. In the other parent study, Lichtenstein *et al*, 34.1% of patients taking 2.4g/day twice daily, n=88, achieved clinical and endoscopic remission after eight weeks of treatment.

The Panel considered that the leavepieces were not sufficiently clear about the basis of the data from Kamm *et al* (2008) ie that the per-protocol patients in the maintenance study were the minority of patients from the acute studies who had achieved complete remission. The Panel considered that the way the data was presented, together with other claims about the induction or achievement of remission, would lead many readers to assume that Mezavant XL induced and maintained remission in 68% of patients which was not so.

The Panel did not consider that the claim at issue '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12' in the context of the leavepieces was sufficiently clear that Kamm *et al* (2008) measured maintenance of remission and not induction of remission. Although a footnote gave some information as to the basis of the study, the supplementary information to the Code stated that claims must be capable of standing alone and that they should not, in general, be qualified by the use of footnotes and the like. The Panel considered that each leavepiece was misleading as to the basis of the Kamm *et al* (2008) data as alleged. Thus the Panel ruled each in breach of the Code.

Procter & Gamble Pharmaceuticals UK Limited complained about the promotion of Mezavant XL (mesalazine prolonged release) by Shire Pharmaceuticals Limited. Inter-company dialogue had been unsuccessful.

Mezavant XL was indicated for the induction of clinical and endoscopic remission in patients with mild to moderate active ulcerative colitis. It was also indicated for maintenance of remission.

COMPLAINT

Procter & Gamble noted that patients who were treated with Mezavant XL for 8 weeks to induce remission (Kamm *et al* 2007 and Lichtenstein *et al*) were entered into a third trial (Kamm *et al* 2008) to determine the number of patients who were maintained in remission over 12 months. Patients who completed the 8 week trials reported by Kamm *et al* (2007) and Lichtenstein *et al* but who were not in remission, could enter an 8 week extension and if they were then in remission, could be recruited into the maintenance study. This was further complicated by the additional enrolment of patients who did not quite meet the strict clinical and endoscopic remission endpoints but who were considered by their doctor to be well enough to be recruited. In leavepieces UK/MEZ/08/0195 and UK/MEZ/08/0203 Shire presented data for patients who were maintained in remission whilst taking Mezavant XL. The figures presented were 68% and 88%. Procter & Gamble alleged that the difference between these figures was due to stricter criteria to define remission in the group that achieved 68% versus 88%.

Procter & Gamble alleged that the leavepieces did not explain that 68% of patients who maintained 'complete remission' represented 68% of the proportion who achieved remission in the original trials (Kamm *et al* 2007 and Lichtenstein *et al*) and extension, ie 68% of the approximately 40% or less of patients who achieved remission and which included the placebo and comparator groups also in remission.

Procter & Gamble noted that page 1 of the leavepiece UK/MEZ/08/0195, stated that 'Mezavant XL once-daily maintained clinical and endoscopic remission over 12 months' followed by 'Efficacy to induce complete remission'. Procter & Gamble alleged that these were separate endpoints in separate trials. Page 2, whilst providing Shire's definition of 'complete remission' stated, 'Patients maintained the stringent endpoints of complete remission' and was followed by the claim, '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12'. There was no indication of how many patients achieved remission and the reader could be mistaken for thinking that the 68% referred to patients who achieved and maintained remission.

Similarly in leavepiece UK/MEZ/08/0203, Procter & Gamble acknowledged that Shire had presented the percentage of patients who achieved remission, albeit only those data reported by Kamm *et al* (2007) on page 4. However, whilst a footnote on page 5 explained that the 68% and 88% figures were from those patients who achieved remission in parent trials, it did not clearly connect the reader to the number of patients who achieved remission to put the 68% and 88% figures into context.

Procter & Gamble alleged that the presentation of these data in this way was misleading and in breach of Clause 7.2.

RESPONSE

Shire submitted that the exact nature of the complaint was not clear. It appeared that Procter & Gamble had suggested that Shire had misled prescribers by accurately describing the results of a maintenance of remission study. Shire denied that the presentation of information about the maintenance of remission study was misleading. The allegation appeared to arise out of Procter & Gamble's misunderstanding as to the nature of the clinical trial data used to support claims of maintenance of remission and the way studies in support of this indication were designed, executed and reported. The claims in question were based on a maintenance of remission study (Kamm *et al* 2008).

Shire submitted that in common with any maintenance of remission study, patients were required to comply with the entry criteria specified in the protocol. Since patients enrolled complied with the protocol definition of remission, it followed that those patients assessed at a later timepoint still in protocol-defined remission had experienced maintenance of remission. The only legitimate way to express such results was by a simple statistical comparison of the proportion in remission at the end of the study (68%) compared with those in remission at the start (100%). The same rationale applied to patients who were in remission at the start of the study and were found to be relapse-free at the end of the study (at 12 months, 88% were relapse-free, a less stringent clinical definition than clinical and endoscopic remission, as set out prospectively in the study protocol).

In each instance cited by Procter & Gamble, Shire noted that the data was presented on patients after 12 months' treatment in Kamm *et al* (2008) and the difference between the criteria for 68% patients maintained in remission and the criteria for the 88% who remained relapse-free was explained by the respective definitions of these measurements on both leavepieces. Furthermore the prominent labelling of the two different concepts drew the reader's attention to the fact that these were different concepts. As a result, Shire did not accept that the presentation of the maintenance of remission and relapse-free data in the leavepieces was confusing or misleading and that the differences in criteria were not adequately explained.

Shire submitted that because the maintenance study was a self-contained clinical trial with its own protocol and analysis plan, it was inappropriate of Procter & Gamble to suggest that the results of this study should be qualified in any way by the results of any other study which might or might not have fed patients into this specific maintenance study.

Concerning the other points raised, Shire agreed with Procter & Gamble's interpretation of the clinical study designs and was reassured that the company had understood these study designs correctly.

Shire had also considered the points raised by Procter & Gamble concerning patients' response to Mezavant XL in the acute studies (in which remission of active disease was induced) and their relevance to the long-term, 12 month study (in which remission of ulcerative colitis was maintained).

