PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 40 MAY 2003

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.

Updated Code of Practice agreed by ABPI members

At the Annual General Meeting of The Association of the British Pharmaceutical Industry (ABPI) on 3 April, member companies agreed a revised version of the Code of Practice for the Pharmaceutical Industry. The new Code will come into operation on 1 July but, during the period 1 July to 30 September inclusive, no promotional material or activity will be regarded as being in breach of the Code if it fails to comply with its provisions only because of requirements newly introduced.

Also agreed was a revised version of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority. This will apply to complaints received on and after 1 July.

The main changes to the Code and the Constitution and Procedure are set out below. Full details have been sent to the chief executives of ABPI member companies and those companies which though not ABPI members have agreed to comply with the Code and accept the jurisdiction of the Authority.

It is anticipated that printed copies of the new Code will be available around the end of May. A copy will be sent to everyone on the mailing list for the Code of Practice Review and bulk orders from campanies will be dispatched as soon as possible.

Changes to the Code of Practice

The following are the main changes to the Code of Practice:

- the exclusion from the Code by Clause 1.2 of European public assessment reports (EPARs)
- in the supplementary information to Clause 3 it is made clear that if promotional material is to be shown at an international exhibition in the UK for a product with no UK marketing authorization, then it must have been authorized in at least one major industrialised country
- the supplementary information to Clause 7 is augmented to remind companies that claims must be capable of standing alone as regards accuracy etc and that in general claims should not be qualified by the use of footnotes
- the supplementary information to Clause 7.6 is augmented to point out that the requirement to give references where published studies are referred to applies to references to published material, including the use of quotations, tables, graphs and other illustrative material
- Clause 9.1, which requires high standards to be maintained and refers to the need for promotional activities and materials to recognise the special nature of medicines and the professional standing of the audience to which they are directed, has been split into two clauses, Clause 9.1 now being concerned solely with the maintenance of high standards
- the Medicines and Healthcare products Regulatory Agency has been added to the list in Clause 9.4 of organisations which may not be referred to in promotional material unless this is specifically required by the licensing authority
- in Clause 9.8, which stipulates that the telephone etc must not be used for promotional purposes without the prior consent of recipients, telex has been deleted and text messages have been added
- the supplementary information to both Clause 9.9 and Clause 10.2 has been augmented to ensure that the identity of a company which has commissioned market research would be made known to the Authority by the agency concerned should that information be requested

Public reprimand for Lilly

Eli Lilly and Company Limited has been publicly reprimanded by the ABPI Board of Management for the promotion of Cialis (tadalafil) prior to the grant of its marketing authorization.

Full details can be found at page 3 in this issue of the Review in the report for Case AUTH/1346/7/02.

Disease Awareness Campaigns Guidelines

Guidelines on disease awareness campaigns developed by the Medicines and Healthcare products Regulatory Agency (formerly the Medicines Control Agency) were published in April. This was one of the agreed action points arising from the Pharmaceutical Industry Competitiveness Task Force (PICTF) a joint Government/pharmaceutical industry (ABPI) task force.

Copies of the guidelines are available from the Agency and its website (www.mhra.gov.uk).

- the supplementary information to Clause 14.1 now makes it clear that certification applies to promotional material made available on the Internet
- in the supplementary information to Clause 18.2, a low value phone card has been deleted from the examples of acceptable gifts and guidance has been added on the acceptability of gifts of textbooks
- in the supplementary information to Clause 20 it is pointed out that it is good practice to include the summary of product characteristics with a press release or a press pack relating to a medicine and the existing guidance on disease awareness and public health campaigns has been expanded.

Changes to the Constitution and Procedure

The following are the main changes to the Constitution and Procedure:

- Paragraph 7.1 now provides that the complainant, as well as the respondent company, will be advised of the Code of Practice Panel's ruling where a breach has been ruled – at present this information need be given to the complainant only if there is an appeal by the respondent company or the case has been completed
- Paragraph 7.2 now provides that where no breach is ruled by the Panel both the complainant and the respondent company are given the reasons for the decision; similarly Paragraph 10.1 now provides that the reasons for the decision are given to both parties where the Code of Practice Appeal Board rules no breach – neither of these represents a change in practice
- Paragraph 7.4 now provides that where the complainant appeals and the complainant comments on the respondent company's comments on its appeal, the complainant's comments will be sent to the respondent company; similarly Paragraph 7.5 now provides that where the respondent company appeals it will be sent the complainant's comments on its appeal – neither of these represents a change in practice
- Paragraph 10.4 now makes clear that following an audit of a company's procedures required by the Appeal Board, the Appeal Board can impose requirements on the company to improve its procedures in relation to the Code of Practice
- Paragraph 16.2 now makes clear that the lower level of administrative charge only is payable by the respondent company if a ruling of the Panel that there was no breach of the Code is overturned by the Appeal Board – this is already the practice
- Paragraph 16.3 now confirms that where two or more respondent companies are ruled in breach of the Code in a matter involving co-promotion, each company is liable to pay three-quarters only of the charge that would otherwise be payable – this is already the practice as was agreed by ABPI member companies at their Half-Yearly General Meeting in 2001.

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 at the Royal College of Nursing 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.

Forthcoming Code of Practice seminar dates on which places remain available are:

Tuesday, 1 July

Friday, 18 July

Tuesday, 9 September

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 Jean Rollingson for details (020 7930 9677 extn 1443).

How to contact the Authority

Our address is:

Prescription Medicines
Code of Practice Authority
12 Whitehall
London SW1A 2DY

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7930 9677 extn 1473).

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/1346/7/02

PFIZER v LILLY

Promotion prior to grant of marketing authorization

Pfizer had had numerous reports of the promotion of tadalafil (Cialis) and knew of specific examples of Lilly representatives in one part of England discussing erectile dysfunction (ED) with urologists. Pfizer believed that this was a national phenomenon. As a result of at least one such meeting, a paper on tadalafil (Padma-Nathan *et al* 2001) was delivered to a urologist by a Lilly representative. No other literature which might have balanced the tadalafil paper was delivered at the same time. The paper gave a highly favourable impression of tadalafil and so its distribution in these circumstances was alleged to constitute a breach of the Code.

Pfizer was concerned that Lilly representatives were actively detailing urology health professionals and discussing erectile dysfunction. As tadalafil was unlicensed Pfizer alleged a breach of the Code. Pfizer stated that the paper on tadalafil was given to a urologist by the representative. This was entirely inappropriate. Even if the medical information department responded to the request and sent the paper, it would be unacceptable, as the request was not unsolicited in that it was prompted by the meeting with the representative. Pfizer had been told by another a customer in the same geographical area that he had been 'detailed' on tadalafil. Pfizer alleged that the representative had failed to comply with the Code.

In addition, Pfizer alleged that Lilly's representatives' briefing materials were in breach of the Code and that promotion in advance of a marketing authorization brought discredit upon the industry in breach of Clause 2 of the Code.

The Panel noted that the Code permitted certain activities prior to the grant of the marketing authorization. For example the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited providing that any such information or activity did not constitute promotion prohibited by the Code.

The definition of promotion in the Code did not include replies made in response to individual enquiries from members of the health professions or in response to specific communications whether of enquiry or comment, including letters published in professional journals, but only if they related solely to the subject matter of the letter or enquiry, were accurate and did not mislead and were not promotional in nature. Statements relating to human health or diseases were also exempt from the definition of promotion provided there was no reference either direct or indirect to specific medicines.

In the Panel's view it was not necessarily unacceptable for companies to have employees focussing on the provision of information prior to the grant of the marketing authorization. The arrangements and activities of such employees had to comply with the Code. The area was difficult and companies needed to ensure that the arrangements and activities were very carefully controlled and managed. The importance of documentation and instruction could not be overestimated.

The Panel noted that tadalafil was not licensed in the UK. It appeared that Lilly was using its medical representatives to profile customers ahead of the product launch. A Lilly/Icos 'ED Specialists Survey' was designed to collect information on a clinician's patients, clinics, role and responsibility, ED services, use of literature/services from the Impotence Association and membership of the 'Men's Health Forum'. The representatives had also been given an ED sales aid to help them structure their discussions with their customers.

The sales aid introduced Lilly and Icos and informed the customer of the partnership between the two companies which was designed to produce new solutions in ED. The prevalence of ED was discussed together with the fact that although effective treatments were available 90% of men in the UK with the condition did not receive treatment. On a page headed 'ED Treatment – Past to Present' a diagram showed the therapeutic progress made over the last 40 years. One part of the diagram indicated that in 1998 oral treatment became available, adjacent to this was the statement 'Erection but constraints'. The diagram ended with '2002+ Advanced oral treatments' and the statement 'What do patients need now? Return to a more 'normal' sex life'.

A page of the sales aid headed 'ED Treatment – The Future?' described the design of a study to understand the emotional impact of ED on the lives of men and their partners and to assess treatment needs of both men and clinicians. It was stated that in the respondent population 50% of relationships were assisted by sildenafil (Pfizer's product Viagra) and that the other 50% of respondents were lapsed sildenafil users, users of other treatments, or no treatment. The next page referred to the results of the survey which showed that ED had a profoundly adverse effect on men's lives and that some patients felt that current ED treatments were artificial and too much planning was needed in order to have sex. The next page referred to the limitations associated with current treatments and listed the attributes that men wanted from an ED treatment.

The last two pages of the sales aid stated 'What do you look for in an ED treatment?', there then followed a list of product attributes which doctors considered desirable including 'Efficacious and reliable', 'As few side effects as possible', 'Rapid onset', 'Easy to take' and 'Extended period in which to have sex'.

The Panel did not accept Lilly's submission that the activity of its representatives was not subject to the Code due to the exemption of 'Statements relating to human health or diseases provided there is no reference, either direct or indirect, to specific medicines'. The sales aid used by the representatives referred to sildenafil in particular and to 'current ED treatments' and 'advanced oral

treatments' in general. The Panel noted the involvement of medical representatives and that they were critically discussing what, on the launch of tadalafil, would be competitor products. Criticising competitor products was a promotional activity. In addition they were introducing the Lilly/Icos partnership which existed solely for the development of tadalafil. In the Panel's view the sales aid, and the activity of the representatives, were thus subject to the Code. The Panel considered that the sales aid was designed to solicit questions about tadalafil. The Panel considered that in effect the sales aid promoted tadalafil prior to the grant of a marketing authorization. A breach of the Code was ruled.

With regard to Clause 2, the Panel noted that it was reserved for use as a sign of particular censure. The Panel considered that Lilly's activities brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

The representatives' briefing notes for the ED sales aid clearly stated that they must not get involved in any discussions on Cialis in the pre-launch period and referred them to a Questions and Answers document which listed a number of anticipated questions; the answers to many showed that representatives were to refer the questions to medical information. Nonetheless the Panel considered that as such questions about an unlicensed product had been solicited via a visit and the use of a sales aid, they could not take the benefit of the exemption to the definition of promotion for replies in response to enquiries. The Panel noted its rulings above and considered that although the representatives were instructed by Lilly, they had nonetheless not complied with all the relevant requirements of the Code. A breach of the Code was ruled. The Panel considered that the briefing material advocated a course of action likely to lead to a breach of the Code and thus a breach was ruled.

The Panel noted that Lilly's records showed that a urologist had been supplied with a number of papers via medical information in response to his asking the representative for more information on tadalafil. One of those papers was that by Padma-Nathan *et al*. The Panel had no evidence before it that the package of information provided was unbalanced as alleged. No breach of the Code was ruled.

Upon appeal by Lilly, the Appeal Board noted that Lilly's only product in the ED therapy area was tadalafil. Tadalafil had received its European marketing authorization only a week or so prior to the appeal hearing. At the time that Lilly's representatives were talking to ED specialists the product was not licensed in the UK.

The Appeal Board was extremely concerned about the scale of the activities undertaken by Lilly. From March to October the company had employed 18 representatives to use the ED sales aid to discuss ED with relevant health professionals; over 9000 calls had been made. The ED sales aid was to enable discussions with customers to be structured in the pre-launch phase for Cialis. Two of the key communication points of the ED sales aid were to ensure that customers knew that Lilly/Icos was a joint venture for new solutions in ED and that there was a need for new ED treatments. The two other key communication points were that the goal of ED treatment was to enable a man with ED to have as near to a normal sex life as possible and that the concept of less planning around sex was what men with ED wanted. The representatives were instructed to refrain from getting involved in any discussions on Cialis at all and to adhere to the Questions and Answer document. When using page 6 of the ED sales aid which depicted ED treatments, past to present, representatives were to stress that there were still seen to be constraints with the currently available medicines. This page of the ED sales aid indicated that in 2002+ there would be advanced oral treatments.

In the Appeal Board's view the activities amounted to a 'softening up' exercise designed to heighten awareness of the Lilly/Icos partnership and to raise expectations that a new product would be available from Lilly/Icos which might meet the perceived constraints of the currently available medicines. The Appeal Board did not accept Lilly's submission that the activity of its representatives was not subject to the Code due to the exemption of 'Statements relating to human health or diseases provided there is no reference, either direct or indirect, to specific medicines'. The ED sales aid used by the representatives referred to sildenafil in particular and to 'current ED treatments' and 'advanced oral treatments' in general. The Appeal Board considered that as questions about an unlicensed product had been solicited via a visit and the use of the ED sales aid, Lilly could not take the benefit of the exemption to the definition of promotion for replies in response to enquiries.

The Appeal Board considered that Lilly's actions amounted to the promotion of tadalafil prior to the grant of a marketing authorization permitting its sale or supply. The Appeal Board thus upheld the Panel's ruling of a breach of the Code. The Appeal Board considered that the briefing material, the Cialis – March 2002 ED sales aid guide given to the representatives telling them how to use the ED sales aid and what messages to convey, was such that it advocated a course of action which would lead to a breach the Code. The Panel's ruling of a breach was upheld.

The Appeal Board noted that the Code required representatives to maintain a high standard of ethical conduct in the discharge of their duties and to comply with the relevant requirements of the Code. The Appeal Board noted that although the representatives were only acting upon instructions given to them by their company they were nonetheless not complying with the relevant requirements of the Code in that their actions were such as to promote tadalafil before it had been granted a marketing authorization. In that respect the Appeal Board upheld the Panel's ruling of a breach of the Code.

The Appeal Board considered that Lilly's campaign brought discredit upon and reduced confidence in

the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2.

The Appeal Board considered the circumstances warranted reporting the company to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure for it to decide whether further sanctions should be applied.

The ABPI Board of Management decided that Lilly should be reprimanded and details of that reprimand published. This would send out an unequivocal message regarding the ABPI Board's view of this serious matter.

COMPLAINT

Pfizer Limited stated that it had had numerous reports of the promotion of tadalafil (Cialis) and knew of specific examples of Eli Lilly and Company Limited representatives discussing erectile dysfunction (ED) with urologists in the North-West of England. Pfizer believed that this was a national phenomenon. As a result of at least one such meeting, a paper on tadalafil (Padma-Nathan *et al* 2001) was delivered to a staff-grade urologist by a Lilly representative. No other literature which might have balanced the tadalafil paper was delivered at the same time. The Padma-Nathan paper gave a highly favourable impression of tadalafil and so its distribution in these circumstances constituted a breach of Clause 7.2.

In the light of this and other pre-marketing authorization 'noise' from the Lilly sales force, Pfizer spoke to Lilly and followed up the conversation with a letter. Pfizer stated that the subsequent telephone call and letter from Lilly failed to answer its concerns, which were:

- Lilly representatives were actively detailing health professionals in the field of urology when they did not have a licensed product which they could be discussing.
- They were openly discussing erectile dysfunction. As tadalafil was unlicensed, Pfizer considered this constituted illegal pre-marketing authorization promotion and was in breach of Clause 3.1 of the Code.
- Pfizer noted that it had asked Lilly to provide it with a copy of its representatives' briefing materials in the therapy area. Lilly had not provided this.
- Pfizer stated that to its knowledge the paper on tadalafil (as above) was given to a urologist by the representative. During informal discussion, Lilly did not see this as inappropriate. It was of course entirely inappropriate. Even if the medical information department responded to the request and sent the paper, it would be unacceptable, as the request was not unsolicited in that it was prompted by the meeting with the representative. Pfizer noted, however, that the written response from Lilly claimed that the paper was sent out by the medical information department in response to the urologist's request.
- Pfizer stated that it had received another specific complaint from a customer in the same geographical area. He might be complaining to the Authority in his own right. He had told Pfizer that he had been 'detailed' on tadalafil. Pfizer alleged that this was a breach of Clause 15.2. Clearly it was a breach of Clause 3.1. Even were tadalafil licensed, there would have been a clear breach of Clauses 4.1 and/or 15.8 as neither prescribing information nor a summary of product characteristics (SPC) were seen.

Pfizer requested that Lilly's representatives' briefing materials and the justification for its representatives to discuss ED with customers were scrutinised. Pfizer alleged breaches of Clauses 3.1, 7.2, 15.2 and 15.9.

Pfizer contended that promotion in advance of a marketing authorization was illegal and as such brought discredit upon the industry. A breach of Clause 2 was alleged.

RESPONSE

Lilly stated that tadalafil was not yet licensed anywhere in the world. The marketing authorization application for Europe was submitted in July 2001.

Lilly provided copies of its representatives' instructions, training material and briefing documents. The company stated that its representatives had not received product training on tadalafil and had had strong verbal instructions forbidding them from entering into discussion about it as well as the written instructions contained in the briefing document. The only factual information they were aware of concerning tadalafil was that covered in the questions and answers briefing document. The representatives had only been given background information on the disease area of erectile dysfunction.

There was no briefing material for the use of the Padma-Nathan paper as the representatives had neither been trained in its use, nor had the company made them aware of it, nor did they have access to it via the company. The publication was handled entirely from within head office via medical information as per Clause 13 of the Code.

Lilly stated that it was shocked that Pfizer alleged a breach of the Code for discussing a therapeutic area with physicians. Clause 1.2 stated as such. The Code did not cover 'statements relating to human health or diseases provided there was no reference, either direct or indirect to specific medicines'. This activity was accepted practice within the industry prior to the grant of a licence in order to commence the customer relationship process. Specifically in this case the representatives were rolling out a programme of 'target validation' in order to ascertain physician interest in this therapeutic area for future business activity. Lilly stated that its representatives were not discussing or detailing tadalafil. Clause 3.1 was not being breached.