Shire submitted that clearly these two issues were completely unrelated. For the maintenance study, of all the patients who met the endoscopic and clinical criteria for remission at the start of this 12 month period (ie 100%, the per-protocol population), 68% of this group were still in remission after 12 months. (The study publication stated: 'In the "per-protocol" population in which, by definition, 100% of patients in both groups met the strict remission criteria at month 0, endoscopic and clinical remission were maintained at month 12 in 67.8% of the once-daily group…', Kamm *et al* 2008). The opposite was true of the acute studies at baseline. Although the maintenance study accepted patients from the acute studies, it was an entirely separate clinical study as Procter & Gamble acknowledged. The acute studies were different protocols, different patient populations with different aims and outcomes. The maintenance study only enrolled patients who met the strictly-defined clinical and endoscopic criteria for remission and were thus eligible for inclusion. Hence the acute studies from which the patients originated had no relevance to the complaint about the validity of the results for the maintenance study itself.

Having reviewed page 1 of the leavepiece (ref UK/MEZ/08/0195), Shire agreed that the claim 'Efficacy to induce complete remission' should not appear below 'Mezavant XL once-daily maintained clinical and endoscopic remission over 12 months'. Shire agreed with Procter & Gamble's assertion that these were separate endpoints in separate studies and as the leavepiece was communicating the maintenance of remission data, the claim 'Efficacy to induce complete remission' could be potentially confusing. Shire, however, noted that this complaint had not been specifically raised in inter-company correspondence.

In summary in relation to Procter & Gamble's remaining points, Shire submitted that it did not consider that the results from acute studies were relevant to the consideration of allegations about the presentation of the results from the maintenance of remission study. As Procter & Gamble clearly understood the separate nature of the various study designs, it was odd that it had suggested that these studies should be considered as forming some sort of continuum with the maintenance study. Shire thus denied a breach of Clause 7.2, save that the claim 'Efficacy to induce complete remission' should not have appeared below the maintenance data.

Shire wanted to correct the impression that all the points Procter & Gamble had complained of had been raised and discussed in detail in inter-company dialogue. As was evident from Procter & Gamble's correspondence of 6 and 29 April, as well as the final correspondence of 26 May, the company's complaints had been numerous and evolved over time. The predominant issue was not raised by Procter & Gamble until 29 April and then only as a subset of its main complaint that 'Presentation of the data to support the maintenance claims for Mezavant XL, 68% of patients remaining in 'complete remission' and 88% of patients being relapse free was misleading and in breach of Clause 7.2 of the Code'. Furthermore the complaint was not raised in the level of detail it had been presented to the Authority.

As was highlighted above, Procter & Gamble's complaint about the claim 'Efficacy to induce complete remission' had never been specifically raised in inter-company correspondence.

Shire confirmed that the claim 'Efficacy to induce complete remission' would be removed from the Mezavant XL leavepiece UK/MEZ/08/0195.

PANEL RULING

The Panel noted that Shire had agreed to cease use of a number of claims referring to complete remission in its promotional material including the leavepieces now at issue (UK/MEZ/08/0195 and UK/MEZ/08/0203).

The Panel noted that each leavepiece included on its front page 'Efficacy to induce complete remission' together with the tag line 'Discover complete remission'. Each included the claim '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12' followed by an asterisk which directed readers to the footnote 'Results in patients who achieved clinical and endoscopic remission in parent trials. These patients then entered into a 12 month maintenance study'. The claim was referenced to Kamm *et al* (2008).

In the parent studies (Lichtenstein *et al* and Kamm *et al* 2007) patients were treated for acute disease for up to 8 weeks. Both parties agreed that as well as including patients maintained in remission at the end of 8 weeks, patients not in remission at this point could be entered into an 8 week extension study and then if in remission could be entered into Kamm *et al* (2008). The position was further complicated in that although not defined by the protocol, patients who were not in strictly defined remission but deemed by their doctor to be well enough at the end of the parent studies or the 8 week extension phase could enter the randomised maintenance study. However the per-protocol population included only those patients who met the strict protocol defined criteria for remission. In the per-protocol group 100% of patients met the strict remission criteria at month 0 and these were maintained at month 12 in 67.8% of patients in the

once daily group. At 12 months 88.7% of patients in the per-protocol population had not relapsed.

One of the leavepieces (ref UK/MEZ/08/0203) included the data from one of the parent studies (Kamm *et al* 2007) showing that 40.5% of patients taking 2.4g/day once daily, n=84, achieved complete remission defined by clinical and endoscopic endpoints at week 8. In the other parent study, Lichtenstein *et al*, 34.1% of patients taking 2.4g/day twice daily, n=88, achieved clinical and endoscopic remission after eight weeks of treatment.

The Panel considered that the leavepieces were not sufficiently clear about the basis of the data from Kamm *et al* (2008) ie that the per-protocol patients in the maintenance study were the minority of patients from the acute studies who had achieved complete remission. The Panel considered that the way the data was presented, together with other claims about the induction or achievement of remission, would lead many readers to assume that Mezavant XL induced and maintained remission in 68% of patients which was not so.

The Panel did not consider that the claim at issue '68% of patients taking Mezavant XL 2.4g/day once daily (n=171) remained in complete remission at month 12' in the context of the leavepieces was sufficiently clear that Kamm *et al* (2008) measured maintenance of remission and not induction of remission. Although a footnote gave some information as to the basis of the study the supplementary information to Clause 7.2 stated that claims must be capable of standing alone and that they should not, in general, be qualified by the use of footnotes and the like. The Panel considered that each leavepiece was misleading as to the basis of the Kamm *et al* (2008) data as alleged. Thus the Panel ruled each in breach of Clause 7.2 of the Code.

Complaint received **8 June 2009**

Case completed **10 July 2009**

CASE AUTH/2239/6/09

CONSULTANT RADIOLOGIST v BRACCO

Letter to radiology health professionals

A hospital consultant complained about an unsolicited letter dated 21 April 2009 received from Bracco.

The complainant alleged that the letter was sent to radiology centres across the UK, to inform clinicians of the outcomes of a legal case in the US. The findings of the case, as described in the letter, were very negative for GE Healthcare and as the complainant was familiar with that company he had contacted it to see if it agreed with Bracco's description. GE Healthcare wrote to the complainant with a more detailed description of the outcome of the legal case; a copy of the letter was provided.