Lilly stated that briefing materials were not supplied as requested to Pfizer as such a request fell outside the scope of the Code in this case.

Lilly stated that any requests for product information were referred to medical information. The

representative in question had never had access to the Padma-Nathan publication and indeed would not be aware of its existence as part of a company process. Lilly provided a copy of a medical request form which showed that on 25 March 2002 it received a request from a doctor, via one of its representatives, for information on tadalafil. The doctor had stated that he had heard of the product from 'urology meetings/colleagues'. Subsequently having seen the data sent from head office he requested clarification on the use of nitrates. The heading on the subsequent covering letter sent by medical information was sent direct to the physician's address.

Lilly stated that having investigated this matter with the representative concerned it had assurance that she did not source the paper of her own accord. In addition the company had no knowledge of any other representatives acting in such a manner.

Lilly stated that since Pfizer had not supplied precise details about a 'complaint from another customer' it was impossible to comment on the matter.

Lilly stated that the tadalafil product team's position was that the furnishing of a paper by a representative prior to the granting of a marketing authorization was inappropriate. The supply of a paper by medical information was in response to a direct request. Lilly emphasised that its representatives were under strict instructions not to enter into discussion about tadalafil as evidenced by its briefing document.

Lilly wholly contested the challenge that discussions involving a disease state to appropriate professionals was in breach of the Code.

Lilly denied breaches of Clauses 3.1, 7.2, 15.2 and 15.9 of the Code.

In response to a request for further information Lilly provided a copy of the representatives' briefing material which was what the representative used in her visit to the urologist in the North West of England whom the company believed was very enthusiastic about erectile dysfunction and new treatment approaches. A copy of the representative's business card was provided. Lilly emphasised that the representative referred the urologist's questions to its medical information department as per the Code and as highlighted above.

Lilly stated that the objective of the visit was to find out more about physicians' views on treatment for ED and to understand what their goals of therapy were. The representatives were given a standard set of questions to ask and a copy of these was provided. A copy of the briefing material about the Lilly/Icos partnership was also included. The Lilly/Icos partnership did not currently exist for anything other than the development of tadalafil. The Cialis team did not currently promote any products.

PANEL RULING

The Panel noted that the Code permitted certain activities prior to the grant of the marketing authorization. The supplementary information to Clause 3 stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited providing that any such information or activity did not constitute promotion prohibited by Clause 3 or any other clause.

The definition of promotion in Clause 1.2 did not include replies made in response to individual enquiries from members of the health professions or in response to specific communications whether of enquiry or comment, including letters published in professional journals, but only if they related solely to the subject matter of the letter or enquiry, were accurate and did not mislead and were not promotional in nature. Statements relating to human health or diseases were also exempt from the definition of promotion provided there was no reference either direct or indirect to specific medicines.

In the Panel's view it was not necessarily unacceptable for companies to have employees focussing on the provision of information prior to the grant of the marketing authorization. The arrangements and activities of such employees had to comply with the Code. Such employees should be comprehensively briefed about the Code. The area was difficult and companies needed to ensure that the arrangements and activities were very carefully controlled and managed. The importance of documentation and instruction could not be overestimated.

The Panel noted that tadalafil was not licensed in the UK. It appeared that Lilly was using its medical representatives to profile customers ahead of the product launch. A Lilly/Icos 'ED Specialists Survey' was designed to collect information on a clinician's patients, clinics, role and responsibility, ED services, use of literature/services from the Impotence Association and membership of the 'Men's Health Forum'. The representatives had also been given an ED sales aid to help them structure their discussions with their customers. The key communications points according to the ED sales aid guide were:

- 'The goal of ED treatment is to enable the man with ED to have as near to normal sex life as possible
- Lilly/Icos a joint venture for new solutions in ED
- The concept of less planning around sex is what men with ED want
- There is a need for new ED treatments.'

The sales aid introduced Lilly and Icos and informed the customer of the partnership between the two companies which was designed to produce new solutions in ED. The prevalence of ED was discussed together with the fact that although effective treatments were available 90% of men in the UK with the condition did not receive treatment. On a page headed 'ED Treatment – Past to Present' a diagram showed the therapeutic progress made over the last 40 years. One part of the diagram indicated that in 1998 oral treatment became available, adjacent to this was the statement 'Erection but constraints'. The diagram ended with '2002+ Advanced oral treatments' and the statement 'What do patients need now? Return to a more 'normal' sex life'.

A page of the sales aid headed 'ED Treatment – The Future?' described the design of a study to understand the emotional impact of ED on the lives of men and their partners and to assess treatment needs of both men and clinicians. It was stated that in the respondent population 50% of relationships were assisted by sildenafil (Pfizer's product Viagra) and that the other 50% of respondents were lapsed sildenafil users, users of other treatments, or no treatment. The next page referred to the results of the survey which showed that ED had a profoundly adverse effect on men's lives and that some patients felt that current ED treatments were artificial and too much planning was needed in order to have sex. The next page referred to the limitations associated with current treatments and listed the attributes that men wanted from an ED treatment.

The last two pages of the sales aid stated 'What do you look for in an ED treatment?', there then followed a list of product attributes which doctors considered desirable including 'Efficacious and reliable', 'As few side effects as possible', 'Rapid onset', 'Easy to take' and 'Extended period in which to have sex'.

The Panel did not accept Lilly's submission that the activity of its representatives was not subject to the Code due to the exemption in Clause 1.2 of 'Statements relating to human health or diseases provided there is no reference, either direct or indirect, to specific medicines'. The sales aid used by the representatives referred to sildenafil in particular and to 'current ED treatments' and 'advanced oral treatments' in general. The Panel noted the involvement of medical representatives and that they were critically discussing what, on the launch of tadalafil, would be competitor products. Criticising competitor products was a promotional activity. In addition they were introducing the Lilly/Icos partnership which existed solely for the development of tadalafil. In the Panel's view the sales aid, and the activity of the representatives, were thus subject to the Code. The Panel considered that the sales aid was designed to solicit questions about tadalafil. The Panel considered that in effect the sales aid promoted tadalafil prior to the grant of a marketing authorization. A breach of Clause 3.1 was ruled.

With regard to Clause 2, the Panel noted that it was used as a sign of particular censure and reserved for such occasions. The Panel considered that Lilly's activities brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The representatives' briefing notes for the ED sales aid clearly stated that they must not get involved in any discussions on Cialis in the pre-launch period and referred them to a Questions and Answers document. The Questions and Answers document listed a number of anticipated questions; the answers to many showed that representatives were to refer the questions to medical information. Nonetheless the Panel considered that as such questions about an unlicensed product had been solicited via a visit and the use of a sales aid, they could not take the benefit of the exemption to the definition of promotion in Clause 1.2 for replies in response to enquiries. The Panel noted its rulings above and considered that although the representatives were instructed by Lilly, they had nonetheless not complied with all the relevant requirements of the Code. A breach of Clause 15.2 was ruled. The Panel considered that the briefing material advocated a course of action likely to lead to a breach of the Code. A breach of Clause 15.9 was ruled.

The Panel noted that Lilly's records showed that the urologist in the North West of England had been supplied with a number of papers via medical information in response to his asking the representative for more information on tadalafil. One of those papers was that by Padma-Nathan *et al*. The Panel had no evidence before it that the package of information provided was unbalanced as alleged. No breach of Clause 7.2 was ruled.

APPEAL BY LILLY

Lilly noted that this appeal related to discussions held between its representatives and specialist health professionals on ED. The company was new to the therapy area and so its intention in asking its representatives to talk about ED was to: identify and start developing relationships with relevant health professionals; learn more about the healthcare transaction model ie what process a patient went through to get treated, who played the critical roles, etc; further understand the needs of health professionals and patients; and understand the health professional's views on ED and its desired treatment outcomes.

The interchange between the representative and the health professional was essentially a fact-finding exercise designed to achieve the above. This was reflected in the Questions and Answers document where, in response to a question on why Lilly was talking about ED, it stated that it was conducting research in this area and was trying to understand the needs of physicians who treated the condition. It also expressly stated 'during the course of our fact finding conversations and discussions on ED…'. The detail aid and the survey used by the representatives were simply tools to facilitate a discussion around this topic.

Clearly, gaining all this feedback from health professionals was very beneficial to Lilly, however, the company was cognisant that it could not expect to take up their valuable time without enabling them to gain benefit from the meeting too; hence, the detail aid and the sharing of the information about the study into the emotional impact of ED. There was also an opportunity to participate in a survey and gain the benefit of regional and national results on ED treatment. At the same time, Lilly was able to help the patient groups (Men's Health Forum and the Impotence Association) by raising awareness about them. This all fitted in with Lilly's corporate branding of providing 'Answers that matter' (ie solutions that went beyond products).

It was never Lilly's intention to promote tadalafil. Lilly would not intentionally do anything to damage its own reputation or that of the industry. This was a new disease area for Lilly and it did not make any sense, from a business and future customer

perspective, for the company to be seen to be blatantly breaching the Code in the way implied by Pfizer. This was not how Lilly operated.

Lilly noted that Pfizer had alleged that Lilly was promoting tadalafil. Pfizer provided no actual evidence of this and merely referred to 'numerous reports', a 'national phenomenon' and a complaint from a customer who was, it implied, going to complain to the Authority directly. As far as Lilly was aware, no such complaint materialised and no evidence of this complaint was ever provided. Pfizer had also alleged that Lilly was 'actively detailing' and 'openly discussing' ED. If what Pfizer meant by this was that Lilly was talking to physicians (with the use of tools to structure the conversation and make best use of the health professional's time) about the disease area of ED, then it was correct. Pfizer was incorrect, Lilly believed, in asserting that this was an illegal action before marketing authorization. It was, at the time Lilly prepared the materials, and still was Lilly's belief that the activities in question did not come within the Code, as they constituted 'statements relating to human health or diseases' which were expressly excluded from the Code under Clause 1.2 because they were not promotional.

Lilly noted that Pfizer alleged that it had 'intelligence' that one of Lilly's representatives had at one of these meetings delivered an unsolicited scientific paper (and that no other literature had been provided to present a balanced picture – the Panel found Lilly not in breach of this allegation) and that Lilly did not see this as inappropriate. Again, no actual evidence was provided of this. Lilly provided the Panel with real evidence that the request for this information from the doctor was unsolicited; the doctor had heard about tadalafil from urology meetings/colleagues and therefore requested further information on it. The data (ie the paper in question and seven others) were provided to the doctor by Lilly's Medical Information Department. Indeed, Lilly had not even made the representatives aware of the paper in question. Nor did they have access to it via the company. Hence, the comment that Lilly did not see this as inappropriate, which was taken out of context, was correct. The representative's actions were not, as Pfizer suggested, inappropriate; Lilly believed they came within another exemption to Clause 1.2 (responses to unsolicited requests). Lilly considered its response complied with Clause 7.2.

From experience, representatives frequently complained about what other companies were doing in the field. However, many of these complaints turned out to be incorrect. Unless a representative had some evidence to support a complaint, Lilly did not automatically send off a complaint to the Authority. If Lilly did, it would be sending in complaints all the time. Lilly would rather focus its attention and resources on more positive actions like making life saving medicines more available to the patients who needed them. It was as a result of Lilly's belief, that this was a spurious claim from an aggressive competitor (using the Code as a tool to distract Lilly from its primary focus) about activities that did not, it believed, even come within the Code, that resulted in its refusing to provide Pfizer with a copy of its representatives' briefing materials (a document that it believed was confidential).

Clause 3.1 A medicine must not be promoted prior to the grant of the marketing authorisation which permits its sale or supply

The Panel concluded that Lilly were in breach of that Clause 3.1 as the detail aid was promotional in nature because: Lilly was not exempted under Clause 1.2 due to references in the detail aid to sildenafil and to 'current ED treatments' and 'advanced oral treatments'; it critically discussed competitor products, which was a promotional activity; it introduced the Lilly/Icos partnership, which existed solely for the development of tadalafil and it was designed to solicit questions about tadalafil.

Lilly did not agree. Lilly did not consider that referring to 'advanced oral treatments' or 'current ED treatments' in this context was unacceptable under the Code. These were generic descriptors and did not describe specific products. How was this promotional? Also, the reference to sildenafil was solely in relation to a description of a study population in market research carried out to identify the emotional impact of ED on patients and/or their partners. The reference was a purely factual reference required in order to accurately describe the research. It would have been nonsense to exclude it.

There was nothing critical about the reference to sildenafil. Indeed, the reply in the Questions and Answers document to a question about sildenafil and tadalafil was '… I am not allowed to discuss the molecule [tadalafil] in any way…I really do not know…'. There was no other reference to a specific product in the ED sales aid. There was no reference to tadalafil anywhere in the ED sales aid. The ED sales aid contained factual information about ED and the views of ED patients. The ED sales aid used the study results to generate a discussion around patient needs and what future developments in ED should look like from the health professional's perspective ie what did he want to see. Bearing in mind that Lilly/Icos was a joint venture set up to do research in this area, it did not seem inappropriate for the company to seek feedback of this type. Lilly did not, therefore, consider that the ED sales aid was promotional and it certainly was not intended to be so. Nor had Lilly received any complaints from anyone other than Pfizer about these meetings. Lilly continued to be of the view that this was outside of the Code under Clause 1.2. Lilly considered that it was important to look at the intent behind the words of Clause 1.2 and not to take too literal an interpretation in relation to the reference to 'specific medicines' and sildenafil.

The reference to Lilly/Icos was by way of background. The logo went on all Lilly materials relating to ED and resulted in questions about what it was. Also, these representatives were paid for by Lilly/Icos and so it seemed reasonable to explain whom they worked for. Lilly did not believe it was a breach of the Code to inform its customers about the joint venture it had with Icos and the fact that it was carrying out research in this area and wanted to understand their needs. The ED sales aid explained

the reason for the partnership ie Icos had experience in early discovery/development and Lilly had expertise in research and bringing products to market. No timeframe was mentioned in relation to outputs from the research activities ie new products. Neither did the ED sales aid state that the partnership had got a new product coming out, it just stated that the parties were working together. Again, there was no mention of tadalafil and the reference to Lilly/Icos was simply to put into context why Lilly was talking about ED.

The ED sales aid was not designed to solicit questions about tadalafil for the reasons already discussed. It was designed to solicit questions around ED and patients' and health professionals' needs. This was an entirely different situation. What was the point of the representative soliciting questions about tadalafil when (s)he was not trained on the product and had no information to answer the question with? Lilly acknowledged that it was possible that a health professional could ask a question about the product if he already knew about it. However, this would be an unintended outcome/indirect effect of Lilly's activities and was covered by the Questions & Answers document that the representatives were trained on, by strong verbal instructions forbidding them from entering into discussions about tadalafil, but to refer customers to the Medical Information Department. The ED Sales Aid Guide contained the following emboldened written instruction: 'It is important that you still refrain from getting involved in any discussions on Cialis at all in this pre launch period. The Q & A document that you were issued with at your ED training should still be adhered to'.

The Questions & Answers document was created to ensure that if there was an unintended outcome and such questions were asked, the representatives were prepared to handle them in a professional manner and in a way that would keep Lilly in compliance with the Code. The representative was required to stop the conversation and, if appropriate, refer the request for information to Lilly's Medical Information Department. The Questions and Answers document stated 'we should not get involved in any discussions on Cialis at all'. As Lilly stated in the Questions and Answers document, this was a 'difficult area'; so Lilly did as the Panel suggested in its ruling and ensured that the issue was 'very carefully controlled and managed' by putting it in writing and by training the representatives on it. As the Panel suggested in its ruling: 'the importance of documentation and instruction could not be overestimated'. What was Lilly/Icos supposed to do…not talk about ED as soon as it developed a new medicine just in case it got a question on it as a result?

Lilly did not understand how the Panel could state, 'in effect the sales aid promoted tadalafil' when there was no reference whatsoever to either the generic or brand name of the product in the aid. Neither was there any evidence to show that any questions about tadalafil were so solicited. Lilly had received 142 queries on tadalafil since March 2002. This equated to less than 8 queries per representative over a 7-month period, or just more than one per month. This supported the fact that the detail aid had not led to undue numbers of questions on tadalafil.

Clause 3.1 allowed the 'legitimate exchange of medical and scientific information during the development of a medicine' provided it was not promotional. The definition of promotion did not include replies made in response to individual queries from members of the health professions or statements relating to human health or diseases provided there was no reference to specific medicines. Even the Panel acknowledged that it was not necessarily unacceptable for company employees to provide information prior to the grant of marketing authorization provided they complied with the Code and were briefed upon it. Lilly stated that all of its representatives were so briefed through the ABPI representatives examination and as above. Lilly believed these materials were not promotion prior to the grant of marketing authorization. Lilly carefully controlled the materials used by the representatives and their exact responses in sensitive areas. In conclusion, therefore, Lilly did not understand how the ED sales aid and hence Lilly was in breach of Clause 3.1. Lilly was not promoting tadalafil, a product that the representatives were not even trained on yet.

Clause 15.2 Representatives must at all times maintain a high standard of ethical conduct in the discharge of their duties and must comply with all relevant requirements of the Code

Lilly did not understand how its representatives could be seen to personally have failed to maintain a high standard of ethical conduct and compliance with the Code in this case. The materials were supplied by Lilly and they had simply followed them. It was important to remember that the allegations raised by Pfizer were unfounded. There was no evidence that any of Lilly's representatives had actively promoted tadalafil or handed over reprints or done anything other than comply with the materials handed to them. Lilly also drew attention to Case AUTH/1310/4/02 where it was ruled that a Pfizer representative using material given by head office was found not in breach of Clause 15.2. This judgment seemed very harsh on the representatives.

Clause 15.9 Companies must prepare detailed briefing material for medical representatives on the technical aspects of each medicine which they will promote. A copy of such material must be made available to the Medicines Control Agency and the Authority on request. Briefing material must comply with the relevant requirements of the Code and, in particular, is subject to the certification requirements of Clause 14. Briefing material must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code

A ruling by the Panel that Lilly had been in breach of Clause 15.9 was unclear. Lilly's representatives had not been trained on tadalafil to date and hence Lilly had no briefing material available at this time. The company was not promoting the product and hence there was no need for this material at this time. In any event, for the reasons stated above, Lilly did not agree that the briefing materials advocated a course of action likely to lead to a breach of the Code.