The complainant was concerned that Bracco's letter clearly only covered those aspects that were positive for Bracco and negative for GE Healthcare, when in fact the judge also criticised Bracco's activities. Bracco's letter implied that GE Healthcare was misleading clinicians everywhere, where in fact the activities in question only took place in the US and occurred a number of years ago. In contrast, the aspects of the case that were negative for Bracco concerned studies that it continued to use to promote its products in the UK.

The detailed response from Bracco is given below.

The Panel considered that the letter in question promoted Bracco products; although it did not mention any products by name it did refer to Bracco's low osmolar contrast media. Bracco's letter wrongly implied that the published outcome of the trial stated that GE Healthcare employed very aggressive marketing techniques. The Bracco letter stated that GE Healthcare had been ordered to pay Bracco $11.4 million (although the actual amount GE Healthcare was ordered to pay was $11,376,500) but did not make it clear that this was in relation to Bracco's corrective advertising costs incurred as a result of GE Healthcare's wrongful conduct and that no other damages were awarded.

The letter did not mention that because Bracco had discontinued advertisements GE Healthcare had alleged to be false in its counterclaim, GE Healthcare was not entitled to injunctive relief. Nor did it give any indication of the relevance of the US action to the UK. The letter did not state where or when GE Healthcare has disseminated the misleading claims.

The Panel considered that by not giving accurate or sufficient information about the detail of the legal case, its outcome and the counterclaim the letter was misleading and unfair. A breach of the Code was ruled. The misleading account disparaged GE Healthcare and a breach was ruled. High standards had not been maintained in breach of the Code.

The Panel was concerned that misleading information had been supplied by Bracco in a letter which specifically referred to Bracco's commitment to providing scientific information in a thorough, fair and balanced manner. The Panel considered that the letter would give recipients a poor view of the industry but on balance did not consider the circumstances warranted a ruling of a breach of Clause 2.

A consultant in radiology complained about an unsolicited letter dated 21 April 2009 received from Bracco UK Ltd.

The complainant had advised the Authority that he was not an employee or ex-employee of either Bracco or GE Healthcare. The complainant had received honoraria from GE Healthcare for speaking at a sponsored symposium. The complainant had also received honoraria from another pharmaceutical company for similar activity. Bracco had been informed.

COMPLAINT

The complainant alleged that the letter was sent to radiology centres across the UK, clearly with the intention of informing clinicians of the outcomes of a legal case in the US. The findings of the case, as described in the letter, were very negative for GE Healthcare and as the complainant was familiar with that company he had contacted it to see if it agreed with Bracco's description of the outcome. GE Healthcare then wrote to the complainant with a more detailed description of the outcome of the legal case; a copy of the letter was provided.

The complainant had a number of concerns. Bracco's letter clearly only covered those aspects of the outcome that were positive for Bracco and negative for GE Healthcare, when in fact there were a number of criticisms made by the judge of Bracco's activities. Bracco's letter implied that GE Healthcare was guilty of misleading clinicians everywhere, where in fact the activities in question only took place in the US and occurred a number of years ago. In contrast, the aspects of the case that were negative for Bracco concerned studies that it continued to use to promote its products in the UK.

When writing to Bracco the Authority asked it to respond in relation to Clauses 2, 7.2, 8.1 and 9.1 of the Code.

RESPONSE

Bracco submitted that the letter at issue was sent to 3,221 UK health professionals in radiology. As a responsible pharmaceutical manufacturer, Bracco was committed to ensuring that its communications complied with the Code at all times. The letter, approved in accordance with Bracco's internal clearance procedures, complied with the requirements of the Code.

Bracco noted that there had been a number of disputes between it and GE Healthcare recently, both in the US and other markets, including the UK.

As background to the case in the US Bracco explained that it had brought a number of claims against GE Healthcare, including for dissemination of false and misleading advertising, violation of unfair competition law and negligent misrepresentation; GE Healthcare counterclaimed for false advertising against Bracco. The outcome of the trial was set out in an Order of the United States District Court, District of New Jersey (the Order). This document (copy provided) confirmed that GE Healthcare had disseminated false messages in its advertising for Visipaque and, as a result, several orders were made against it, including that the company must:

- not make certain claims relating to Visipaque and limit the content of future advertising based on the studies in question
- issue a press release regarding the Court's decision and issue corrective advertisement
- pay over $11 million to Bracco for the corrective advertising costs it incurred as a result of GE Healthcare's wrongful conduct.

Bracco submitted that no orders were made against it in relation to its advertising and no damages or other relief were awarded to GE Healthcare.

Bracco submitted that the letter was a factual, accurate and informative summary of the outcome of the US case between Bracco and GE Healthcare. The Order referred to above was the outcome of this trial, following the lengthy arguments put forward by Bracco and GE Healthcare. The letter provided a fair and balanced view of the Order, which contained numerous orders against GE Healthcare and no orders against Bracco. The letter also provided a very brief and accurate synopsis of the case brought by Bracco against GE Healthcare.

Bracco submitted that the letter kept health professionals up-to-date as to the outcome of this case (and not to reiterate the lengthy arguments from each party). The letter did not disparage or criticise GE Healthcare or its products but summarised the factual outcome of the case, which was publicly available. Critical references to another company's products were permitted under the Code, provided that they complied with Clause 8.

Bracco submitted that the letter clearly stated that the ruling was from a Federal Court in the US. It was evident to the reader that the case related to activities in the US. The outcome of the trial was, however, of relevance and interest to UK health professionals as the materials and claims in question in the US had also been distributed globally by GE Healthcare, including the UK market.

Bracco submitted that it was also common knowledge that court cases took time to reach trial, hence recipients would not interpret the letter as referring to activities taking place presently but rather to activities that occurred in the past.

Bracco submitted that the letter complied with the Code and that it had maintained its usual high standards when circulating this information.

Bracco's decision to inform health professionals of the US ruling on GE Healthcare's claims did not discredit or reduce confidence in the pharmaceutical industry. Instead, by communicating the summary of the US court decision, Bracco had confirmed that advertising material produced by pharmaceutical companies was heavily regulated and that such regulation was an effective way of maintaining standards across the industry.