Clause 2 Activities or materials associated with promotion must never be such as to bring discredit

upon, or reduce confidence in, the pharmaceutical industry

Lilly did not consider it was in breach of Clauses 3.1, 15.2 or 15.9 and did not, therefore, believe it was in breach of Clause 2. Even if Lilly was to be found in breach of Clause 3.1, Lilly did not believe it should be found in breach of Clause 2. If Lilly had breached Clause 3.1, it was due to a mistake on the company's part and a misinterpretation of an area that was difficult and for which Lilly apologised if that was the case. However, that was not Lilly's intent and such a breach did not seem sufficient to justify Lilly receiving the ultimate sanction of a Clause 2 breach, a sign of censure, which was reserved for such circumstances. Surely this would be more appropriate if Lilly had intentionally gone out to promote a product pre-launch without any care for the consequences and when there had been numerous complaints. That was clearly a million miles from the current situation.

COMMENTS FROM PFIZER

Pfizer noted that Lilly's intentions in asking its representatives to talk about ED were to: identify and start developing relationships with relevant health professionals; learn more about the healthcare transaction model ie what process a patient goes through to get treated, who plays the critical roles, etc; further understand the needs of health professionals and patients; understand the health professional's views on ED and its desired treatment outcomes.

Of these points, the first was a statement that Lilly was indeed developing relationships with potential customers. In the 'Cialis – March 2002, ED Sales Aid, A Guide' (the ED sales aid guide), the word 'customers' was mentioned twice. This was clearly promotional as described in Clause 1.2 of the Code. Pfizer did not see how an alternative interpretation could be made. The second, third and fourth points made by Lilly appeared to be describing market research. The conduct of such activities by representatives was highly questionable. Pfizer regarded these as disguised promotion, suggesting also further potential breaches of the Code. Pfizer did not consider that such activity was legitimate.

The ED sales aid guide described a staged process which appeared to lead the customer to come to various pre-determined conclusions, largely around the inadequacy of – and lack of satisfaction with – current treatment, especially time to onset and duration of action. Pfizer agreed wholeheartedly with the Panel's view as to the promotional nature of these materials.

Additionally, the ED sales aid began by stating 'A partnership for new solutions in Erectile Dysfunction (ED)'. This was an overt claim for a new product (albeit unnamed in this piece) with efficacy in ED.

The chart 'ED Treatment – Past To Present', the final box – '2002+ Advanced Oral Treatments' implied – as a teaser – that the new medicines would be an improvement over the 'oral treatment' mentioned above as introduced in 1998 – the year of sildenafil's introduction. The representation of research on both patients and doctors gave the clear impression that existing treatments suffered from the disadvantages described above.

On another page two overt claims were also made for Prozac and Zyprexa. No prescribing information was included.

Pfizer noted that Lilly had stated that 'it was never Lilly's intention to promote tadalafil' and 'This was not how Lilly operated'. Lilly had, however, already been found in breach of Clause 3.1 this year when tadalafil was promoted at a European meeting in Birmingham (Case AUTH/1291/3/02). Then the only defence was that the materials used were supplied by the US parent company and that the UK company had not had the opportunity to review them. It could have been expected, therefore, that Lilly would have taken considerable care thereafter to ensure future compliance with the Code.

Another example of Lilly promoting itself in the area of ED was that of a series of meetings organised under the banner 'Trends in Neurology, Gynaecology and Sexual Health'. Pfizer provided a copy of an invitation to a meeting on current issues in Sexual Dysfunction which had been sent to a GP in Edinburgh. This particular meeting was scheduled to have taken place on 3 October 2002. Pfizer did not know whether the section on 'Future Developments …' contained information on tadalafil.

Pfizer maintained that Lilly was indeed actively promoting itself (and Icos) as having an interest in ED, as well as actively promoting its product, tadalafil. Pfizer had highlighted Lilly's activity. It was not Pfizer's responsibility to produce 'evidence' and indeed Lilly had now admitted the activity to which Pfizer had drawn the Authority's attention and had supplied the materials which Pfizer considered showed evidence of a concerted promotional campaign. In the case of Pfizer's Medical Liaison Executives (Case AUTH/1186/5/01), concluded earlier this year, pre-licence activity by a team from the Medical Department was ruled in breach of the Code. Such activity by representatives could not, therefore, be acceptable.

Lilly's activities in this area clearly came within the Code. Pfizer agreed with the Panel that the activity of Lilly's representatives was not covered by the exemption in Clause 1.2.

Multiple reports of Lilly's activities had been received by Pfizer. Lilly had given an account of how the paper was delivered to the urologist who gave Pfizer the information about his contact with Lilly's representative. Clearly the two accounts were at odds and Pfizer could shed no further light on the course of events.

With regard to Lilly's appeal against the Panel's ruling of a breach of Clause 3.1, Pfizer stated that 'Return to a more normal sex life', 'erection but constraints', 'advanced oral treatments', and 'the concept of less planning' were all, it could only be assumed, comparative claims for future treatments, such as tadalafil, against existing oral treatments, including Pfizer's own sildenafil. The reference to sildenafil in the ED sales aid was unacceptable. Pfizer rejected Lilly's argument about a distinction between 'literal' and 'specific' interpretation of the wording of Clause 1.2. Lilly specifically mentioned 'sildenafil' and a health professional meeting a Lilly

representative would only be led to infer that the new Lilly product had advantages over existing treatments, including sildenafil.

Pfizer did not understand what possible interest a collaboration between Lilly and Icos could have for a health professional except in so much as it would give rise to a specific product.

The instruction to representatives not to get 'involved in any discussion on Cialis at all…' did not exonerate Lilly from blame. On the contrary it demonstrated that Lilly had predicted the inevitable outcome of the meeting, which was that the health professional would ask for information about Lilly's unlicensed product. How the information was supplied then became immaterial.

Pfizer was surprised to see the prominent use of the trade name – Cialis – in the ED sales aid guide. If the purpose of the ED sales aid guide was truly only to educate Lilly representatives in ED, Pfizer could see no reason to feature Cialis in its title. This showed a disregard for best practice and was in keeping with the promotional spirit of Lilly's activities.

The fact that there was no mention of tadalafil in the ED sales aid made no difference in Pfizer's opinion. There was a reference to competitor products and this proved that this was a piece of promotional material.

With regard to Lilly's comments in response to the Panel's findings of a breach of Clause 15.2, Pfizer considered that the Lilly representatives were put into a highly equivocal position by their management. Clearly their activities were designed to raise interest in developments in the field of ED and they were ill-equipped to handle them. Pfizer noted that Lilly had drawn attention to Case AUTH/1310/4/02. This case referred to the mistaken use by representatives of proscribed materials inadvertently reissued by Pfizer. In that case, Pfizer accepted full responsibility. In the case now under discussion, it was not necessarily the materials themselves – although Pfizer believed it had already shown that these were indeed highly promotional in themselves – which were the issue with specific regard to the representatives' activities, it was the activity itself – that was visiting health professionals for promotional purposes.

Pfizer noted that Lilly, in responding to the Panel's finding of a breach of Clause 15.9, stated that there was 'no briefing material available at the time'. As Pfizer had stated above, it concurred with the Panel's view that the activity was promotional and that the materials issued were unacceptable in that they were clearly promotional in nature. In so much as the briefing materials supporting the representatives in a promotional situation were promotional in themselves, they would inevitably have caused a breach of the Code.

Pfizer believed that Lilly had intentionally set out to promote a product pre-launch. The fact that there had been no complaints apart from Pfizer's was irrelevant. Pfizer maintained that Lilly was clearly in breach of Clauses 3.1, 15.2 and 15.9 of the Code. Pfizer could only speculate on how these breaches might have been permitted by Lilly's internal governance systems. Whether it was through a lack of attention to detail or through a deliberate policy to disregard the Code, Pfizer could not be sure. Now that Pfizer had seen the materials used to brief the representatives and the ED sales aid which was used with customers, it believed that their nature supported the latter view and it therefore concurred with the Panel's findings of a breach of Clause 2.

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In response to a question at the appeal hearing itself about the number of calls made by representatives, Lilly stated that over the six month period (March 2002-October 2002) the eighteen medical representatives involved (who had been part of the diabetes care sales force) had made over 9,000 calls on health professionals. Lilly further stated that this had resulted in approximately one enquiry to medical information per representative per month.

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APPEAL BOARD RULING

The Appeal Board noted that Lilly's only product in the ED therapy area was tadalafil. Its European marketing authorization had been received only a week or so prior to the appeal hearing. At the time that Lilly's representatives were talking to ED specialists the product was not licensed in the UK.

The Appeal Board was extremely concerned about the scale of the activities undertaken by Lilly. From March to October the company had employed 18 representatives to use the ED sales aid to discuss ED with relevant health professionals; over 9000 calls had been made. The ED sales aid was to enable discussions with customers to be structured in the pre-launch phase for Cialis. Two of the key communication points of the ED sales aid were to ensure that customers knew that Lilly/Icos was a joint venture for new solutions in ED and that there was a need for new ED treatments. The two other key communication points were that the goal of ED treatment was to enable a man with ED to have as near to a normal sex life as possible and that the concept of less planning around sex was what men with ED wanted. The representatives were instructed to refrain from getting involved in any discussions on Cialis at all and to adhere to the Questions and Answers document. When using page 6 of the ED sales aid which depicted ED treatments, past to present, representatives were to stress that there were still seen to be constraints with the currently available medicines. This page of the ED sales aid indicated that in 2002+ there would be advanced oral treatments.

In the Appeal Board's view the activities amounted to a 'softening up' exercise designed to heighten awareness of the Lilly/Icos partnership and to raise expectations that a new product would be available from Lilly/Icos which might meet the perceived constraints of the currently available medicines. The Appeal Board did not accept Lilly's submission that the activity of its representatives was not subject to the Code due to the exemption in Clause 1.2 of

'Statements relating to human health or diseases provided there is no reference, either direct or indirect, to specific medicines'. The ED sales aid used by the representatives referred to sildenafil in particular and to 'current ED treatments' and 'advanced oral treatments' in general. The Appeal Board considered that as questions about an unlicensed product had been solicited via a visit and the use of the ED sales aid, Lilly could not take the benefit of the exemption to the definition of promotion in Clause 1.2 for replies in response to enquiries.

The Appeal Board considered that Lilly's actions amounted to the promotion of tadalafil prior to the grant of a marketing authorization permitting its sale or supply. The Appeal Board thus upheld the Panel's ruling of a breach of Clause 3.1 of the Code. The Appeal Board considered that the briefing material, the Cialis – March 2002 ED sales aid guide given to the representatives telling them how to use the ED sales aid and what messages to convey, was such that it advocated a course of action which would lead to a breach the Code. The Panel's ruling of a breach of Clause 15.9 was upheld.

The Appeal Board noted that Clause 15.2 of the Code required representatives to maintain a high standard of ethical conduct in the discharge of their duties and to comply with the relevant requirements of the Code. The Appeal Board noted that although the representatives were only acting upon instructions given to them by their company they were nonetheless not complying with the relevant requirements of the Code in that their actions were such as to promote tadalafil before it had been granted a marketing authorization. In that respect the Appeal Board upheld the Panel's ruling of a breach of Clause 15.2.

The Appeal Board considered that Lilly's campaign brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2.

The appeal was unsuccessful on all points.

The Appeal Board considered the circumstances warranted reporting the company to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure for it to decide whether further sanctions should be applied.

REPORT TO THE ABPI BOARD OF MANAGEMENT

The ABPI Board of Management decided that Lilly should be reprimanded and details of that reprimand published. This would send out an unequivocal message regarding the ABPI Board's view of this serious matter.

Complaint received	**26 July 2002**
PMCPA proceedings completed	**16 December 2002**
ABPI Board proceedings completed	**11 February 2003**

CASE AUTH/1354/8/02

LILLY v JANSSEN-CILAG

Risperdal Consta press release

Lilly complained about a four page Risperdal Consta (risperidone) press release issued by Janssen-Cilag headed 'First long-acting atypical antipsychotic launched in the UK'. The sub-heading read 'Risperdal Consta a treatment breakthrough for people with schizophrenia'. Lilly marketed Zyprexa (olanzapine). Both Risperdal and Zyprexa were atypical antipsychotics.

Lilly alleged that the claim '… Risperdal is the only oral atypical antipsychotic to have demonstrated clinical superiority in reducing the risk of relapse over haloperidol, a conventional antipsychotic traditionally considered previously to be the treatment 'gold standard'', suggested that Risperdal was effective in preventing relapse, however Risperdal was not indicated for relapse prevention. In Case AUTH/1325/5/02 the Panel had noted that prevention of relapse was not the same as maintenance of a response. The Risperdal summary of product characteristics (SPC) listed maintenance therapy but not relapse prevention as an indication. Lilly also alleged that the claim was false. Tran *et al* (1998) reported relapse data derived from studies in which olanzapine had been compared to haloperidol; the estimated one year relapse rate on olanzapine (Kaplan-Meier estimate) was 19.7%, compared with 28% on haloperidol.

The Panel noted that Risperdal was indicated for the treatment of acute and chronic schizophrenic psychoses in which positive and/or negative symptoms were prominent and that it was also effective in maintaining the clinical improvement during continuation therapy in patients who had shown an initial treatment response (ref SPC). In the Panel's view the aim of long-term management of schizophrenia was to prevent relapse and the return of acute symptoms. The Panel considered that reducing the risk of relapse was not inconsistent with the licensed indications for Risperdal. No breach of the Code was ruled.

In Case AUTH/1325/5/02, a claim that Zyprexa demonstrated a significant reduction in relapse rates compared to risperidone was based upon a study which measured clinical response to the two products. In the Panel's view the study had not been designed to measure relapse rates; maintenance of response as defined by two parameters was not the same as prevention of relapse. The Panel had considered that the claim did not accurately represent the findings of the study on which it was based and a breach of the Code had been ruled. In the present case the issues were quite different. The claim in question did not refer to relapse rates. The claim was based upon a double-blind prospective study which compared risperidone and haloperidol for the prevention of relapse in schizophrenia. Relapse was defined by any one of five parameters. The data showed that adult outpatients with clinically stable schizophrenia, or schizoaffective disorder, had a lower risk of relapse if they were treated with risperidone than if they were treated with haloperidol. However the claim at issue stated that Risperdal was the only oral atypical to have demonstrated such benefits compared to haloperidol. This was not so. There was some data to show that olanzapine reduced the risk of relapse compared to haloperidol. The Panel thus considered that the claim for Risperdal being the only oral atypical antipsychotic to demonstrate that particular clinical advantage over haloperidol was misleading and not capable of substantiation. Breaches of the Code were ruled.

Lilly stated that the claim '… may lead to a preference for this delivery system for longer-term relapse prevention over oral dosing …' suggested that Risperdal Consta would be a preferred treatment for longer-term relapse prevention but Risperdal Consta was not indicated for relapse prevention. The quotation suggested that Risperdal Consta could be used for the unlicensed indication relapse prevention. The same precedent as for the point above applied (Case AUTH/1325/5/02).

The Panel noted its comments above with regard to whether a claim for relapse prevention was inconsistent with the licence for Risperdal. Unlike Risperdal, Risperdal Consta was a long-acting preparation and was not licensed for acute use. Nonetheless the Panel considered that its relevant comments at point 1 applied here also and thus ruled no breach of the Code.

Lilly alleged that the claim 'The UK is the first market in the world to launch Risperdal Consta which has been developed to fulfil a previously unmet medical need – to have the means to provide long-term atypical treatment' was misleading. Long-term treatment with atypicals had been available for many years. Lilly further alleged that the claim disparaged other atypical antipsychotics licensed for maintenance therapy.

The Panel considered that the claim implied that before the introduction of Risperdal Consta clinicians had not been able to provide long-term atypical treatment. Risperdal Consta was the first long-acting atypical but clinicians had been able to give other atypicals long-term in the past. The Panel considered that the claim was misleading and ruled a breach of the Code. The Panel did not consider that the claim disparaged other atypical antipsychotics and no breach of the Code was ruled.

Lilly questioned the 'burden' of once daily medication in the context of Risperdal Consta which had to be given by intramuscular injection via a wide bore needle. Once daily oral treatment was known to present little burden to patients and was reported to be associated with good levels of compliance even in chronic disorders. Lilly alleged that in the absence of any evidence that once daily oral therapy was a 'burden' compared to once a fortnight intramuscular injection, the claim 'Requiring administration just once every fortnight, Risperdal Consta relieves the burden of daily medication …' was misleading.

The Panel noted that Risperdal Consta was to be administered every fortnight by deep intramuscular

gluteal injection. Other atypical antipsychotics had to be taken orally once or twice daily. The Panel considered that the claim 'relieves the burden of daily medication' was not misleading as alleged. No breach of the Code was ruled.

Lilly stated that the claim 'Currently, up to 40% of people with schizophrenia in the UK are treated with older (conventional) injectable antipsychotic formulations. These are often painful when administered, fail to control negative symptoms and cause debilitating side effects, particularly pronounced movement disorders. Risperdal Consta will benefit, not only these patients but will be an option for all patients requiring long-term treatment …' implied that Risperdal Consta would benefit, *inter alia*, patients who suffered pain on injection of older (conventional) antipsychotics. Risperdal Consta, however, had to be given by intramuscular injection via a wide bore needle once a fortnight whereas older depot antipsychotics were given by intramuscular injection through a smaller needle only once a month. Lilly alleged that the claim was misleading and incapable of substantiation.

The Panel considered that the claim in question implied that those people who suffered pain on injection of the older antipsychotic depots would not find Risperdal Consta injections painful. The Panel considered that the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

Lilly alleged that the use of the term 'highly efficacious' was exaggerated. Risperdal Consta had been shown to be about as efficacious as other formulations of risperidone, a medicine which was not licensed for use in indications such as treatment resistant schizophrenia where efficacy would indeed be evidence of the medicine being highly efficacious. The claim 'For the first time, we have a long-term treatment solution which offers continuous, consistent symptom control through a highly efficacious and well-tolerated agent' was too strong in the context of the supporting evidence and was therefore exaggerated.

The Panel noted Janssen-Cilag's submission that the claim was a quotation from a consultant psychiatrist. Any quotation chosen by a company for use in promotional material must, however, comply with the requirements of the Code. The Panel considered that the claim implied that Risperdal Consta was the first highly efficacious agent with which to treat schizophrenia and this was not so. The Panel considered that the claim was exaggerated as alleged and ruled a breach of the Code. The ruling was appealed.