With specific reference to Clause 2 of the Code, the criticisms of the letter raised by the complainant were not of a similar nature to the examples listed in the supplementary information accompanying this clause in the Code. Given this, and the information provided above, Bracco submitted that its letter was not in breach of Clause 2 of the Code.

Notwithstanding that Bracco believed that the letter fully complied with the Code, the company did not intend to recirculate it or write further to the recipients, particularly given that GE Healthcare had also written to UK health professionals about the outcome of the trial (a copy of which was received by the complainant). On this basis, health professionals had already been provided with sufficient information from both companies to be able to form their own view of the outcome of the trial. Bracco submitted that it had been in direct discussions with GE Healthcare regarding both companies' UK communications on the US trial, and it had resolved the issue to both parties' satisfaction, with no further action being required by either company.

PANEL RULING

The Panel considered that the letter in question was promotional material for Bracco products. The letter did not mention any Bracco products by name but did refer to Bracco's low osmolar contrast media.

Bracco's letter implied that the Order stated that GE Healthcare employed very aggressive marketing techniques; the Order made no such statement. The Bracco letter stated that GE Healthcare had been ordered to pay Bracco $11.4 million but did not make it clear that this was in relation to Bracco's corrective advertising costs incurred as a result of GE Healthcare's wrongful conduct and that no other damages were awarded. The amount that GE Healthcare was ordered to pay was $11,376,500, ie less than that quoted in the letter.

The letter did not mention that the Order stated that because Bracco had discontinued advertisements GE Healthcare had alleged to be false in its counterclaim, GE Healthcare was not entitled to injunctive relief. Nor did it give any indication of the relevance of the US action to the UK. The letter did not state where or when GE Healthcare had disseminated the misleading claims.

The Panel considered that by not giving accurate or sufficient information about the detail of the legal case, Order and the counterclaim the letter was misleading and unfair. A breach of Clause 7.2 was ruled. The Panel considered that the misleading account disparaged GE Healthcare and a breach of Clause 8.1 was ruled. The Panel considered that high standards had not been maintained and thus ruled a breach of Clause 9.1.

The Panel was concerned that misleading information had been supplied by Bracco in a letter which specifically referred to Bracco's commitment to providing scientific information in a thorough, fair and balanced manner. The Panel considered that the letter would give recipients a poor view of the industry but on balance did not consider the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

Complaint received **10 June 2009**

Case completed **14 July 2009**

REGULATORY AFFAIRS CONSULTANT v ROCHE

Articles about MabThera in the lay press

A regulatory affairs consultant and scientist/writer, complained about articles discussing the early use of MabThera (rituximab) in rheumatoid arthritis (RA) which were published in the Daily Telegraph and The Times and mentioned on television. MabThera was marketed by Roche Products.

Mabthera was indicated *inter alia*, in combination with methotrexate (MTX) for RA patients with severe active disease who had had an inadequate response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs).

The complainant alleged that the reproduced Roche press release describing the wonders of off-label use of rituximab was advertising. It was unbalanced and pushed dangerous medicines to the public. There was no mention of the extremely dangerous side effects. Was this allowed? It made a joke of the medicine approval procedure.

In subsequent correspondence the complainant noted that although MabThera was indicated for rheumatoid arthritis in some cases it was indicated to be used as the articles described. The complainant alleged that the newspaper and television articles were a marketing campaign disguised as news. The article in The Times was almost a copy of a press release reporting details of a clinical trial. It made claims for the medicine, including a 30% efficacy rate, which appeared rather low. However, the article did not mention any of the serious side effects or even refer to the prescribing information.

The complainant alleged that the material was designed to get patients to campaign for doctors to give them MabThera while not making clear that it had life threatening side effects; the list of severe adverse reactions should be included to give them a balanced view.

The complainant alleged that there was clearly a conflict of interest and the lead investigator who was mentioned in the press was obviously employed by Roche.

The complainant found the blatant use of the press for medicine marketing to be cynical.

The detailed response from Roche is given below.

The Panel noted that although the complainant had complained about articles in the UK press, she had provided a copy of the global press release. The global press release had not been issued in the UK. The UK press release detailed trial results as presented at a major European conference. It was stated that 30.5% of the RA patients taking rituximab and MTX achieved remission vs 12.5% of those taking MTX alone. The Panel considered that the UK press release was written in a factual, balanced and non promotional manner; it clearly stated that rituximab was not licensed for early RA. A short paragraph also referred to side effects such as hypertension, nausea and upper respiratory tract infections. It was stated that as with all RA therapies, a small proportion of more serious side-effects were seen.

The Panel did not consider that the press release raised unfounded hopes of successful treatment or was misleading with respect to the safety of the product.

The Panel considered that any good news story about a medicine would have an inevitable positive impact but nonetheless it did not consider that statements had been made for encouraging patients to ask their health professional to prescribe rituximab. The press release was not an advertisement *per se* for rituximab and nor was it disguised promotion. The Panel noted that rituximab was not indicated for use in early RA however it did not consider that the press release promoted an unlicensed indication. In the Panel's view Roche had not failed to maintain high standards. No breaches of the Code were ruled including no breach of Clause 2.

A regulatory affairs consultant and scientist/writer, complained about articles discussing MabThera (rituximab) that appeared in the Daily Telegraph ('Drug hope for arthritis victims') and The Times ('Drug can curb joint damage at the very start of arthritis') and mentioned on television on 16 June 2009. MabThera was marketed by Roche Products Limited.

MabThera was indicated, *inter alia*, in combination with methotrexate (MTX) for rheumatoid arthritis (RA) patients with severe active disease who had had an inadequate response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs).

COMPLAINT

The complainant alleged that the advertisement (well, reproduced Roche press release) describing the wonders of off-label use of rituximab, which was represented as an article, was in fact advertising. The article was unbalanced and pushed dangerous medicines to the public. There was no mention of the extremely dangerous side effects. Was this allowed? It made a joke of the medicine approval procedure.

In a subsequent response the complainant noted that she had made a mistake. MabThera was indicated for RA in some cases. However, she was not sure that it was indicated to be used as the articles described. The complainant alleged that the articles printed in The Times, The Telegraph and mentioned on television on 16 June 2009 were a marketing campaign disguised as news. The article in The Times was almost a copy of a press release reporting details of a clinical trial. It made claims for the medicine, including a 30% efficacy rate, which appeared rather low. However, the article did not mention any of the serious side effects or even refer to the prescribing information.