The Appeal Board noted that the psychiatrist's quote had been split into two paragraphs in the press release such that the claim at issue appeared at the start of the second paragraph '[the psychiatrist] continues, 'For the first time, we have a long-term treatment solution which offers continuous, consistent symptom control through a highly efficacious and well tolerated agent''. In the Appeal Board's view this added emphasis. The Appeal Board noted that the introduction of Risperdal Consta meant that for the first time clinicians could use a long-acting atypical antipsychotic, however the quote referred to long-term and not long-acting. Further by also including 'highly efficacious' in the same sentence the press release additionally implied that for the first time clinicians also had a highly efficacious agent to use. The Appeal Board considered that this was misleading and exaggerated and upheld the Panel's ruling of a breach of the Code.

Lilly alleged that the claim 'In one 12-month study, only 18% of patients taking Risperdal Consta experienced rehospitalisation' was not a fair representation of the study in which the overall hospitalisation rate was 36%, the rehospitalisation rate for those in hospital at baseline but later discharged was 25% and for those who were out-patients at baseline was 16%. Since the study showed that baseline status had a sizeable impact on the risk of rehospitalisation (25% vs 16%) the claim should have made this clear.

The Panel noted that the baseline status of patients had an impact on hospitalisation rates; in-patients were much more likely to be readmitted than out-patients. Janssen-Cilag had quoted a figure which combined the hospitalisation rates for both groups of patients but without stating how that figure had been calculated. Although the 18% as quoted was a conservative figure for out-patients it was too low for in-patients. The Panel considered that the claim was misleading and a breach of the Code was ruled. This ruling was appealed.

The Appeal Board considered that whilst the figure of 18% was supported by the study, there was no indication in the press release as to how it had been calculated. The Appeal Board queried whether like was being compared with like. The Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of the Code.

Lilly claimed that the citation of the reference given to the claim 'Treatment with Risperdal Consta has also been shown to reduce re-hospitalisation rates …' was inadequate and incorrect. The Panel noted that the reference had not been cited accurately. A breach of the Code was ruled.

Lilly alleged that a reference cited in support of a claim which referred to the study being 'presented at CINP 2002' was inadequate for the purposes of sourcing a copy of the information. The Panel did not accept Lilly's allegation; the poster was easily found on the CINP website as submitted by Janssen-Cilag. No breach of the Code was ruled.

Eli Lilly and Company Limited complained about a four page Risperdal Consta (risperidone) press release issued by Janssen-Cilag Ltd. The press release was headed 'First long-acting atypical antipsychotic launched in the UK'. The sub-heading read 'Risperdal Consta a treatment breakthrough for people with schizophrenia'.

Lilly marketed Zyprexa (olanzapine). Both Risperdal and Zyprexa were atypical antipsychotics.

1 Claim '… Risperdal is the only oral atypical antipsychotic to have demonstrated clinical superiority in reducing the risk of relapse over haloperidol, a conventional antipsychotic traditionally considered previously to be the treatment 'gold standard"

COMPLAINT

Lilly alleged that the claim suggested that Risperdal was effective in preventing relapse, however Risperdal was not indicated for relapse prevention. In Case AUTH/1325/5/02 the Panel noted that prevention of relapse was not the same as maintenance of a response. Lilly accepted this ruling and agreed with it; maintenance of a response implied continuation therapy, however, relapse prevention could be started in a patient who was well at the time and on no treatment but had been identified as being at risk of relapse. The Risperdal summary of product characteristics (SPC) listed maintenance therapy but not relapse prevention as an indication. Lilly alleged a breach of Clause 3.2.

Lilly also alleged that the claim was false, in breach of Clauses 7.2 and 7.4. Tran *et al* (1998) reported relapse data derived from studies in which olanzapine had been compared to haloperidol; the estimated one year relapse rate on olanzapine (Kaplan-Meier estimate) was 19.7%, compared with 28% on haloperidol.

RESPONSE

Janssen-Cilag noted that the Risperdal SPC stated:

'Risperdal is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperdal also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperdal is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.'

Schizophrenia was a chronic illness characterized by remissions and exacerbations. Antipsychotic drugs were a critical modality in managing this disease in all phases – acute, stabilization and relapse prevention and long-term treatment with medication was critical in optimizing outcome. Several reviews had summarized the data on the impact of continued antipsychotic medication on relapse rates and outcome, and at present continuous medication was the treatment of choice for patients diagnosed with schizophrenia.

As a result patients were prescribed antipsychotic medications initially to control the acute symptoms of schizophrenia but they remained on medication even after the acute symptoms appeared to have abated in order to control chronic symptoms and prevent the return of acute symptoms ie acute exacerbation/ relapse. Therefore Risperdal (or any other antipsychotic) would be prescribed to treat the initial symptoms and to keep that patient well in the long-term ie to prevent relapse. It was not credible to suggest that in doing so a physician was going outside the product licence.

Prevention of relapse was the main goal of maintenance therapy, and was a major factor in the treatment of chronic schizophrenia. Clearly, successful maintenance therapy and treatment of chronic schizophrenia required reduction in the risk of relapse. This statement was therefore consistent with the SPC.

Janssen-Cilag did not understand Lilly's reference to Case AUTH/1325/5/02. Lilly had somehow interpreted this case to mean that the Panel considered that prevention of relapse was not the same as maintenance of a response. In fact, the Panel was asked to consider whether Tran *et al* was sufficient to make a claim of superiority of olanzapine over risperidone in terms of relapse prevention (in terms of the balance of existing evidence). The Panel decided it was not and accordingly ruled a breach of Clause 7.2.

Janssen-Cilag considered therefore, that this previous case had no bearing on the current case in which Lilly alleged that a claim for relapse prevention was outside of the SPC. The company considered that an indication for the treatment of acute and chronic schizophrenia and the statement 'Risperdal is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response' meant that 'relapse prevention' was consistent with Risperdal's licence.

The recent publication of a double-blind controlled study of 365 patients (Csernansky *et al* 2002) in which the risk of relapse was significantly reduced for patients receiving Risperdal compared to haloperidol, further confirmed the role of Risperdal in relapse prevention compared to haloperidol. The statement in the press release was made in light of this publication in the New England Journal of Medicine (NEJM). The results of this study demonstrated that adult outpatients with clinically stable schizophrenia or schizoaffective disorder had a significantly lower risk of relapse if they were treated with risperidone than if they were treated with haloperidol. As a result of this publication, Dr John Geddes (University of Oxford and Cochrane Collaboration), wrote an editorial, also in the NEJM, in which he stated 'There is little reliable evidence of long-term efficacy of other atypical drugs. Studies on the use of the other atypical drugs for the prevention of relapse are therefore required'.

The Tran (1998) publication cited by Lilly was a study in which the results of three separate studies were pooled. The pooled results showed a significant difference in the estimated one-year risk of relapse but no statistically significant difference in the absolute relapse incidences. Janssen-Cilag questioned the relative validity of results of the 'pooled' study compared to that of a single double-blind controlled study, especially given the results if the pooled studies were assessed individually: the first study revealed no statistically significant difference in the incidence of

relapse between olanzapine and haloperidol, in the second study there was not a statistically significant difference in the incidence of relapse between the two groups and finally, in the third study, although there was a difference in the Kaplan-Meier survival analysis at time to relapse for the olanzapine group, there was not a statistically significant difference in the incidence of relapse between the two groups. The clinical significance was therefore of question.

Janssen-Cilag contended on the balance of the currently available evidence, Risperdal remained the only atypical antipsychotic with reliable evidence in the relapse setting, as supported by Geddes. Janssen-Cilag submitted that there had been no breach of the Code.

PANEL RULING

The Panel noted that according to its SPC Risperdal was indicated for the treatment of acute and chronic schizophrenic psychoses in which positive and/or negative symptoms were prominent. It was also effective in maintaining the clinical improvement during continuation therapy in patients who had shown an initial treatment response. In the Panel's view the aim of long-term management of schizophrenia was to prevent relapse and the return of acute symptoms. The Panel considered that reducing the risk of relapse was not inconsistent with the licensed indications for Risperdal. No breach of Clause 3.2 was ruled.

The Panel noted that in Case AUTH/1325/5/02, a claim that Zyprexa (olanzapine) demonstrated a significant reduction in relapse rates compared to risperidone was based upon Tran *et al* (1997) which measured clinical response to the two products. In the Panel's view the study had not been designed to measure relapse rates; maintenance of response as defined by two parameters was not the same as prevention of relapse. The Panel had considered that the claim did not accurately represent the findings of the study on which it was based and a breach of the Code had been ruled.

Turning now to the case before it, Case AUTH/1354/8/02, the Panel considered that the issues were quite different. The claim in question did not refer to relapse rates. The claim was based upon a double-blind prospective study by Csernansky *et al* which compared risperidone and haloperidol for the prevention of relapse in schizophrenia. Relapse was defined by any one of five parameters. The data showed that adult outpatients with clinically stable schizophrenia, or schizoaffective disorder, had a lower risk of relapse if they were treated with risperidone than if they were treated with haloperidol. However the claim at issue stated that Risperdal was the only oral atypical to have demonstrated such benefits compared to haloperidol. This was not so. Tran *et al* (1998) pooled data from the extension phases of three double-blind acute studies which had compared the efficacy of olanzapine and haloperidol. Relapse was defined as hospitalisation for psychopathology. The results showed that olanzapine-treated patients experienced less relapse than those treated with haloperidol. The Panel noted that there were major differences in study design between Tran *et al* and Csernansky *et al*. There was, nonetheless, some data to show that olanzapine reduced the risk of relapse compared to haloperidol. The Panel thus considered that the claim for Risperdal being the only oral atypical antipsychotic to demonstrate that particular clinical advantage over haloperidol was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled.

2 Claim '… may lead to a preference for this delivery system for longer-term relapse prevention over oral dosing …'

COMPLAINT

Lilly stated that this claim suggested that Risperdal Consta would be a preferred treatment for longer-term relapse prevention but Risperdal Consta was not indicated for relapse prevention. The quotation suggested that Risperdal Consta could be used for the unlicensed indication relapse prevention. The same precedent as for point 1 above applied (Case AUTH/1325/5/02). Thus this claim was in breach of Clause 3.2.

RESPONSE

Janssen-Cilag noted that the claim was a quote from a practising psychiatrist who viewed Risperdal Consta as a significant advance.

Janssen-Cilag stated that the Risperdal Consta SPC indication was similar to that of oral Risperdal and the arguments in point 1 above applied. Furthermore, the National Institute of Clinical Excellence (NICE) in its guidelines (2002) on the treatment and management of schizophrenia recognised the importance of depots in preventing relapse in schizophrenia and stated: 'For optimum efficacy for relapse prevention, depot preparations should be prescribed within the standard recommended dosage and interval range'.

Janssen-Cilag contended that there was no breach of the Code.

PANEL RULING

The Panel noted its comments at point 1 above with regard to whether a claim for relapse prevention was inconsistent with the licence for Risperdal. Risperdal Consta was licensed for the treatment of schizophrenic psychoses and other psychotic conditions in which positive and/or negative symptoms were prominent. Unlike Risperdal, Risperdal Consta was a long-acting preparation and was not licensed for acute use. Nonetheless the Panel considered that its relevant comments at point 1 applied here also and thus ruled no breach of Clause 3.2.

3 Claim 'The UK is the first market in the world to launch Risperdal Consta which has been developed to fulfil a previously unmet medical need – to have the means to provide long-term atypical treatment'

COMPLAINT

Lilly contended that 'the means to provide long-term atypical treatment' had been available for many years as witnessed by the many patients treated long-term with oral atypical agents including Janssen-Cilag's product Risperdal. Lilly alleged that the claim was misleading in breach of Clause 7.2. Lilly further alleged that the claim disparaged other atypical antipsychotics licensed for maintenance therapy including its product Zyprexa. A breach of Clause 8.1 was alleged.

RESPONSE

Janssen-Cilag submitted that the claim was neither misleading nor disparaging taken within the context of the press release. The focus of the press release was to announce the launch of Risperdal Consta – a long-acting injectable atypical antipsychotic that had been developed to fulfil a previously unmet medical need. Clearly, the obvious inference in the unmet medical need – 'to have the means to provide long-term atypical treatment' was by a long-acting injection. As Lilly noted, in addition to Risperdal Consta Janssen-Cilag manufactured Risperdal, the most widely prescribed oral atypical antipsychotic in the world and therefore the company would not wish to disparage oral atypical antipsychotics. Janssen-Cilag contended that there had been no breach of the Code.

PANEL RULING

The Panel considered that the claim implied that before the introduction of Risperdal Consta clinicians had not been able to provide long-term atypical treatment. This was not so. Risperdal Consta was the first long-acting atypical but clinicians had been able to give other atypicals long-term in the past. The Panel considered that the claim was misleading as alleged and ruled a breach of Clause 7.2 of the Code. The Panel did not consider that the claim disparaged other atypical antipsychotics as alleged and no breach of Clause 8.1 was ruled.

4 Claim 'Requiring administration just once every fortnight, Risperdal Consta relieves the burden of daily medication …'

COMPLAINT

Lilly questioned the 'burden' of once daily medication in the context of a medicine ie Risperdal Consta which had to be given by intramuscular injection via a wide bore needle. Once daily oral treatment was known to present little burden to patients and was reported to be associated with good levels of compliance even in the context of chronic disorders (Bloom 2001). Lilly alleged that in the absence of any evidence that once daily oral therapy was a 'burden' compared to once a fortnight intramuscular injection, the claim was misleading in breach of Clause 7.2.

RESPONSE

Janssen-Cilag considered that receiving any medication, whatever the regimen, and for any condition could be classed as being a burden. Indeed personal experience of receiving treatment for minor ailments eg antibiotics suggested that even once daily medication must be a burden as very few people would complete the full course. Extensive research had been done in many therapy areas to develop long-acting formulations, particularly through the use of different delivery systems. All long-acting (depot) preparations, which only required fortnightly administration, regardless of how they were administered, would remove the daily responsibility of a patient having to remember to take their medication.

In schizophrenia there were many subjective risk factors for non-compliance including perceptions and attitudes such as lack of insight, denial of illness and beliefs regarding medication and the carer. As a result compliance with oral medication was difficult. Mann (1986) suggested that roughly one in three patients with schizophrenia taking oral medication failed to comply reliably, though higher estimates had been reported as well. Data obtained from 'trawling' GP systems for a period of a year demonstrated that more than 50% of patients receiving risperidone or olanzapine failed to collect their repeat prescription on time and therefore were not continuously compliant.

Lack of compliance was difficult to identify and was often a common reason for relapse and reappearance of symptoms. Depot preparations that were administered every 1-6 weeks did not prevent non-compliance but when it did occur it was immediately detectable and therefore could be responded to productively.

Depot medications were widely used in UK practice and still held a market share of around 20%. This provided clear evidence that daily administration must be a burden to a high number of patients as the inability of conventional preparations to control the symptoms of schizophrenia and the motor side effects were well known.

Walburn *et al* (2001) reviewed the literature to explore patient and nurse satisfaction with depot antipsychotics. Of the 12 studies, which met the inclusion criteria and contained relevant data, 10 conveyed a positive opinion of depot medication. Five out of six studies comparing depot with oral medication showed patient preference for depot. The authors proposed that one possible explanation was convenience. Wistedt (1995) found that just fewer than 70% of their sample thought it easier to have an injection than taking tablets every day.

The depot antipsychotic strategy meant fewer conflicts in the therapy situation. Instead of frequent (possibly daily) negotiations with the patient about medicine intake, necessary instructions could be given in connection with relatively infrequent injections.

Janssen-Cilag submitted that the statement was reasonable and not in breach of the Code.

PANEL RULING

The Panel noted that Risperdal Consta was to be administered every fortnight by deep intramuscular

gluteal injection. Other atypical antipsychotics had to be taken orally once or twice daily. The Panel considered that the claim 'relieves the burden of daily medication' was not misleading as alleged. No breach of Clause 7.2 was ruled.

5 Claim 'Currently, up to 40% of people with schizophrenia in the UK are treated with older (conventional) injectable antipsychotic formulations. These are often painful when administered, fail to control negative symptoms and cause debilitating side effects, particularly pronounced movement disorders. Risperdal Consta will benefit, not only these patients but will be an option for all patients requiring long-term treatment …'

COMPLAINT

Lilly stated that this claim implied that Risperdal Consta would benefit, *inter alia*, patients who suffered pain on injection of older (conventional) antipsychotics. Risperdal Consta, however, had to be given by intramuscular injection via a wide bore needle once a fortnight whereas older depot antipsychotics were given by intramuscular injection through a smaller needle only once a month. Lilly alleged that the claim was misleading and incapable of substantiation in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Janssen-Cilag objected to Lilly's description of the needle used to administer Risperdal Consta which was a 20 gauge thin walled needle. The thin wall design ensured that the bore (internal diameter) of the needle was as wide as possible but its outer diameter (gauge) was not substantially larger than that recommended for use with other depot antipsychotics. The only other depot to specify the size of the needle within its SPC was Haldol Decanoate – where it stated it must be at least 21 gauge. Janssen-Cilag noted that Lilly stated that the other depots were administered once a month. This was not the case as their licensed dose regimen ranged from between 1-6 weeks.

Risperdal Consta, unlike other depot preparations available in the UK, was water based. The vehicle in which preparations were administered was known to have an effect on the injection site and might lead to pain. Oil based injections were associated with pain on injection, which might be due to the viscosity or even possibly allergies to nut products within the oil. Aqueous injections were believed to result in less pain. There were published reports of the injection site becoming edematous, tender and pruritic following administration of conventional depots (Hamann, 1990). There were no such reports following administration of Risperdal Consta.

Hagstrom and Hanson (2002) reported an attitude survey on the practical handling aspects of Risperdal Consta. 110 questionnaires were sent out and 74 were returned. The results showed that 55% of nurses felt that Risperdal Consta was associated with no pain versus 33% for oil based antipsychotics. The authors concluded that the advantage of Risperdal Consta was less pain at the injection site. Less pain on injection might contribute positively to an increase in patient compliance to antipsychotic medication.

Janssen-Cilag submitted that the claim was not misleading, it was capable of substantiation and there was no breach of the Code.

PANEL RULING

The Panel noted that Risperdal Consta had to be injected once a fortnight. Older, typical antipsychotic depot injections were to be administered generally at intervals of one to four weeks although flupenthixol injections could be given five weeks apart. They were not all once monthly as stated by Lilly (ref BNF).

The Panel considered that the claim in question implied that those people who suffered pain on injection of the older antipsychotic depots would not find Risperdal Consta injections painful. The Panel noted Janssen-Cilag's submission there was a greater incidence of pain with the older antipsychotic injections than with Risperdal Consta but considered that some patients would report pain with both. In terms of pain Risperdal Consta would thus not benefit these patients. The Panel considered that the claim was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

During the consideration of this point the Panel noted its comments about the difference between long-acting treatment and long-term treatment in point 3 above and requested that this be drawn to Janssen-Cilag's attention. This also applied to point 6 below.

6 Claim 'For the first time, we have a long-term treatment solution which offers continuous, consistent symptom control through a highly efficacious and well-tolerated agent'

COMPLAINT

Lilly alleged that the use of the term 'highly efficacious' was exaggerated. Risperdal Consta had been shown to be about as efficacious as other formulations of risperidone, a medicine which was not licensed for use in indications such as treatment resistant schizophrenia where efficacy would indeed be evidence of the medicine being highly efficacious. The claim was too strong in the context of the supporting evidence and was therefore exaggerated in breach of Clause 7.10.

RESPONSE

Janssen-Cilag noted that the claim was a quote, in the context of a press release, from a consultant psychiatrist based on his clinical experience of both Risperdal Consta and oral formulations of Risperdal.

As noted by Lilly, Risperdal Consta had been shown to have a comparable efficacy to oral Risperdal – a product in which efficacy had been consistently demonstrated in numerous published controlled studies. Risperidone and olanzapine, the two most

widely prescribed atypical antipsychotics were both established as being highly effective, hence their licensing and the recent recommendation by NICE that these products, and other atypical antipsychotics, should be chosen as a first line medication.

Janssen-Cilag considered that it had not breached the Code.

PANEL RULING

The Panel noted Janssen-Cilag's submission that the claim was a quotation from a consultant psychiatrist. Any quotation chosen by a company for use in promotional material must, however, comply with the Code.

The Panel considered that the claim implied that Risperdal Consta was the first highly efficacious agent with which to treat schizophrenia and this was not so. The Panel considered that the claim was exaggerated as alleged and ruled a breach of Clause 7.10 of the Code.

APPEAL BY JANSSEN-CILAG

Janssen-Cilag stressed the fact that this was a press release allowed under Clause 20 of the Code. It was not a piece of promotional material to be used directly with health professionals. Janssen-Cilag acknowledged that the Code governed such information. The statements within the press release were not intended to be used as marketing claims in isolation and were also made in the context of a general press release specifically about Risperdal Consta. Janssen-Cilag therefore requested that the document was treated as a whole when considering the appeal.

Janssen-Cilag stressed that the claim at issue was a quote from a leading consultant psychiatrist based on his knowledge of the data and clinical experience of both Risperdal Consta and Risperdal.

Janssen-Cilag asked the Appeal Board to consider the quote in its entirety:

'The development of Risperdal Consta marks a key advance in antipsychotic therapy. The psychiatric community has known for some decades of the advantages of long-acting formulations, namely, consistent delivery, dose reduction, lower risk of relapse and improved treatment adherence. However up until now, only typical antipsychotics have been available in long-acting formulations. For the first time, we have a long-term treatment solution which offers continuous, consistent symptom control through a highly efficacious and well-tolerated agent. A large number of patients stand to benefit from this and its profile may lead to a preference for this delivery system for longer-term relapse prevention over oral dosing for a much broader group of patients.'

Janssen-Cilag noted that the Panel had considered that the psychiatrist had implied that Risperdal Consta was the first highly efficacious agent with which to treat schizophrenia and that this was not so and therefore exaggerated. The psychiatrist, like other psychiatrists, had experience with a variety of antipsychotics and knew that Risperdal Consta was not the first agent licensed to treat schizophrenia. In the context of the full quote and the press release in its entirety, it was clear that the word 'first' referred to the first atypical to become available as a long-acting injection.

The 'highly efficacious and well-tolerated agent' referred to was risperidone. Risperdal Consta delivered risperidone via a novel long-acting injection. Risperidone had been available in its oral form in the UK for 9 years and there was now a wealth of clinical evidence supporting its efficacy and tolerability. Details were provided.

Janssen-Cilag noted that Lilly had alleged that the use of the term 'highly efficacious' was too strong in the context of the supporting evidence and was therefore exaggerated. Lilly's original argument was that Risperdal was not licensed for treatment-resistant schizophrenia and so it could not be highly efficacious. The NICE guidance defined treatment-resistant schizophrenia as 'a lack of satisfactory clinical improvement despite the sequential use of the recommended doses for 6-8 weeks of at least two antipsychotics, at least one of which should be an atypical'. The NICE guidance also stated that clozapine was the only antipsychotic licensed for treatment-resistant schizophrenia. This was clearly a separate indication and at no point in the press release was there reference to treatment-resistant patients. The press release referred to the majority of patients with schizophrenia who were not treatment-resistant. It was therefore inappropriate to judge Risperdal in an unlicensed indication. Janssen-Cilag therefore appealed the ruling of a breach of Clause 7.10.

COMMENTS FROM LILLY

Lilly took issue with the suggestion by Janssen-Cilag that a lesser standard of exactness was required for statements made in press releases (covered by Clause 20 of the Code). In fact the opposite ought to apply. In writing press releases great care should be taken not to mislead or to make statements which could be misleading if taken out of context since the quotation of selected snippets was a predictable outcome of the journalistic use of press releases on technical subjects. As a result it was not appropriate to read the press release as a whole: each sentence and clause should be considered on its own since this was how the document might be used by journalists compiling a story. Indeed failure to maintain the highest standards of scientific and linguistic exactness when preparing a press release might amount to a breach of Clause 9.1.

Lilly considered that even taken in the context of the surrounding sentences it was difficult to see how the claim at issue could mean anything other than 'Risperdal Consta is the first long-term treatment for schizophrenia'. This was not true since various other formulations of risperidone, as well as other typical and atypical antipsychotic medicines, had been available for the long-term treatment of schizophrenia for many years. Thus Lilly alleged that this was misleading in breach of Clause 7.2.

For the same reason Risperdal Consta was not the first highly efficacious treatment for schizophrenia, if the term highly efficacious was accepted as being a reasonable description of the efficacy of risperidone. The most fundamental problem was the opening phrase 'for the first time' when used in the context of providing a long-term solution to the problem of treating schizophrenia. The argument advanced by Janssen-Cilag, which first referred to 'first atypical to become available as a long-acting injection', made no grammatical sense: first clearly related to time.

Lilly noted that in defending the use of the descriptor 'highly efficacious and well-tolerated' Janssen-Cilag had cited a wide range of evidence including the results of an assortment of clinical trials. However, based on meta-analysis information, it was clear that the advantages of most atypical antipsychotics (including risperidone) over typical agents such as haloperidol were modest (Geddes *et al* 2000 and additional data posted on the BMJ website) and that the efficacy of, *inter alia*, clozapine was much more marked than that of the other atypicals, so much so that it often worked in cases of schizophrenia where other medicines failed – not a different indication, just the most problematical end of the treatment spectrum. Thus the use of the term 'highly efficacious' might indeed be exaggerated as originally suggested, in breach of Clause 7.10.

APPEAL BOARD RULING

The Appeal Board noted that the psychiatrist's quote had been split into two paragraphs in the press release such that the claim at issue appeared at the start of the second paragraph '[the psychiatrist] continues, 'For the first time, we have a long-term treatment solution which offers continuous, consistent symptom control through a highly efficacious and well tolerated agent''. In the Appeal Board's view this added emphasis. The Appeal Board noted that the introduction of Risperdal Consta meant that for the first time clinicians could use a long-acting atypical antipsychotic, however the quote referred to long-term and not long-acting. Further by also including 'highly efficacious' in the same sentence the press release additionally implied that for the first time clinicians also had a highly efficacious agent to use. The Appeal Board considered that this was misleading and exaggerated and upheld the Panel's ruling of a breach of Clause 7.10 of the Code. The appeal on this point was unsuccessful.

7 Claim 'In one 12-month study, only 18% of patients taking Risperdal Consta experienced rehospitalisation'

COMPLAINT

Lilly alleged that this was not a fair representation of the study reported by Chue *et al* in which the overall hospitalisation rate was 36%, the rehospitalisation rate for those in hospital at baseline but later discharged was 25% and for those who were out-patients at baseline was 16%. Since the study showed that baseline status had a sizeable impact on the risk of rehospitalisation (25% vs 16%) the claim should have made this clear. Lilly alleged that the claim was misleading, in breach of Clause 7.2, because it was not specific enough.

RESPONSE

Janssen-Cilag stressed that the claim was taken directly from the poster to which it was referenced; moreover it clearly reflected the author's conclusion. The figure of 18% (65/369) was an overall figure derived from combining the 1-year hospitalisation rate for those patients who were out-patients at baseline (16% – 48/301) and the 1-year hospitalisation rate for those who were in-patient at baseline (25% – 17/68). As the majority of patients were out-patients at the start of the study, the overall percentage was weighted towards the out-patient figure. This was the most balanced way to present the data from this study in the context of a press release.

Janssen-Cilag stated that the figure quoted must be taken in context with the whole paragraph in which it was written ie in comparison to relapse and rehospitalisation rates with conventional and atypical antipsychotics derived from previously published studies. In the other relapse studies referenced by Llorca all patients were out-patients at the start and so in contrast to what Lilly alleged, quoting the combined figure of 18% (instead of the 16% for patients who were outpatients at the start) was conservative. Janssen-Cilag therefore submitted there had been no breach of the Code.

PANEL RULING

The Panel noted that the baseline status of patients had an impact on hospitalisation rates; in-patients were much more likely to be readmitted than out-patients. Janssen-Cilag had quoted a figure which combined the hospitalisation rates for both groups of patients but without stating how that figure had been calculated. Although the 18% as quoted was a conservative figure for out-patients it was too low for in-patients. The Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

APPEAL BY JANSSEN-CILAG

Janssen-Cilag stated that the results were taken directly from the poster which was clearly referenced. In the conclusions section of the poster it was stated that the overall 1-year rehospitalisation rate was 17.6%. This figure, derived by Chue *et al* by means of a weighted average – a standard statistical technique – accounted for the fact that there were an unequal number of in- and out-patients at baseline. There were significantly more out-patients (301) than in-patients (68) at the start of the trial and so the overall 1-year rehospitalisation rate was weighted towards the out-patients result.

Janssen-Cilag stated that in the context of a press release for a generalist audience it was uncommon to provide details of how figures were derived statistically. A generalist audience wished to know the overall picture and for all patients, both in- and

out-patients, and so the weighted average was the most appropriate figure for the recipients to understand. The figure of 18% was used to provide a balanced picture, rather than a misleading one. Furthermore, in the context of this press release, the other rehospitalisation results quoted in the press release were all from studies where all patients were in the community at baseline (Llorca *et al* 2002). The rehospitalisation rate for out-patients in Chue *et al* was only 16%, 2% less than the overall figure of 18%. Despite this, Janssen-Cilag submitted it was a fairer reflection of Chue *et al* to use the overall weighted average in the press release. Janssen-Cilag therefore appealed the Panel's ruling of a breach of Clause 7.2.

COMMENTS FROM LILLY

Lilly considered that the detailed explanation of the statistical derivation of the 18% figure was most interesting. However the use of this weighted summary statistic to amalgamate two widely differing results in patient populations with different prognoses was misleading regardless of the quality of the mathematics. Whilst Lilly agreed that it would not be appropriate to explain how the sums were done in the context of a press release, the company considered that this placed a much greater onus on Janssen-Cilag not to amalgamate data in a way that obscured important differences. Because the quoted weighted average percentage (18%) was noticeably lower than the greater of the two figures from which it was derived (25%), it was possible that the result presented would give unfounded hope to patients in the poorer prognosis group. In fact the risk of relapse in the group who were out-patients at baseline was 16% (<1 in 6) compared to 25% (1 in 4) in those who were in-patients at baseline. Lilly therefore supported the Panel's ruling that the way the results of the study were presented was misleading by over simplification and thus in breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted that Chue *et al* stated that as a proxy measure for relapse the one year rehospitalisation rate was defined as the first hospitalisation for out-patients and a new hospitalisation after discharge for in-patients at baseline. The Appeal Board noted that the baseline status of patients had an impact on subsequent hospitalisation rates; in-patients were much more likely to be admitted than out-patients. The Appeal Board noted that 28 of 96 patients already in hospital at the start of the study were not discharged during the study and could not, therefore, be included in the calculations. Janssen-Cilag had quoted a figure of 18% for rehospitalisation which combined the rehospitalisation rates for both in- and out-patients. Although 18% was a conservative figure for out-patients (16%) it was too low for in-patients (25%). The Appeal Board noted Janssen-Cilag's submission that the other rehospitalisation results given in the press release were from studies where all patients were in the community at baseline (Llorca *et al*) although this information did not appear to be given in Llorca *et al*.

The Appeal Board considered that whilst the figure of 18% was supported by Chue *et al*, there was no indication in the press release as to how it had been calculated. The Appeal Board queried whether like was being compared with like. The Appeal Board considered that the claim was misleading as alleged and upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

8 Claim 'Treatment with Risperdal Consta has also been shown to reduce re-hospitalisation rates …'

COMPLAINT

Lilly claimed that the reference given to this claim [Chue *et al* Value in Health 2002, Vol 2] was inadequate and incorrect; the volume of the journal and the year of publication did not tally. In addition, searching the publisher's website indicated that the journal had not contained the article stated. Lilly alleged a breach of Clause 7.6.

RESPONSE

Janssen-Cilag noted that there was a typographical error in the citation – instead of volume 2, 2002 it should have read volume 5, 2002. Janssen-Cilag apologized for the inconvenience this error might have caused Lilly or anyone else, and stressed as with all enquiries for substantiating data, that its medical information department would have been more than happy to assist Lilly in sourcing the reference.

PANEL RULING

The Panel noted that the reference had not been cited accurately. A breach of Clause 7.6 was ruled.

9 Claim 'Importantly, data illustrates that patients on Risperdal Consta achieve real improvements in their emotional health and social functioning over a one year period, thus experiencing an increased quality of life'

COMPLAINT

Lilly alleged that the reference cited in support of this claim, 'Nasrallah H, Duchesne I, Long acting risperidone injection improves quality of life, presented at CINP 2002' was inadequate for the purposes of sourcing a copy of the information. CINP was a very large scientific meeting at which thousands of posters and papers were presented. The abstract number was in fact P.4.E.043. Failure to provide clear references was a breach of Clause 7.6 – indeed, in this press release, all references to studies presented at conferences were equally inadequate ie references 2, 4, 5, 6 and 7.

RESPONSE

Janssen-Cilag stated that as with most posters presented, an abstract was available from the CINP website. Whilst the company acknowledged that the CINP was a very large scientific meeting at which

thousands of posters and papers were presented, the information given was sufficient to very easily source the poster. Clause 7.6 of the Code stated that clear references must be given. The addition of an abstract number, as Lilly suggested, would not have simplified the search or made the references clearer, as the CINP website relied on author's name and date to track posters. As an alternative, the poster was readily available from Janssen-Cilag's medical information department if required.

Janssen-Cilag stated that it was surprised that Lilly would suggest a poster presented at an international scientific meeting such as the CINP was inadequate. Lilly had, in its own materials, used posters presented at scientific meetings eg ECNP to support promotional claims. Janssen-Cilag stated that it fully supported this action, as publication in prestigious, peer-reviewed journals was a lengthy process.

PANEL RULING

The Panel did not accept that the cited reference was inadequate for sourcing the relevant information as alleged; the poster was easily found on the CINP website as submitted by Janssen-Cilag. No breach of Clause 7.6 was ruled.

Complaint received **29 August 2002**

Case completed **13 February 2003**

CASES AUTH/1361/9/02 and AUTH/1390/11/02

LILLY v JANSSEN-CILAG and ORGANON LABORATORIES

Risperdal 'Dear Doctor' letter

Lilly complained about a Risperdal (risperidone) 'Dear Doctor' letter sent by Janssen-Cilag and Organon Laboratories. The letter discussed the results of Koro *et al* (2002) and stated 'The study concluded: 'Olanzapine is associated with a clinically important and significant increased risk of diabetes'. The study also showed: Risperidone is not associated with a significantly increased risk of diabetes. I hope that the conclusions of this study, combined with the weight of evidence for the efficacy of Risperdal, give you confidence to continue to prescribe the Risperdal range as a first choice antipsychotic therapy'. Lilly marketed Zyprexa (olanzapine).

Lilly alleged that the heading 'Can your patients with schizophrenia handle diabetes too?' and the opening statement 'For people with schizophrenia, living with the disorder can be enough of a struggle without having the added burden of diabetes' indicated that the topic of diabetes and schizophrenia was important enough to warrant the issuing of a 'Dear Doctor' letter. The question posed exaggerated the importance of the topic and caused alarm. This was evidenced by the fact that a number of doctors had already contacted Lilly as a result of reading the letter.

The heading and patient picture painted by the first paragraph were alleged to be misleading in the context of the information provided in the letter. Based on Koro *et al* it was most unlikely that a psychiatrist would face the dilemma posed: of 19,637 patients studied by Koro only 7 receiving olanzapine and 7 receiving risperidone developed treatment-emergent diabetes. Furthermore results from the prescription-event monitoring (PEM) study conducted on olanzapine by the Drug Safety Research Unit (Biswas *et al* 2002) showed that the incidence of new cases of diabetes possibly related to starting treatment with olanzapine was 0.09% (8/8,858). The scenario outlined was spurious and designed to alarm unnecessarily.

The Panel considered that it was a question of whether the findings of Koro *et al* as stated in the letter reflected the clinical situation. The Panel noted that Koro *et al* set out to quantify the risk of diabetes associated with olanzapine and risperidone in patients with schizophrenia. Of 19,637 patients, 451 developed diabetes during a mean follow-up period of 5.2 years. The incidence rate of diabetes among all patients with schizophrenia treated with antipsychotics was 4.4/1000 person years. Olanzapine significantly increased the risk of developing diabetes compared with non-users of antipsychotics (odds ratio 5.8, 95% confidence interval 2.0 – 16.7, p=0.001) and those taking conventional antipsychotics (odds ratio 4.2, 95% confidence interval 1.5 to 12.2, p=0.008). Patients taking risperidone had a non-significant increased risk of developing diabetes than non-users of antipsychotics (odds ratio 2.22, 95% confidence interval 0.9 to 5.2, p=0.079) and those taking conventional antipsychotics (odds ratio 1.6, 95% confidence interval 0.7 to 3.8, p=0.290). The statistical significance of the difference between olanzapine and risperidone was not given.