The complainant alleged that this article was designed to get patients to campaign for doctors to give them the medicine while not making clear that the medicine had life threatening side effects.

This made the complainant very angry to constantly see newspapers publishing obvious marketing related material.

In a subsequent response the complainant enclosed a copy of the Roche press release. The complainant alleged that there was clearly a conflict of interest and the lead investigator who was mentioned in the press was obviously employed by Roche.

However, the complainant was not sure that Roche was the problem, but it was the newspapers which printed the stuff. The newspapers were simply reproducing press releases, meant to support the share price of the pharmaceutical company, and, of course, to ensure the public made a big noise to be prescribed the medicines. The complainant found the blatant use of the press for medicine marketing to be cynical.

The actual article was unbalanced, there was no mention that the proposed treatment caused many adverse events.

The complainant alleged that the newspapers, not the pharmaceutical company, were at fault here. They had not checked out the story, but simply reproduced a press release and should be held to account for the inaccuracy of the story.

The complainant was not based in the UK and had only seen the Internet version of these articles, but assumed that the content was the same.

The complainant provided a list of severe adverse reactions, many were obviously life threatening, taken from the MabThera summary of product characteristics (SPC).

> Serious adverse reactions observed in post-marketing surveillance: *Serious viral infection. Late neutropenia, pancytopenia, aplastic anaemia. Severe events in patients with prior cardiac condition or cardiotoxic chemotherapy, heart failure, myocardial infarction. Hearing loss. Severe vision loss. Multi-organ failure. Infusion related reactions, anaphylaxis, tumour lysis syndrome, cytokine release syndrome, serum sickness. Very rare cases of Hepatitis B reactivation, including fulminant hepatitis with fatal outcome. Progression of pre-existing Kaposi's sarcoma, mainly in patients with HIV. Cranial neuropathy, peripheral neuropathy, facial nerve palsy, loss of other senses. Renal failure. Bronchospasm, respiratory failure, pulmonary infiltrates, interstitial pneumonitis. Gastro-intestinal perforation. Severe bullous skin reactions, toxic epidermal necrolysis. Vasculitis (various types)*.

The complainant alleged that if the article was aimed at the public who were unfortunate enough to suffer with arthritis, then the list of severe adverse reactions should be included to give them a balanced view.

When writing to Roche the Authority asked it to respond in relation to Clauses 2, 3.2, 9.1, 12.1, 22.1 and 22.2 of the Code.

RESPONSE

Roche noted that the articles at issue were published in The Times and The Daily Telegraph on 16 June 2009 following the presentation of data from the rituximab IMAGE trial at the European League against Rheumatism (EULAR) meeting in Denmark on 11 June 2009. Roche UK had issued a press release around the presentation of these data to the medical and consumer press on 15 June. Roche UK issued this press release to the UK media including The Times and Daily Telegraph and not the global press release as sourced by the complainant who stated that she was not based in the UK. The global press release was not issued in the UK.

Roche noted that the IMAGE trial was the first radiographic trial using rituximab in combination with MTX in RA patients who had previously been naïve to traditional DMARDs. Up until now rituximab had only shown a disease modifying effect via radiographic measurements in patients who had failed to respond to anti-TNF therapies.

Roche noted that IMAGE was a Phase III, randomized, controlled, double-blind trial involving 755 patients to evaluate the safety and efficacy of rituximab in combination with MTX compared with MTX alone, in MTX-naïve patients with active RA. Patients in the rituximab arms were either treated with 2 x 1000mg or 2 x 500mg. At week 24 patients with disease activity score (DAS) >2.6 received a second course of rituximab. Those with DAS <2.6 were re-treated if and when their DAS exceeded 2.6. The primary endpoint was the change from screening in the modified radiographic total sharp score (mTSS) at week 52.

In patients treated with 2 x 1000mg rituximab and MTX, the baseline to one year data showed a significantly smaller change (0.359) in mean mTSS compared with patients on MTX alone (1.079; p=<0.001) – a lower progression of joint damage. By week 52, 65% of these patients achieved a 50% improvement in symptoms (ACR50), while 47% had achieved a 70% improvement (ACR70), compared with 42% and 25% on MTX alone.

Roche submitted that it was of particular clinical interest that in the second half of the study (between 6 and 12 months) there was near complete inhibition of further joint damage in patients treated with rituximab plus MTX (0.03 mean mTSS vs 0.38 mean change for MTX alone; p=0.0013). This finding was extremely valuable in terms of significantly inhibiting the progression of the destructive nature of rheumatoid arthritis and thus limiting the impact of the disease on a patient's ability to undertake normal physical activity. By limiting early damage by pharmacological intervention it was known that the long term outcome for patients could be significantly improved.

Given that this was the first time that an anti CD20 medicine had demonstrated such effects in this early RA patient population it was deemed to be newsworthy both medically and financially and thus Roche legimately issued a press release to both the consumer and medical press. This was evidenced by the statement made by the President Elect of EULAR a globally respected academic rheumatologist who independently stated to The Daily Telegraph that 'This is important news'. Roche had submitted a licence application for the use of rituximab in this patient population.

Roche considered that the press release had been written and issued in line with the principles outlined in Clause 22 of the Code. The release was non promotional, factually correct regarding the outcome of the study, placed both the efficacy and safety of the medicine in a balanced way, included a paragraph on the adverse event profile and did not use language that could be considered to encourage members of the public to ask their health professional to prescribe rituximab.

With regard to Clause 12.1, the press release was written, reviewed and certified as a non promotional piece of material in line with established internal Roche UK standard operating procedures. Roche strongly refuted any suggestion that it either directly, or via a third party, used this press release as a method of disguised promotion. Roche noted that Clause 3.2 stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization. Roche submitted that the press release reported the outcome of a pivotal clinical development trial and thus its content was outside the current marketing authorization, however as stated previously, it was non promotional and was financially and medically newsworthy. Similarly it was clearly stated in the main body of the release that rituximab was not currently licensed for use in early RA. Overall Roche considered it was produced in line with Clause 22 and Roche strongly refuted that the press release was in breach of Clause 3.2.

Roche submitted that given the information outlined above it did not consider that the production and release of this material to be in breach of either Clauses 9.1 or 2.

Roche was concerned that the complainant was dissatisfied about newspapers publishing stories about medicine development and considered these to be marketing related material. However Roche was very careful to ensure only financially and medically newsworthy information was put into the public domain. Roche did not accept that the press release pushed medicines to the public, nor did it accept that it made no mention of the side effects, it was a balanced piece of information that was of press interest and produced in line with the principles set out in the Code.

PANEL RULING

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. Clause 22.1 prohibited the advertising of prescription only medicines to the general public. Clause 22.2 permitted information to be supplied directly or indirectly to the general public but such information had to be factual and provided in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific medicine.

The Panel noted that although the complainant had complained about articles in the UK press, she had provided a copy of the global press release. The global press release had not been issued in the UK. The UK press release detailed results from the IMAGE trial as presented at the EULAR conference. It was stated that 30.5% of the RA patients taking rituximab and MTX achieved remission vs 12.5% of those taking MTX alone. The Panel considered that the UK press release was written in a factual, balanced and non promotional manner. The press release clearly stated that rituximab was not licensed for early RA. A short paragraph also referred to side effects such as hypertension, nausea and upper respiratory tract infections. It was stated that as with all RA therapies, a small proportion of more serious side-effects were seen.

The Panel did not consider that the press release raised unfounded hopes of successful treatment or was misleading with respect to the safety of the product.

The Panel considered that any good news story about a medicine would have an inevitable positive impact but nonetheless it did not consider that statements had been made for encouraging patients to ask their health professional to prescribe rituximab. The Panel ruled no breach of Clause 22.2 of the Code. The press release was not an advertisement *per se* for rituximab and nor was it disguised promotion; no breach of Clauses 22.1 and 12.1 were ruled. The Panel noted that rituximab was not indicated for use in early RA however it did not consider that the press release promoted an unlicensed indication. No breach of Clause 3.2 was ruled. In the Panel's view Roche had not failed to maintain high standards and no breach of Clause 9.1 of the Code was ruled. Given the rulings above, there could be no breach of Clause 2 and the Panel ruled accordingly.

Complaint received **16 June 2009**

Case completed **22 July 2009**

ANONYMOUS v TAKEDA

Sponsorship of 'One Stop Shops' for Diabetes.

An anonymous non contactable complainant was concerned about Takeda UK's sponsorship of One Stop Shops whereby a third party would complete annual diabetes checks for diabetics at one appointment. The complainant presumed that a chiropodist, dietician and a retinal screener would be on hand but was concerned that there was no way to check their professional credentials.

Other concerns were that as the service had its own diabetologist, was it agreed with local consultants and did it take into account local prescribing protocols? Who managed any titration of medicines? Was follow-up care arranged? Were all diabetics seen for this annual evaluation or only patients on oral medicines? If so was it an exclusive service?

The service provider was run by an ex-employee of Takeda – was this therefore a truly independent service? Would Takeda feel any loyalty to this person? Or the third party to Takeda? Was return on pharmaceutical company investment more important than patient outcomes?

Whilst the complainant understood the value of the concept and realised that the GPs would be assisted in ticking Quality and Outcomes Framework (QOF) boxes, he was suspicious of a service that was sponsored by a pharmaceutical company, which understandably would expect a return on its considerable investment.

The detailed response from Takeda is given below.

The Panel noted that it appeared from the company's submission that it had little to do with the service other than funding the third party. It was not entirely clear how the service was promoted to health professionals and Takeda's role, if any, in that regard. The third party was solely responsible for promoting the One Stop Shop service to the NHS. It was unclear from the contract who told the NHS about the nurse review service. However the complainant had made no specific allegation about the promotion of the service.

The third party document 'Type 2 Diabetes, Annual Review and Patient Segmentation' clearly stated that it was provided as a service to medicine by Takeda UK; it appeared to be aimed at GPs and made no mention of PCT approval. The document stated that the third party was providing assistance to GPs to help ensure that patients with type 2 diabetes had the best possible care. The practice was in control of all processes thoughout and any change to a patient's medicine had to be authorized by the GP. The GP remained responsible for patient care including follow up. There appeared to be two offerings firstly, a nurse-led review, patient identification and profiling and secondly a diabetes One Stop Shop. The One Stop Shop included a podiatry check, retinal screening, education and dietary advice.

The contract set out the disease indicators which were assessed within the One Stop Shop. The third party had to ensure that all personnel were trained and accredited to the professional standard required by their role.

The nurse-led review was limited to patients with type 2 diabetes. It was not clear whether a similar limitation applied to the One Stop Shop.

The fact that the third party provider was run by a previous Takeda employee was not necessarily unacceptable and neither was the fact that Takeda had a commercial interest in the therapeutic area. The document 'Type 2 Diabetes Annual Review and Patient Segmentation' did not mention any medicines by name other than insulin. The Panel had no information as to how this document was used.

The Panel noted that some aspects of the service were not examined as they fell outside the scope of the complainant's narrow allegations. No evidence had been provided by the complainant who was anonymous and non contactable. The Panel considered that much would depend on the health professionals who controlled the process. The practice could decide what action to take. It was vital that those conducting the nurse-led review or One Stop Shop followed instructions and complied with their own professional codes. There was no evidence that they had not done so or to indicate that the arrangements in principle amounted to an inducement to prescribe a specific medicine or that they failed to satisfy the criteria for a therapeutic review programme. No breach of the Code was ruled including Clause 2.

An anonymous non contactable complainant was concerned about Takeda UK Ltd's sponsorship of One Stop Shops for diabetes and urged the Authority to investigate the service to ascertain whether it was in keeping with the Code.

COMPLAINT

The complainant stated that clinics, called 'One Stop Shops', were planned in an area of London in which he worked. Under the service, diabetics would complete their annual diabetes check all at

one appointment. In that regard the complainant presumed that there would be a chiropodist, dietician and a retinal screener in attendance. The complainant, however, was concerned that there was no access to details of professionals to check credentials.