The Panel noted that Biswas *et al* was a pharmacovigilance study of 8,858 patients using prescription-event monitoring to assess the post-marketing safety profile of olanzapine in patients managed by GPs in primary care. There were 8 reports of diabetes assessed as possibly due to olanzapine.

The Panel considered that the overall tone of the letter suggested that olanzapine-treated patients were likely to develop diabetes whereas those treated with Risperdal were not. The letter stated

that 'Olanzapine is associated with a clinically important and significant increased risk of diabetes'. The Panel noted, however, that Section 4.4 of the Zyprexa summary of product characteristics (SPC) stated that 'Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases'. Section 4.8 of the SPC stated 'In clinical trials with olanzapine in over 5,000 patients with baseline non-fasting glucose levels ≤ 7.8mmol/l, the incidence of non-fasting plasma glucose levels ≥ 11mmol/l (suggestive of diabetes) was 1%, compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels ≥ 8.9mmol/l but < 11mmol/l (suggestive of hyperglycaemia) was 2%, compared to 1.6% with placebo'. Thus although there was an increased risk of diabetes with Zyprexa it was still not a very common side-effect. The Panel considered that by not quantifying the risk of diabetes and referring only to a 'clinically important and significant increased risk' the letter was alarmist and misleading as alleged and ruled a breach of the Code. This ruling was appealed.

The Appeal Board considered that the heading to the letter 'Can your patients with schizophrenia handle diabetes too?' would raise concern. The subsequent text implied that there was a clinically important and significant difference between olanzapine and risperidone in their propensity to cause diabetes. This had not been proven. The letter gave the reader no indication as to the incidence of diabetes caused by either medicine. The Appeal Board considered that the heading to the letter was alarmist and misleading as alleged and upheld the Panel's ruling of a breach of the Code.

Lilly noted that the letter drew the doctor's attention to only one publication on the epidemiology of diabetes in patients with schizophrenia (Koro *et al*). Two statements about the risk of diabetes in relation to two medicines used to treat schizophrenia were made in the letter, both referenced to Koro *et al*. The second of these, 'Risperidone is not associated with a significantly increased risk of diabetes' did not reflect the totality of the literature on the topic in respect of risperidone (Koller *et al* 2002). The claim did not reflect the international regulatory status of Risperdal in that SPCs for risperidone in Australia and Japan recorded an association between Risperdal and diabetes. The claim was alleged to be misleading.

The Panel noted that the current Risperdal SPC did not refer at all to either hyperglycaemia or diabetes as possible side-effects of therapy. The Panel considered that the claim implied that there was thus some risk of diabetes but not a significant one. The Panel did not consider that the claim itself was inconsistent with the data for Risperdal and so ruled no breach of the Code. This ruling was appealed.

The Appeal Board noted that the claim 'Risperidone is not associated with a significantly increased risk of diabetes' was referenced to Koro *et al*. What Koro *et al* had actually stated was that 'Patients taking risperidone had a non-significant increased risk of developing diabetes than non-users of antipsychotics (2.2, 0.9 to 5.2) and those taking conventional antipsychotics (1.6, 0.7 to 3.8)'. The Appeal Board also noted that when the 'Dear Doctor' letter had been sent Janssen-Cilag was in discussion with the MCA to amend the SPC so as to include the statement 'Hyperglycaemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment'.

The Appeal Board considered that the claim at issue did not accurately reflect the available evidence. Readers would assume that there was no association at all between risperidone and altered glucose metabolism and that was not so. The Appeal Board considered that the claim was misleading and ruled a breach of the Code.

Lilly alleged that 'Olanzapine is associated with a clinically important and significant increased risk of diabetes' was a strong claim based on very flimsy data. In the discussion section of the paper by Koro *et al* the authors acknowledged the failure of the study methodology to control for a number of important confounding factors. In addition the number of cases on which the findings for both medicines were based was tiny and the size of the confidence interval around the hazard ratio for olanzapine was very large. Considerable doubt about the validity of Koro *et al* had been expressed in correspondence posted on the BMJ website. The claim was not based on a sound statistical evaluation of the data. Furthermore, the clinical importance of the association was exaggerated. Biswas (2001) showed that the incidence of new onset diabetes possibly related to starting treatment with olanzapine was 0.09%. Indeed the claim had proved impossible to substantiate by clinical experience, even using very large databases of medical records.

The Panel noted Sections 4.4 and 4.8 of the Zyprexa SPC. The claim in question stated 'Olanzapine is associated with a clinically important and significant increased risk of diabetes'. The letter gave no further information such that the reader could put that risk into a clinical context. The Panel noted that a number of limitations were referred to by the authors of Koro *et al* and there was no information about the statistical significance of the difference between olanzapine and risperidone. The Panel considered that by not quantifying the risk of diabetes associated with olanzapine the claim was misleading, exaggerated and did not reflect all the available evidence. Breaches of the Code were ruled which were appealed.

The Appeal Board noted that the claim at issue 'Olanzapine is associated with a clinically important and significant increased risk of diabetes' was a quote from the conclusion of Koro *et al*. In that regard the Appeal Board noted that the bullet point 'Risperidone is not associated with a significantly increased risk of diabetes' which followed the claim had paraphrased the findings of Koro *et al*. The Appeal Board also noted the letter did not quantify the risk. The Appeal Board considered that although the claim at issue was true, and a direct

quote from Koro *et al*, in the context of the 'Dear Doctor' letter it was misleading, exaggerated and did not reflect all the available evidence. The Appeal Board upheld the Panel's rulings of breaches of the Code.

Lilly stated that the letter was alarmist and contained a number of misleading and inappropriate statements. For this reason Lilly alleged that Janssen-Cilag had failed to maintain the high standards expected of the pharmaceutical industry.

The Panel considered that by not quantifying the risk of diabetes associated with olanzapine and referring to a 'clinically important and significant increased risk' the 'Dear Doctor' letter was alarmist; Janssen-Cilag had not maintained a high standard. The Panel therefore ruled a breach of the Code. This was appealed.

The Appeal Board considered that that by not quantifying the risk of diabetes associated with olanzapine and by referring to a 'clinically important and significant increased risk with olanzapine' the 'Dear Doctor' letter was alarmist; high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Lilly alleged that by distributing this letter Janssen-Cilag had breached a previous undertaking made in an earlier case of scaremongering about diabetes (Case AUTH/1236/10/01). The net effect of these various shortcomings was such that Janssen-Cilag had brought discredit upon and reduced confidence in the pharmaceutical industry.

The Panel noted that in Case AUTH/1236/10/01 it had ruled that Janssen-Cilag representatives were misleading health professionals about data in relation to glucose monitoring. The Mir and Taylor paper stated that blood glucose monitoring was essential for all patients starting on clozapine or olanzapine. The SPC for Zyprexa stated that appropriate clinical monitoring was advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus. There was no mention of mandatory monthly glucose monitoring. The Panel had considered that all the available evidence had not been reflected. Breaches of Code had been ruled.

Turning to the case now before it, Case AUTH/1361/9/02, the Panel considered that the claims and material at issue were sufficiently different to those considered in Case AUTH/1236/10/01 such that they were not caught by the undertaking given in that case and no breach of the Code was ruled. No breach of Clause 2 was also ruled.

Eli Lilly and Company Limited complained about a 'Dear Doctor' letter (ref APIVER020802 03054a) promoting Risperdal (risperidone) sent by Janssen-Cilag Ltd and Organon Laboratories Limited. The letter headed 'Can your patients with schizophrenia handle diabetes too?' discussed the results of a recently published paper, Koro *et al* (2002), and stated 'The study concluded: 'Olanzapine is associated with a clinically important and significant increased risk of diabetes'. The study also showed: Risperidone is not associated with a significantly increased risk of diabetes. I hope that the conclusions of this study, combined with the weight of evidence for the efficacy of Risperdal, give you confidence to continue to prescribe the Risperdal range as a first choice antipsychotic therapy'.

Janssen-Cilag stated that the letter was distributed to consultant psychiatrists, specialist registrars and certain GPs. Lilly marketed Zyprexa (olanzapine).

Janssen-Cilag responded throughout on behalf of both itself and Organon Laboratories.

1 Heading 'Can your patients with schizophrenia handle diabetes too?' and the opening statement 'For people with schizophrenia, living with the disorder can be enough of a struggle without having the added burden of diabetes'

COMPLAINT

Lilly alleged that the heading set the tone of the letter indicating that the topic of diabetes and schizophrenia was important enough to warrant the issuing of a 'Dear Doctor' letter. The question posed exaggerated the importance of the topic and the effect was to cause alarm. This was evidenced by the fact that a number of doctors had already contacted Lilly as a result of reading the heading and letter.

In fact the heading and patient picture painted by the first paragraph were misleading in the context of the information provided in the body of the letter. Based on Koro *et al* it was most unlikely that an individual psychiatrist would find himself facing the dilemma posed: of 19,637 patients studied by Koro only 7 receiving olanzapine and 7 receiving risperidone developed treatment emergent diabetes. Furthermore results from the prescription-event monitoring (PEM) study conducted on olanzapine by the Drug Safety Research Unit (Biswas *et al* 2002) showed that the incidence of new cases of diabetes possibly related to starting treatment with olanzapine was 0.09% (8/8,858). The scenario outlined was spurious (breach of Clause 7.2) and designed to alarm unnecessarily.

RESPONSE

Janssen-Cilag stated that the mailer was considered necessary because the BMJ had published an important new study, using the most up-to-date methodology, which provided additional information on the subject of antipsychotics and diabetes (a subject which was very topical and clinically relevant to psychiatrists and other interested groups).

Janssen-Cilag noted that the Zyprexa summary of product characteristics (SPC) stated:

'Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring

is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.'

The addition of this warning to the Zyprexa prescribing information was the subject of a 'Current Problems in Pharmacovigilance' publication by the Committee on Safety of Medicines (CSM) and the Medicines Control Agency (MCA).

Currently and at the time of issuing the mailer, there was no mention of diabetes or hyperglycaemia in the Risperdal SPC. Janssen-Cilag stated that it had, however, submitted for a variation. All of the available evidence regarding Risperdal and diabetes/hyperglycaemia (including the publication by Koro *et al*) had been supplied to the MCA and this had been subject to an independent review. As a result Janssen-Cilag had proposed to the MCA the addition of the following text in the Undesirable Effects of the SPC:

'Hyperglycaemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment.'

This information was supplied in confidence until the wording was finalised by the MCA. Janssen-Cilag had received verbal agreement on the wording but it was unable to allow the above information to be released until it was confirmed in writing by the MCA.

The importance in the difference between the wordings in the respective SPCs was shown by the CSM and MCA's concerns on Zyprexa being such to require issuing a 'Current Problems' article.

The purpose of the mailer was not, as Lilly alleged, to cause alarm, but to promote Risperdal and to clarify the misinformation that was currently in the market with respect to diabetes and hyperglycaemia and their relationship to certain antipsychotic medicines. Misinformation relating to this (particularly that misconception that hyperglycaemia and diabetes were a class effect and that all antipsychotics had an equal effect in this regard) was in part the result of Lilly's promotional activity and its own medical information letter. An example of a Lilly promotional piece, in which a selective study was quoted, was provided. This piece remained in circulation despite the availability of other studies (including Koro *et al*), which was blatantly an attempt to alter the balance of information. Lilly only withdrew this piece following a direct request from Janssen-Cilag. The Lilly medical information letter on this issue was subject to a previous ruling (Case AUTH/1325/5/02) in which it was found to be in breach of Clause 8.1.

It was difficult to overestimate the importance to a patient of becoming diabetic as a consequence of a treatment for schizophrenia. Diabetes was a life threatening illness, often requiring continuous, lifelong daily medication in order to avoid grave consequences for health. These consequences could include considerable risk of coma, death, blindness, infection, kidney failure, heart attack, stroke and amputation if diabetes was not well controlled. For schizophrenics, who already suffered from an increased risk of cardiac mortality, and who typically had difficulty remembering to take medication regularly, the risks were particularly severe. Additionally, since many doctors did not yet recognize the long-term risks inherent in some antipsychotics of precipitating hyperglycaemia and diabetes, they might not expect to see early warning signs of hyperglycaemia in schizophrenics, adding more risk for patients.

The topic of diabetes and schizophrenia was therefore an area of great scientific and medical interest and this was reflected in the increasing number of publications on the subject and the number of scientific meetings, both industry sponsored and independent, in which the subject of metabolic disturbances and diabetes had been an important part of the agenda. A search of the scientific literature database EMBASE (search criteria: Neuroleptic Agent and Diabetes Mellitus) revealed an increasing trend for such publications. There were 143 hits for the last 12 months compared to 81 and 63 for the previous 2 years respectively.

Furthermore, as Janssen-Cilag was sure was the case for Lilly, its medical information department had received numerous enquiries from health professionals regarding the relationship between diabetes and Risperdal (a high number of which were specifically asking questions comparing Risperdal and Zyprexa).

The CSM and the MCA were also sufficiently concerned by the association between diabetes and Zyprexa to include emerging clinical data on the topic in their publication entitled 'Current Problems in Pharmacovigilance'. In the April 2002 issue, reference was made to 'Olanzapine (Zyprexa) and diabetes'. It alerted the reader both to the fact that olanzapine could adversely affect blood glucose and also to reports of hyperglycaemia, ketoacidosis and/or coma associated with olanzapine usage including one with a fatal outcome. It also stated that the product information for olanzapine had been amended to include appropriate statements regarding the above and indeed the Zyprexa SPC stated that some cases of hyperglycaemia were fatal.

Janssen-Cilag noted that at point 2 below, Lilly had selectively referred to risperidone in other jurisdictions (notably Japan and Australia) and so in this instance Janssen-Cilag considered it important to note action taken with regard to olanzapine in such countries. In Japan (April 2002), the Ministry of Health, Labour, and Welfare required Lilly to update the Zyprexa label with significant safety changes, including a contraindication in patients with diabetes, and issue of the equivalent of an actual 'Dear Doctor' letter ('Emergency Safety Information'). The Australian Therapeutic Goods Administration had approved text for olanzapine in which 'appropriate clinical monitoring is advisable in diabetic patients' was included.

Janssen-Cilag considered that Lilly's continued minimization of these serious, labelled adverse events in the UK posed a substantial potential public health risk and it was somewhat surprised about Lilly's position that the importance of diabetes was being exaggerated, given that it manufactured treatments for diabetes. Given the warnings to clinicians concerning the need for monitoring in patients with

diabetes and those with risk factors in both the olanzapine SPC and the CSM's Current Problems article, Janssen-Cilag found it impossible to accept that the letter could be classed as exaggerating the importance of the topic. The letter quoted a published paper, which provoked an important question that should be considered when making a decision on whether Zyprexa or Risperdal should be prescribed.

Janssen-Cilag noted that Lilly alleged that the heading and patient picture painted by the first paragraph were misleading in the context of the information provided in the body of the letter as it was most unlikely that an individual psychiatrist would find himself facing the dilemma posed: of 19,637 patients studied by Koro *et al* only 7 receiving olanzapine developed treatment emergent diabetes. This was a serious misrepresentation of the study, which deliberately sought to minimise the importance of the findings. The observed rate was 9 incident cases of diabetes among 970 olanzapine exposed schizophrenia patients, which approximated to 0.9%. In a statement in The Pharmaceutical Journal (August 2002) Lilly agreed with such figures and stated, 'The actual number of cases of new onset diabetes observed in patients on Zyprexa was 7 out of 970 – less than 1 per cent. This was similar to the number of cases found during clinical trials with Zyprexa and noted in the SmPC'.

If recent trends continued, a UK consultant psychiatrist might put several hundred schizophrenic patients on olanzapine during his or her professional life, and so this was an extremely important finding for any general psychiatrist to know about. They might now expect several of these patients to develop diabetes and if they anticipated this then patients were likely to be less at risk because their doctor was more likely to detect new cases early.

Koro *et al* was particularly important to a UK audience because it was a large, good quality study published in the BMJ, used a UK database, and was reflective of the wider literature. In Janssen-Cilag's view the study provided the most recent and up-to-date evidence for an independent effect of olanzapine and risperidone on the risk of diabetes. The study objective was to quantify the association between olanzapine and diabetes, using a population based nested case-control study design using the UK General Practice Research Database comprising 3.5 million patients. Any relationship between diabetes and medicine was adjusted for by other possible co-morbid factors. The study found that olanzapine-treated patients had a significantly increased risk of developing diabetes compared to both non-users of antipsychotics (odds ratio was 5.8 times more, 95% confidence interval 2-16.7) and to users of conventional antipsychotics (odds ratio was 4.2 times more, 95% confidence interval 1.5-12.2). Risperdal treated patients were found to have a non-significant increased risk of developing diabetes compared to non-users of antipsychotics and those taking conventional antipsychotics.

In a response to a letter published in the eBMJ the study authors stated 'We do not view this as inconsequential from a public health perspective since an additional 57,600 cases of new onset diabetes would be expected to occur among the estimated 9,000,000 global olanzapine users. In other words, the 9 cases of diabetes among those exposed to olanzapine within the previous 3 months is 7 more cases than would have been observed by chance (p=0.002). We maintain that this does constitute a moderate degree of evidence for an association'.

Furthermore, the study demonstrated that not all antipsychotics had an equal effect on the risk of diabetes, contrary to what was stated in Lilly's promotional material.

Janssen-Cilag therefore denied that the scenario outlined was spurious or designed to cause unnecessary alarm and it therefore strongly denied a breach of Clause 7.2.