Other concerns were that as the service had its own diabetologist, was it agreed with local consultants and did it take into account local prescribing protocols? This might upset local health professionals, if there was no consultation/ correspondence with them to agree to the service. Who managed any titration of medicines? Was follow-up arranged in the care of this group of patients? Were all patients with diabetes seen for this annual evaluation or only patients on oral medication? If so was it an exclusive service?

Whilst the complainant understood the value of the concept, he was concerned as to the funding arrangements. He understood that these were being carried out by a third party sponsored, at some considerable cost, by Takeda.

Another concern was that the third party was run/directed by a previous employee of Takeda – could this therefore be seen as a truly independent service? Would Takeda feel any loyalty to this person? Or the third party to Takeda? The complainant queried whether return on pharmaceutical company investment was perhaps more important than patient outcomes?

Whilst the complainant realised that the GPs would be assisted in ticking Quality and Outcomes Framework (QOF) boxes, he was suspicious of a service that was run by outside staff sponsored by a pharmaceutical company at undoubtedly great cost, which understandably would expect a return on its investment.

In writing to Takeda attention was drawn to the requirements of Clauses 2, 9.1, 15.2, 18.1 and 18.4 of the Code.

RESPONSE

Takeda provided copies of its contract with the third party and the protocol used for the One Stop Shop.

The targeting of a One Stop Shop was agreed directly between the NHS organisation and the third party which used specific criteria to target the One Stop Shop service, eg:

- Areas with high disease prevalence.
- Primary care trusts (PCTs)/practices which registered patient exclusion levels above average within their diabetes/cardiometabolic service.
- PCTs/practices which experienced significant pressure points in one of more parts of their diabetes service eg:
  - underperformance of their retinal screening service against number of patients seen vs target or unacceptable waiting times.
  - performance against annual review targets within the year.
- PCTs which planned to re-design their current diabetes/cardiometabolic service so as to manage a greater percentage of appropriate patients in a primary care setting as per government guidance.

The decision to contract with particular NHS providers for provision of One Stop Shops was entirely at the discretion the third party. The One Stop Shop was provided by the third party with the approval of the NHS provider, in its own name under a separate written contract with the NHS provider to which Takeda was not a party and had no involvement.

Takeda had financially supported a pilot project of the One Stop Shop, which started in December 2008. This project was supported centrally, with no regional account director (sales) involvement. Takeda's support was solely financial, as a service to medicine. All conduct, including responsibility for selection of regions (eg PCTs) to offer the One Stop Shop resided solely with the third party.

The third party told the NHS provider that the service was funded by Takeda as a 'service to medicine' and ensured that Takeda's involvement was made clear to all relevant health professionals and administrative staff involved in the provision of services.

Takeda believed that the One Stop Shop was an appropriate and valid service to medicine which improved patient care and benefited the NHS, and was not linked in any way to the use of a particular medicine. Takeda therefore denied a breach of Clauses 18.1 and 18.4.

The third party was an independent company; its managing director had worked for Takeda, however this had no bearing on the delivery of the service or the independence of it from Takeda, as reflected in the terms and conditions set out in the contract. As the third party was not in any way a representative of Takeda, it refuted the allegation of a breach of Clause 15.2.

As Takeda did not believe that the activities were in breach of Clauses 15.2, 18.1 or 18.4, it therefore refuted any allegation of a breach of Clause 9.1 or 2.

The third party provided the One Stop Shop service through its own clinical staff. Takeda did not choose the health professionals or other contractors performing the tests. In its contract with Takeda, IMC warranted that all staff were trained and accredited to the professional standard their role required and carried the necessary insurance to undertake the prescribed duties. The third party also ensured that all staff maintained their training to the

required standards as part of their ongoing clinical and professional development.

The service did not include a diabetologist and was not designed to replace secondary care. The One Stop Shop clinics were provided on the basis of a therapy review programme, with the aim of ensuring that patients received optimal treatment following a clinical assessment. The third party ensured that such reviews included a comprehensive range of treatment choices, including non-medical choices where appropriate, and were not limited to Takeda's products. Any treatment protocol would be based upon national or local guidance.

Any decisions to change or start treatment in an individual patient only occurred after review by the relevant third party health professional, and every decision to change an individual's treatment was documented with evidence that it was made on rational grounds. Furthermore any change to a patient's medicine would only be implemented after it had been agreed and signed by a GP from the patient's practice.

Follow-up care was conducted by the patient's own health professional.

The third party worked with NHS providers to offer the One Stop Shop service to any type 2 diabetics agreed with the practice as suitable for the service. There was no exclusion or limitation to patients solely on oral diabetes therapy.

There was no link between the support of this service and the use of any particular product. The service aimed to improve patient care and support the NHS delivery of services for type 2 diabetics. Within this service, patients were evaluated for a variety of diagnostic tests contained within the QOF eg podiatry, retinal screening, HbA1c control. As a result of this it might be appropriate to change a patient's medicine, including those prescribed for type 2 diabetes, however, any change would be agreed with the patient's own GP and be based upon national/local guidance.

Takeda hoped that its response allayed any concerns about the One Stop Shop and its support of the service, and demonstrated that neither this project nor the company's involvement with the third party service provider was in breach of the Code in particular Clauses 2, 9.1, 15.2, 18.1 and 18.4. The project was an initiative set up to benefit patients and the NHS with no link to the use of a particular medicine.

PANEL RULING

The Panel noted that pharmaceutical companies could provide medical and educational goods and services, including therapy review programmes. Such services need to comply with the Code, particularly Clause 18.4. It was not necessarily a breach of the Code for products from the company providing the service to be prescribed.

The Panel examined the two documents provided by Takeda; 'Type 2 Diabetes, Annual Review and Patient Segmentation' and the Takeda/third party contract. It appeared from the company's submission that it had little to do with the service other than providing money. It was not entirely clear how the service was promoted to health professionals and Takeda's role, if any, in that regard. The contract stated that the commercial function of the third party was solely responsible for promoting the One Stop Shop service to the NHS. It was unclear from the contract who told the NHS about the nurse review service. However the complainant had made no specific allegation about the promotion of the service.