PANEL RULING

The Panel considered that risk of diabetes would be a topic of interest to the audience. It was a question of whether the findings of Koro *et al* as stated in the letter reflected the clinical situation. The Panel noted that Koro *et al* set out to quantify the risk of diabetes associated with olanzapine and risperidone in patients with schizophrenia. Of 19,637 patients 451 developed diabetes during a mean follow-up period of 5.2 years. The incidence rate of diabetes among all patients with schizophrenia treated with antipsychotics was 4.4/1000 person years. Olanzapine significantly increased the risk of developing diabetes compared with non-users of antipsychotics (odds ratio 5.8, 95% confidence interval 2.0 – 16.7, p=0.001) and those taking conventional antipsychotics (odds ratio 4.2, 95% confidence interval 1.5 to 12.2, p=0.008). Patients taking risperidone had a non-significant increased risk of developing diabetes than non-users of antipsychotics (odds ratio 2.22, 95% confidence interval 0.9 to 5.2, p=0.079) and those taking conventional antipsychotics (odds ratio 1.6, 95% confidence interval 0.7 to 3.8, p=0.290). The statistical significance of the difference between olanzapine and risperidone was not given. The authors stated that one of the study's limitations was that its analysis lacked power to compare the odds ratios between olanzapine and risperidone users. Other limitations noted by the authors were that medicine use was inferred from automated prescribing data and patient specific data were limited to that recorded in the general practice database. There was no direct information on the severity of schizophrenia, race, social class or weight gain and thus no adjustment for these variables. The use of antipsychotics before the three month exposure period was ignored and therefore patients might have used different antipsychotics during the study period.

The Panel noted that Biswas *et al* was a pharmacovigilance study of 8,858 patients using prescription-event monitoring to assess the post-marketing safety profile of olanzapine in patients managed by GPs in primary care. There were 8 reports of diabetes mellitus assessed as possibly due to olanzapine. The incidence of reported events in the study were lower than those reported in published trials. The reasons given were that clinical trial

subjects were followed up more intensely, whereas patients might not report minor complaints to their GPs. When patients were monitored by the psychiatrist or community psychiatric nurses, events might not be recorded in GP records and GPs might fail to report all events on the green forms.

The Panel considered that the overall tone of the letter suggested that olanzapine-treated patients were likely to develop diabetes whereas those treated with Risperdal were not. The letter stated that 'Olanzapine is associated with a clinically important and significant increased risk of diabetes'. The Panel noted, however, that Section 4.4 of the Zyprexa SPC stated that 'Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases'. Section 4.8 of the SPC stated 'In clinical trials with olanzapine in over 5,000 patients with baseline non-fasting glucose levels ≤ 7.8mmol/l, the incidence of non-fasting plasma glucose levels ≥ 11mmol/l (suggestive of diabetes) was 1%, compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels ≥ 8.9mmol/l but < 11mmol/l (suggestive of hyperglycaemia) was 2%, compared to 1.6% with placebo' (ref eMC). Thus although there was an increased risk of diabetes with Zyprexa it was still not a very common side-effect. The Panel considered that by not quantifying the risk of diabetes and referring only to a 'clinically important and significant increased risk' the letter was alarmist and misleading as alleged. The Panel ruled a breach of Clause 7.2 of the Code.

APPEAL BY JANSSEN-CILAG AND ORGANON

Janssen-Cilag stated that the MCA had now approved the wording in the Risperdal SPC regarding hyperglycaemia and diabetes. The wording, to be positioned under 'Undesirable effects' (section 4.8), would read:

'Hyperglycaemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment'.

This information had now been made public; however it had no bearing on this case.

Janssen-Cilag stated that the effect of antipsychotics on glucose metabolism was an area of emerging scientific debate and reference to such issues were allowed under the Code. It was acceptable under the Code to report the results of a single trial provided the results were not inconsistent with the overall balance of data. Koro *et al* was reflective of the growing weight of scientific evidence on this clinically important issue. Janssen-Cilag acknowledged that any one study in isolation was rarely sufficient to definitively prove a hypothesis, but it was the collective evidence that resulted in changes in medical practice. It was this evidence that Janssen-Cilag wished to present as the basis of its appeal.

Janssen-Cilag noted that the Panel considered that the mailer implied that olanzapine patients were likely to develop diabetes but the statement on the mailer clearly read that olanzapine was associated with an increased risk. Janssen-Cilag disputed that the recipients of the mailer would infer that olanzapine was likely to cause diabetes. The word 'risk' as used in this context was generally accepted to mean relative risk (a relative probability ie patients were n times more likely to develop a condition compared to when on another medicine), whereas the Panel had related this to absolute risk (a frequency ie that n percent of patients on this medicine would develop this condition) by describing the risk as likely.

Janssen-Cilag noted that the Panel considered the tone of the letter suggested that patients receiving olanzapine were likely to develop diabetes whereas patients receiving Risperdal were not. Koro *et al* looked at the relative risk of developing diabetes on olanzapine, Risperdal, typical antipsychotics and no antipsychotics. The conclusion of the study, reflected in the mailer, was that patients on olanzapine were significantly more likely to develop diabetes. The statement 'Olanzapine is associated with a significant increased risk of diabetes' was consistent with the relative measure of risk adopted by the study and did not mean or imply that olanzapine was likely to cause diabetes in terms of absolute risk.

Alarmism was the unnecessary raising of concern. The mailer did not state nor was it intended to state that olanzapine was likely to cause diabetes, which would have been alarmist, as the statement only referred to a significant increased risk ie significantly increased relative risk. The absolute risk of diabetes according to the olanzapine SPC was common (1-10%) however the mailer only referred to an increased risk. Even if the absolute risk were low, the relative risk was found to be increased by Koro *et al* and it was this which was reflected in the mailer.

The Panel had noted the wording on the olanzapine SPC with regard to glucose and diabetes. Janssen-Cilag stated that the available evidence, including Koro *et al*, was not inconsistent with the olanzapine SPC. The olanzapine SPC stated that in clinical trial patients, the incidence of non-fasting plasma glucose levels >11mmol/l suggestive of diabetes was 1% compared with 0.9% with placebo. However, Koro *et al* looked at a very different set of patients in the community based on nested GP observations. Clinical trial patients were carefully selected and consequently were usually healthier than the general disease population. The statements were therefore not inconsistent with the olanzapine SPC because they referred to a different population and were therefore not misleading.

Janssen-Cilag thus considered that the mailer was not alarmist and was consistent with the olanzapine SPC and therefore appealed against the ruling of a breach of Clause 7.2. The aspect of not quantifying the risk of diabetes was dealt with below (point 3).

COMMENTS FROM LILLY

Lilly noted that the Risperdal SPC was updated in December to include the statement 'Hyperglycaemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment', a fact not previously communicated to Lilly by Janssen-Cilag. Whilst Lilly acknowledged that this change had not happened at the time of use

of the 'Dear Doctor' letter, the data that would have led the MCA to approve the updated wording of the Risperdal SPC had, surely, been available to Janssen-Cilag for some considerable time. Lilly took issue with Janssen-Cilag's observation that this change had no bearing on this case.

Lilly had not taken issue with the fact that there were case studies and retrospective database analyses that had highlighted possible, numerically small associations between diabetes and all antipsychotics. Lilly objected to attempts to convey that there was credible and scientifically valid data that could be used to differentiate definitively between antipsychotics. Such data did not exist, as the studies had not been done. Indeed, bearing in mind that the vast majority of the prevalence of diabetes in both the mental health and general populations was present for reasons other than antipsychotic use, any attempt to imply a difference in risk was in itself potentially misleading.

Lilly noted that Janssen-Cilag had acknowledged that any one study in isolation was rarely sufficient to definitively prove a hypothesis, but it was the collective evidence that resulted in changes in medical practice. Lilly supported this view and cited it as one of the key reasons why it considered that attempting to address the issue of diabetes, direct to physicians with the 'Dear Doctor' letter, using only Koro *et al* as a reference, was misleading.

It was Lilly's view that there was nothing in any of the points Janssen-Cilag made that significantly added to the data upon which the Panel had ruled.

APPEAL BOARD RULING

The Appeal Board accepted that the risk of diabetes was a topic of interest to the audience. It noted the statements in both products' SPCs and the data referred to by the parties.

The Appeal Board considered that the heading to the letter 'Can your patients with schizophrenia handle diabetes too?' would raise concern in those who read it. The subsequent text implied that there was a clinically important and significant difference between olanzapine and risperidone in their propensity to cause diabetes. This had not been proven. The letter gave the reader no indication as to the incidence of diabetes caused by either medicine. The Appeal Board considered that the heading to the letter was alarmist and misleading as alleged and upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

2 Claim 'Risperidone is not associated with a significantly increased risk of diabetes'

COMPLAINT

Lilly noted that the letter drew the doctor's attention to only one of the many publications on the subject of the epidemiology of diabetes in patients with schizophrenia (Koro *et al*) – no other literature was cited. Two statements about the risk of diabetes in relation to two medicines used to treat schizophrenia were made in the letter, both referenced to Koro *et al*.

The second of these, 'Risperidone is not associated with a significantly increased risk of diabetes', was alleged not to reflect the totality of the data (Lilly referred to a poster by Koller *et al* 2002 which highlighted the association of risperidone with diabetes based on FDA Medwatch data). The claim did not reflect the international regulatory status of Risperdal in that the SPCs for risperidone in Australia and Japan recorded an association between Risperdal and diabetes. Lilly alleged that the claim was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Janssen-Cilag stressed that this was not a claim. The statement was factual and reflected the conclusion of Koro *et al* that was in agreement with the vast majority of the available literature. Janssen-Cilag noted that the Code did not state that all of the literature on a topic must be cited in promotional material, indeed the Code made no requirement of any company *per se* to acknowledge in print the existence of particular publications which their competitors favoured. The Code, however, required that statements reflected an up-to-date evaluation of the literature.

As previously discussed, there had been a great deal of literature published investigating the involvement of antipsychotic medications in the development of metabolic disturbances, including the more severe manifestations such as diabetes, diabetic ketoacidosis and death. A growing number of these published reports, abstracts, and review papers strongly suggested that in comparison to other newer antipsychotics (eg Risperdal), olanzapine was associated with a greater risk of metabolic disturbances and therefore supported the conclusion of Koro *et al*. This was further supported by the preponderance of published case reports associating metabolic disturbances with antipsychotics, olanzapine in particular.

Janssen-Cilag stressed that the publication by Koro *et al* did not claim that Risperdal was never associated with diabetes. The study merely concluded that, in contrast with olanzapine, any possible increase in incidence was not found to be statistically significant when compared to both non-users of antipsychotics and to users of conventional antipsychotics.

Lambert *et al* had recently reported the results of a Bristol-Myers Squibb sponsored study in which the risk of developing diabetes mellitus in patients with schizophrenia exposed to clozapine, olanzapine, risperidone, quetiapine and various typical antipsychotics was examined. In this matched case control study using a USA population, the results were entirely consistent with those of Koro *et al*. Exposure to olanzapine significantly increased the risk of developing diabetes (odds ratio 1.30, 95% CI 1.17-1.45) compared with conventional antipsychotics. The odds ratio for exposure to risperidone was not reliably greater than 1.

Similarly the results of the study by Gianfrancesco *et al* (2002), which used records from several thousand psychosis patients, suggested that olanzapine

increased the risk of acquiring or exacerbating diabetes whereas the risk was not significantly increased in patients receiving risperidone.

Given this preponderance of evidence and the distinct differences in the SPCs for Risperdal and olanzapine, it was frankly misleading for Lilly not to acknowledge the differences between antipsychotics in its promotional material.

Janssen-Cilag repeated that generally, when it dealt with complaints made under the Code, it commented only on the circumstances pertaining to the UK. However, Lilly had selectively made reference to the prescribing information for Risperdal in Australia and Japan and alleged that the claim 'Risperidone is not associated with a significantly increased risk of diabetes' was not compatible with Risperdal's international regulatory status.

As noted in point 1 above, although there was no current mention of diabetes or hyperglycaemia in the UK Risperdal SPC Janssen-Cilag had submitted a variation. The text was likely to read, 'Hyperglycaemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment'. The same text appeared within the Australian prescribing information. In Japan hyperglycaemia was listed as an undesirable effect. In contrast to the prescribing information for olanzapine in each of these countries, there was no recommendation for appropriate clinical monitoring. Neither was this a recommendation in any of the countries in which Risperdal was licensed.

While the SPC reflected spontaneous reporting of adverse events, the reporting system was not set up to measure risk and was not meant to imply directly causality. Koro *et al* was specifically set up to measure risk and was able to find a statistical difference in terms of risk of developing diabetes between patients treated with olanzapine and those treated with Risperdal.

The claim at issue was both consistent with the SPC in the UK and internationally and was an accurate report of the study, which also reflected the body of current evidence. Janssen-Cilag therefore denied any breach of Clause 7.2.

PANEL RULING

The Panel noted that the current Risperdal SPC did not refer at all to either hyperglycaemia or diabetes as possible side-effects of therapy. The Australian prescribing information for Risperdal read 'Hyperglycaemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment'. In Japan hyperglycaemia was listed as an undesirable effect. The Panel considered that the claim 'Risperidone is not associated with a significantly increased risk of diabetes' implied that there was thus some risk of diabetes but not a significant one. The Panel did not consider that the claim itself was inconsistent with the data for Risperdal and so ruled no breach of Clause 7.2 of the Code. This ruling was appealed.

During its consideration of this case the Panel was concerned about the context of the claim at issue. The 'Dear Doctor' letter stated:

'The study concluded:

Olanzapine is associated with a clinically important and significant increased risk of diabetes.

The study also showed:

Risperidone is not associated with a significantly increased risk of diabetes.'

The Panel noted its comments about Koro *et al* and its ruling at point 1 above. It considered that although there was data to support the claim as stated, the context meant that the claim was misleading. In this regard the Panel noted its ruling at point 3 below. The Panel requested that its concerns be drawn to the attention of Janssen-Cilag.

APPEAL BY LILLY

Lilly noted that Janssen-Cilag agreed that Koro *et al* could not support a claim that Risperdal was not associated with diabetes, indeed due to methodological flaws most of the literature on this subject was incapable of answering such questions. However Lilly noted the findings of Hedenmalm *et al* (2002) which showed that the WHO Drug Surveillance system had identified a definite statistically significant association of diabetes with risperidone. Thus Lilly took the view that the claim 'Risperidone is not associated with a significantly increased risk of diabetes' was misleading in breach of Clause 7.2.

COMMENTS FROM JANSSEN-CILAG AND ORGANON

Janssen-Cilag noted that Lilly had stated that the findings reported by Hedenmalm *et al* 'identified a definite statistically significant association of diabetes with risperidone'. However, the study was designed to look for cases of glucose intolerance, not diabetes. Lilly's interpretation of the results was inaccurate as a significantly increased risk of glucose intolerance was not the same as an increased risk of diabetes. Further Hedenmalm *et al* was published after the letter was sent and was not available to Janssen-Cilag at the time of preparing and distributing the letter. Lilly's argument was therefore invalid on this point and should be dismissed.

Despite the date of publication of Hedenmalm *et al*, Janssen-Cilag submitted that there were numerous limitations of the methodology.

The WHO database was a useful signal detection tool, however many of the reports were incomplete resulting in possible bias. The Bayesian technique had high sensitivity but low specificity and this could result in false positives. The likelihood of a true association was higher when a quantitative association increased over time. The paper showed that the association for both olanzapine and clozapine was increasing but that for Risperdal was decreasing suggesting a false positive result. Furthermore, this was the only study showing an association with Risperdal and the result was not supported by the balance of evidence. The actual number of glucose intolerance cases in the database was much lower with Risperdal (n=138) than clozapine (480) or

olanzapine (253). It was important to note the number of years since marketing authorization as Risperdal had been available for 9 years and olanzapine for 5 years. The investigators noted that the co-existence of insulin or oral hypoglycaemics, indicative of pre-existing diabetes, was itself associated with the highest odds ratio for glucose intolerance. However the individual medicines had not been analysed to see if one group had proportionally more people taking hypoglycaemics than another. Thus Janssen-Cilag did not know whether the groups were equal for this important confounder. The paper stated that Risperdal had been the medicine of choice in patients with diabetes and so it was possible that more Risperdal patients had pre-existing diabetes. The information component was based on the number of case reports with a particular medicine, adverse reaction, specific adverse reaction combination and the total number of reports in the database. Therefore, the information component was skewed by the total number of adverse events in the database and this had a negative impact on any medicine that was generally well-tolerated.

Regardless of the findings of Hedenmalm *et al*, the broad weight of evidence supported the claim that 'Risperdal was not associated with a significantly increased risk of diabetes'.

Janssen-Cilag agreed with the Panel's ruling and concluded that Lilly's appeal had little merit.

FURTHER COMMENTS FROM LILLY

Lilly made no further comments.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'Risperidone is not associated with a significantly increased risk of diabetes' was referenced to Koro *et al*. What Koro *et al* had actually stated was that 'Patients taking risperidone had a non-significant increased risk of developing diabetes than non-users of antipsychotics (2.2, 0.9 to 5.2) and those taking conventional antipsychotics (1.6, 0.7 to 3.8)'. The Appeal Board noted that the findings of Koro *et al* had thus been paraphrased such that within the context of the 'Dear Doctor' letter it gave a misleading impression about the risk of developing diabetes with Risperdal.

The Appeal Board also noted that when the 'Dear Doctor' letter had been sent out the Risperdal SPC made no reference to the precipitation of diabetes or hyperglycaemia. Janssen-Cilag was, however, in discussion at the time with the MCA to amend the SPC so as to include the statement 'Hyperglycaemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment'.

The Appeal Board considered that the claim at issue did not accurately reflect the available evidence. Readers would assume that there was no association at all between risperidone and altered glucose metabolism and that was not so. The Appeal Board considered that the claim was misleading and ruled a breach of Clause 7.2 of the Code. The appeal on this point was successful.

3 Claim 'Olanzapine is associated with a clinically important and significant increased risk of diabetes'

The claim was referenced to Koro *et al*.

COMPLAINT

Lilly stated that this was a very strong claim against olanzapine based on very flimsy data. The significance of the finding was called into question in the discussion section of Koro *et al* where the authors acknowledged the failure of the study methodology to control for a number of important confounding factors. In addition the number of cases on which the findings for both medicines were based was tiny and the size of the confidence interval around the hazard ratio for olanzapine was very large. Considerable doubt about the validity of Koro *et al* had been expressed in correspondence on the BMJ website. The claim was not based on a sound statistical evaluation of the data and was alleged to be in breach of Clause 7.2. Furthermore, the clinical importance of the association was exaggerated (breach of Clause 7.10). Biswas (2001) showed that the incidence of new onset diabetes possibly related to starting treatment with olanzapine was 0.09%. Indeed the claim made by Janssen-Cilag by way of its use of this quotation had proved impossible to substantiate by clinical experience, even using very large databases of medical records and was thus in breach of Clause 7.9.