The document 'Type 2 Diabetes, Annual Review and Patient Segmentation' clearly stated that it was provided as a service to medicine by Takeda UK; it appeared to be aimed at GPs and made no mention of PCT approval. The document stated that the third party was providing assistance to GPs to help ensure that patients with type 2 diabetes had the best possible care. The practice was in control of all processes throughout the service and any change to a patient's medicine had to be authorized by the GP. The GP remained responsible for patient care including follow up. There appeared to be two offerings firstly, a nurse-led review, patient identification and profiling and secondly a diabetes One Stop Shop. The One Stop Shop included a podiatry check, retinal screening, education and dietary advice.

The contract between Takeda and the third party set out the disease indicators which were assessed within the One Stop Shop. It required the third party to ensure that all personnel were trained and accredited to the professional standard required by their role.

The nurse-led review was limited to patients with type 2 diabetes. It was not clear whether a similar limitation applied to the One Stop Shop.

The fact that the third party company was run by a previous Takeda employee was not necessarily unacceptable. No evidence had been provided by the complainant in this regard. Clearly Takeda had a commercial interest in the therapeutic area as it had medicines for treating type 2 diabetes. Again this was not necessarily unacceptable. All the arrangements needed to comply with the Code, in particular Clause 18.4. The document 'Type 2 Diabetes Annual Review and Patient Segmentation' did not mention any medicines by name other than insulin. The Panel had no information as to how this document was used.

The Panel noted that some aspects of the service were not examined as they fell outside the scope of the complainant's narrow allegations. No evidence had been provided by the complainant

who was anonymous and non contactable. The Panel considered that much would depend on the health professionals who controlled the process. The practice could decide what action to take. It was vital that those conducting the nurse-led review or One Stop Shop followed instructions and complied with their own professional codes. There was no evidence that they had not done so. There was no evidence before the Panel to indicate that the arrangements in principle amounted to an inducement to prescribe a specific medicine contrary to Clause 18.1 or that they failed to satisfy the criteria for a therapeutic review programme under Clause 18.4. No breach of Clauses 18.1 and 18.4 was ruled. There was no evidence provided by the complainant that Takeda representatives had failed to comply with the Code or that high standards had not been maintained. No breach of Clauses 9.1 and 15.2 was ruled. The Panel also ruled no breach of Clause 2.

Complaint received **17 June 2009**

Case completed **14 July 2009**

CODE OF PRACTICE REVIEW – AUGUST 2009

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

2205/2/09	**Public Health Registrar v Reckitt Benckiser**	**Insert on Gaviscon Advance**	**Breaches Clauses 6.3, 7.2, 9.10 and 12.1**	**Appeal by complainant**	**Page 3**
2209/2/09	**Pfizer v Leo Pharma**	**Promotion of Innohep**	**Breach Clause 3.2**	**Appeal by complainant**	**Page 10**
2212/3/09	**Takeda v Merck Sharp & Dohme**	**Promotion of Cozaar**	**Two Breaches Clause 7.2 Two Breaches Clause 7.3**	**Appeal by complainant**	**Page 15**
2215/3/09	**Merz Pharma v Allergan**	**Promotion of Botox**	**Breach Clause 3.2 Two Breaches Clause 7.2 Breaches Clauses 7.4 and 7.10**	**No appeal**	**Page 26**
2216/3/09	**ProStrakan v Cephalon**	**Promotion of Effentora**	**Breaches Clauses 3.2 and 7.8**	**No appeal**	**Page 28**
2218/3/09	**Voluntary Admission by AstraZeneca**	**Promotion of Nexium**	**Two breaches Clause 3.2**	**No appeal**	**Page 33**
2219/3/09	Anonymous General Practitioner v Boehringer Ingelheim	Conduct of representative	No Breach	No appeal	Page 39
2220/3/09	**Anonymous v Lilly**	**Conduct of representative**	**Breaches Clauses 15.2 and 15.4**	**No appeal**	**Page 41**
2221/3/09	Public Health Registrar v Reckitt Benckiser	Promotion of Gaviscon Advance	No Breach	No appeal	Page 51
2222/4/09 and 2227/4/09	**Anonymous Lilly Employee v Lilly and and Daiichi-Sankyo**	**Efient press release**	**Breaches Clauses 9.1 and 22.2**	**No appeal**	**Page 55**
2224/4/09	Professor of Cardiology v Merck Sharp & Dohme	Promotion of Cozaar	No Breach	No appeal	Page 60
2225/4/09	Anonymous Doctor v Astellas	Arrangements for a meeting	No Breach	No appeal	Page 63
2226/4/09	**Merz Pharma v Allergan**	**Botox product monograph**	**Three Breaches Clause 7.2 Three Breaches Clause 7.4 Breach Clause 7.5**	**No appeal**	**Page 67**
2229/5/09	**Voluntary Admission by AstraZeneca**	**Arrangements for a meeting**	**Breaches Clauses 9.1, 15.9 and 18.1**	**No appeal**	**Page 72**
2230/5/09	Anonymous v AstraZeneca	Conduct of representative	No Breach	No appeal	Page 75
2232/5/09	**Anonymous Former Representative v Cephalon**	**Training of representatives promoting Effentora**	**Breach Clause 1.7 Two Breaches Clauses 9.1 Breaches Clauses 14.1, 15.9, 16.1 and 16.2**	**No appeal**	**Page 78**

2233/5/09	Anonymous General Practitioner v Leo	Meeting arrangements	No Breach	No appeal	Page 84
2236/6/09	**Pharmacist v Sanofi-Aventis**	**Conduct of representatives**	**Breaches Clauses 15.2 and 19.1**	**No appeal**	**Page 86**
2238/6/09	**Procter & Gamble v Shire**	**Promotion of Mezavant XL**	**Two Breaches Clause 7.2**	**No appeal**	**Page 90**
2239/6/09	**Consultant Radiologist v Bracco**	**Letter to radiology health professionals**	**Breaches Clauses 7.2, 8.1 and 9.1**	**No appeal**	**Page 94**
2240/6/09	Regulatory Affairs Consultant v Roche	Articles about MabThera in the lay press	No Breach	No appeal	Page 97
2243/6/09	Anonymous v Takeda	Sponsorship of 'One Stop Shops' for Diabetes	No Breach	No appeal	Page 101

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.