RESPONSE

Janssen-Cilag stressed that contrary to what Lilly alleged, this was a quotation taken directly from a published paper, which as it had demonstrated, was important, apposite for the UK and in concordance with the available evidence.

Furthermore, this was a publication in the prestigious BMJ. All articles submitted for publication in the BMJ were peer reviewed. A high proportion of submissions were rejected due to insufficient originality, serious scientific flaws, or the absence of a message that was important to a general medical audience. Janssen-Cilag was confident that if Koro *et al* was so seriously flawed and not based on a sound statistical evaluation, as suggested by Lilly, it would not have been published in the BMJ. All studies had limitations and the authors controlled for those limitations as far as were possible. The authors had answered the methodological questions raised in subsequent public correspondence.

The statistical evaluation was sound and Janssen-Cilag therefore strongly denied a breach of Clause 7.2.

Janssen-Cilag had already covered the importance of the clinical association previously in this response. The association of diabetes with antipsychotics was extremely serious and was the subject of much scientific interest at present. The incidence of diabetes for olanzapine was 10.0 (5.2-19.2 95% CI) per 1000 patient years of exposure to the medicine according to the cohort analysis carried out by Koro *et al* – this meant for every hundred patients treated with olanzapine it would take one year for one patient to develop diabetes. This was clearly a clinically

important association. It also occurred in patients receiving olanzapine at nearly twice the rate of patients receiving Risperdal and conventional antipsychotics. This was surely an increased rate that should be regarded as significant, even were it not for the significantly increased rate of association that other analyses in Koro *et al* had found and which were also in line with the other available evidence.

This was not an exaggerated claim and Janssen-Cilag strongly denied a breach of Clause 7.10.

The Code demanded that information and claims about side effects must reflect available evidence or be capable of substantiation by clinical experience. In response to issues raised in the eBMJ, the authors stated: 'this publication is consistent with previous reports from the literature, including studies, case series and post marketing surveillance reports that suggest a unique association between olanzapine use and diabetes'. Given their extensive reference list and publications including Lambert *et al*, Gianfrancesco *et al* etc, Janssen-Cilag submitted that the emerging evidence supported such a quote.

The information about side effects reflected available evidence and Janssen-Cilag strongly denied a breach of Clause 7.9.

PANEL RULING

The Panel noted that Section 4.4 of the Zyprexa SPC stated that 'Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases'. Section 4.8 of the SPC stated 'In clinical trials with olanzapine in over 5,000 patients with baseline non-fasting glucose levels ≤ 7.8mmol/l, the incidence of non-fasting plasma glucose levels ≥ 11mmol/l (suggestive of diabetes) was 1%, compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels ≥ 8.9mmol/l but < 11mmol/l (suggestive of hyperglycaemia) was 2% compared to 1.6% with placebo' (ref eMC). The claim in question stated 'Olanzapine is associated with a clinically important and significant increased risk of diabetes'. The letter gave no further information such that the reader could put that risk into a clinical context. The Panel noted its comments about Koro *et al* and its ruling at point 1 above. A number of limitations were referred to by the authors and there was no information about the statistical significance of the difference between olanzapine and risperidone. The Panel considered that by not quantifying the risk of diabetes associated with olanzapine the claim was misleading, exaggerated and did not reflect all of the available evidence with regard to that particular side-effect. Breaches of Clauses 7.2, 7.9 and 7.10 were ruled. These rulings were appealed.

APPEAL BY JANSSEN-CILAG AND ORGANON

Janssen-Cilag noted that the jury was still out on the exact size of the relative risk. However, the balance of evidence showed that there was a significantly increased relative risk for patients on olanzapine to develop diabetes. What doctors needed to know was not the precise figure for increased relative risk as this was hard to determine and would vary by population. Most doctors would appreciate however that a significantly increased risk meant that they had to think more about what they prescribed and to use their clinical judgement to make the best decision for their patients. It was not necessary to quantify the degree of risk in this situation, neither was it possible to do so precisely, and so this claim was not misleading.

The clinical importance of diabetes for a patient with schizophrenia was not hard to appreciate – patients with schizophrenia already had an increased risk of cardiovascular disease, and often found it hard to adhere to daily medication. Moreover they were often relatively hard for a primary care team to follow up, so they might easily receive sub-optimal care. The clinical importance of Koro *et al* was that it confirmed other literature on diabetes in schizophrenia (see below) and if, according to the olanzapine SPC, 1% of patients in a clinical trial population had glucose evaluation suggestive of diabetes (≥ 11mmol/l), 3% had glucose evaluation (>8.9mmol/l) and diabetes was listed as a special warning, then there was greater implied clinical importance of this finding when it was also proven in a naturalistic setting. This part of the claim was not misleading and so Janssen-Cilag appealed against a ruling of breach of Clause 7.2.

Much of the current debate between Janssen-Cilag and Lilly had centred on the SPCs for Risperdal and olanzapine. Janssen-Cilag noted the example of cerivastatin which was withdrawn last year. At the time, the SPC for cerivastatin stated that myopathy and rhabdomyolysis had been reported rarely. However, 52 deaths worldwide were attributed to the medicine during post-marketing surveillance. This resulted in Bayer voluntarily withdrawing cerivastatin. A second example was the atypical antipsychotic clozapine. The current clozapine SPC summarised the history of the product: 'Clozaril can cause agranulocytosis. A fatality rate of up to 1 in 300 has been estimated when Clozaril was used prior to recognition of the risk of agranulocytosis and the need for routine blood monitoring. Since that time careful monitoring of the patient has been demonstrated to be effective in markedly reducing the risk of fatality'. These two examples demonstrated that an adverse event could be relatively rare and yet be associated with clinically important and serious consequences.

Janssen-Cilag noted that the Panel had considered that the claim 'Olanzapine is associated with a clinically important and significant increased risk of diabetes' was exaggerated when compared to the rates of diabetes quoted in the olanzapine SPC. The key point was that the SPC expressed absolute risks of developing a condition on a treatment, whereas Koro *et al* expressed the relative risk of developing a condition compared to another treatment. The two things were quite different. The claim referred to a significant increased relative risk, which was not quantified and was an accurate reflection both of Koro *et al* and of the balance of evidence. The clinical importance of the finding had already been addressed. The claim was not inconsistent with the olanzapine SPC as it was considering risk in a different manner and was not therefore exaggerated.

Janssen-Cilag noted that the Panel had acknowledged that there was an increased risk of diabetes with olanzapine but had stated that it was not a very common side-effect. Janssen-Cilag acknowledged that it was not very common although the olanzapine SPC cited it as common (1-10%). As discussed above, the incidence of an adverse event did not have to be very common to have serious clinical consequences. The studies highlighted below did not necessarily suggest a rate of diabetes greater to that stated on the olanzapine SPC. The important point was that medicine induced diabetes was a serious condition and prescribing clinicians should be aware of the risks. Janssen-Cilag therefore refuted that the mailer was exaggerated in that respect and appealed against the breach of Clause 7.10.

Janssen-Cilag noted that the Panel had considered that the claim did not reflect all of the available evidence.

The subject of antipsychotics and their effect on glucose and diabetes had generated numerous studies and publications. The most important of these were the pharmacoepidemiological studies, of which Janssen-Cilag was aware of several that independently assessed the number of patients receiving antipsychotic medication and the number of new cases of type 2 diabetes. As with all types of studies, there were limitations and the design varied between them. It was important to note that type 2 diabetes was initially managed by diet and exercise and so monitoring new prescriptions of diabetic treatment might not identify all patients that had new-onset diabetes.

Gianfrancesco *et al* (2002) looked at both new prescriptions and new diagnoses of diabetes and showed that olanzapine had a statistically significant diabetic effect versus no treatment. Risperidone patients were no more likely than untreated patients to develop diabetes.

Caro *et al* (2000) conducted a similar study which showed that olanzapine was associated with an increased risk of developing diabetes compared to risperidone.

Sernyak *et al* (2002) showed that the risk of developing diabetes was increased with clozapine, olanzapine and quetiapine but not risperidone.

Results from Lambert *et al* (2002) showed that olanzapine was associated with a greater risk of developing diabetes compared to conventional treatment. The results for risperidone were not statistically significant.

Kornegay *et al* (2002) looked at the UK General Practice Research Database (GPRD) and found an increased risk of incident diabetes among users of conventionals and atypicals. This trial was not sufficiently powered to identify a difference between the individual medicines.

Shermock *et al* (2002) conducted an analysis of the Veterans Administrative database and found that olanzapine was associated with a statistically significantly higher risk of developing diabetes compared to risperidone.

There were two studies by Cavazzoni *et al*. The first identified new prescriptions in the US for diabetic treatment in patients receiving antipsychotics. The results showed that there was no difference in the risk of diabetes with risperidone and olanzapine. The second used the UK GPRD and found that both typicals and atypicals had an increased hazard ratio for increasing diabetes and this was higher with the atypicals. Assessment of individual antipsychotics was limited by sample size.

Of the above studies, five demonstrated a statistically significant increased risk of diabetes with olanzapine, but not with risperidone. The other three were unable to detect a difference between the two atypicals because they were insufficiently powered. Therefore, the findings of Koro *et al* were corroborated by five of the studies. Furthermore, to Janssen-Cilag's knowledge, no such study existed that showed the opposite of Koro *et al* (ie that olanzapine was not associated with a statistically significantly increased risk of diabetes whereas risperidone was).

Janssen-Cilag noted Lilly's complaint made reference to a study by Koller *et al* entitled 'Risperidone – associated diabetes'. This was an analysis of the FDA's MedWatch Drug Surveillance System assessing case-reports of atypical-associated diabetes and other glucose-related abnormalities and therefore did not have the scientific rigour of a pharmacoepidemiological study. However, although Lilly only made reference to the report on Risperdal, a report had been produced for both olanzapine and risperidone. There were a total of 289 cases with olanzapine out of a total of 29,220 prescriptions, giving a rate of 0.99%. This was compared to 132 out of 43,232 with risperidone, giving a rate of 0.31%. MedWatch identified 23 deaths in olanzapine treated patients and 5 with risperidone.

In Janssen-Cilag's view the conclusions of Koro *et al*, 'Olanzapine is associated with a clinically important and significant increased risk of diabetes', was further substantiated by and was fully reflective of the balance of available evidence. It was therefore appropriate to report the results and conclusions of this study to the doctors who managed patients with schizophrenia. Janssen-Cilag believed that, on balance, the weight of evidence showed an association between olanzapine and the incidence of diabetes. The weight of evidence did not currently suggest that this was applicable to risperidone.

The evidence presented clearly demonstrated that Koro *et al* reflected the available evidence and Janssen-Cilag therefore denied a breach of Clause 7.9.

During the appeal process, it had come to Janssen-Cilag's attention that a study had just been published by Hedenmalm *et al*; as this data was not available at the time the letter was distributed, it had no bearing on this case.

COMMENTS FROM LILLY

Lilly stated that there was nothing in any of the points Janssen-Cilag made that significantly added to the data that the Panel ruled on.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'Olanzapine is

associated with a clinically important and significant increased risk of diabetes' was a quote from the conclusion of Koro *et al*. In that regard the Appeal Board noted that the bullet point which followed 'Risperidone is not associated with a significantly increased risk of diabetes' had paraphrased the findings of Koro *et al* (see point 2 above). The Appeal Board also noted its comments in point 1 above that the letter did not quantify the risk. The Appeal Board considered that although the claim at issue was true, and a direct quote from Koro *et al*, in the context of the 'Dear Doctor' letter it was misleading, exaggerated and did not reflect all of the available evidence with regard to that particular side effect. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.9 and 7.10. The appeal on this point was unsuccessful.

4 Alleged breach of Clause 9.1

COMPLAINT

Lilly considered that the letter was alarmist and contained a number of misleading and inappropriate statements which were in breach of various subsections of Clause 7 of the Code. For this reason Lilly alleged that Janssen-Cilag had failed to maintain the high standards expected of the pharmaceutical industry in breach of Clause 9.1.

RESPONSE

Janssen-Cilag stated that it continued to believe that the letter was in accordance with the Code and it vigorously refuted any allegation that it could be described as failing to maintain the high standards expected of the pharmaceutical industry. Janssen-Cilag maintained that it actually did the opposite, as its purpose was to inform its recipients of an important publication that should reverse the misinformation placed before health professionals by Lilly. In fact it was Lilly which had been at fault here and which was, Janssen-Cilag believed, attempting to conceal the serious nature of the long term, often irreversible and sometimes fatal side effects of diabetes with olanzapine.

Lilly also alleged that the letter was 'alarmist'. The purpose of the letter was to raise the awareness of the recently published article in a peer reviewed journal, the results of which reflected the data seen in numerous other studies and reflected the information recommended to be included in the respective SPCs of Risperdal and olanzapine. In the light of Lilly's promotional material and medical information letter, which incorrectly failed to differentiate the products, Janssen-Cilag rejected the assertion that this mailer could be classed as failing to maintain high standards and also disputed an allegation of a breach of Clause 9.1. Given the substantial amount of misinformation Janssen-Cilag viewed this mailer as an attempt to correct this and therefore maintain the expected standards of the industry, for the benefit of the patients and the prescribing doctors.

Janssen-Cilag therefore strongly denied any breach of Clause 9.1.

PANEL RULING

The Panel noted its rulings at points 1 and 3 above. It considered that by not quantifying the risk of diabetes associated with olanzapine and referring to a 'clinically important and significant increased risk' the 'Dear Doctor' letter was alarmist; Janssen-Cilag had not maintained a high standard. The Panel therefore ruled a breach of Clause 9.1 of the Code which was appealed.

APPEAL BY JANSSEN-CILAG AND ORGANON

Janssen-Cilag stated that accurate and timely reporting of data of particular interest to doctors reflected the highest standards of the pharmaceutical industry. There was now wide literature reporting on the relative risk of diabetes, which was of considerable interest to doctors, and Koro *et al* was one of the most methodologically robust papers available. It was specifically set up to measure relative risk and to arrive at a meaningful conclusion and was reported in a peer-reviewed journal of the highest quality. The paper had also attracted a great deal of attention. There had been 17 letters to the BMJ published in its rapid response site on the internet.

The propensity of atypicals to cause diabetes was also of great interest to health professionals in the UK. For example, The Maudsley Prescribing Guidelines recommended baseline and routine blood glucose monitoring for olanzapine patients but not for risperidone patients. In addition the NICE guidelines on schizophrenia (2002) stated 'If an atypical is causing diabetes or excessive weight gain, this must be monitored or consider changing to a different atypical or a conventional antipsychotic'. Furthermore, the CSM and MCA had considered the subject of sufficient interest to include it within their publication 'Current Problems in Pharmacovigilance'. In the April 2002 issue, reference was made to 'Olanzapine (Zyprexa) and diabetes'. It alerted the reader both to the fact that olanzapine could adversely affect blood glucose and also to reports of hyperglycaemia, ketoacidosis and/or coma associated with olanzapine usage including one with a fatal outcome.

Given this degree of interest in a subject, Janssen-Cilag was surely maintaining the high standards expected of the industry by bringing an important publication to the attention of relevant health professionals.

The mailer was not alarming and it was neither necessary nor possible to precisely quantify the risk. Janssen-Cilag considered dissemination of Koro *et al* to be a useful service to health professionals who cared for patients with schizophrenia.

Finally, Janssen-Cilag was committed to maintaining high standards at all times. The mailer about Koro *et al* recognised the professional standing of its recipients and Janssen-Cilag strongly appealed against a ruling of a breach of Clause 9.1.

COMMENTS FROM LILLY

Lilly stated that there was nothing in any of the points Janssen-Cilag made that significantly added to the data that the Panel ruled on.

APPEAL BOARD RULING

The Appeal Board noted its rulings at points 1 and 3 above and considered that by not quantifying the risk of diabetes associated with olanzapine and by referring to a 'clinically important and significant increased risk with olanzapine' the 'Dear Doctor' letter was alarmist; high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

5 Alleged breaches of Clauses 22 and 2

COMPLAINT

Lilly alleged that by distributing this letter Janssen-Cilag had breached a previous undertaking made in an earlier case of scaremongering about diabetes (Case AUTH/1236/10/01), a clear breach of Clause 22. The net effect of these various shortcomings was such that Janssen-Cilag had brought discredit upon and reduced confidence in the pharmaceutical industry (breach of Clause 2).

RESPONSE

Janssen-Cilag stated that in Case AUTH/1236/10/01 the Panel considered that a representative had misled a psychiatrist about the data relating to glucose metabolism. The representative was using a review paper (Mir and Taylor 2001), which stated that 'Blood glucose monitoring is essential for all patients starting on clozapine and olanzapine'. This was not consistent with the particulars given in the Zyprexa SPC. The SPC information did not appear to have been given to the psychiatrist. The Panel considered that Janssen-Cilag representatives were misleading health professionals about the data in relation to glucose metabolism. All the available evidence had not been reflected and Zyprexa had been disparaged; breaches of the Code were ruled. Janssen-Cilag accepted this ruling and the sales force were instructed to stop using the Mir and Taylor paper.

There was a superficial similarity between the two cases only in that the mailer referred to the same products and diabetes and hyperglycaemia. Apart from this Janssen-Cilag could not see how these two cases could be seen as being connected and therefore strongly refuted the allegation of a breach of Clause 22.

When considering an allegation of a breach of Clause 2, one could consider that the reasons for ruling a Clause 2 in this case could be categorized as follows: breach of an undertaking or a compromise of patient safety.

With regard to this mailer, Janssen-Cilag had clarified that the previous case (Case AUTH/1236/10/01) had no bearing on the case at hand, and therefore there was no breach of an undertaking. In sending this letter Janssen-Cilag was not compromising patient safety. Indeed, Janssen-Cilag argued that bringing the increased incidence of diabetes associated with olanzapine to the attention of psychiatrists would improve patient safety since psychiatrists would be more alert in detecting the symptoms and signs of diabetes or any exacerbation of established diabetes should these occur in one of their olanzapine patients.

Accordingly Janssen-Cilag strongly refuted the allegation of a breach of Clause 2.

PANEL RULING

The Panel noted that in Case AUTH/1236/10/01 it had ruled that Janssen-Cilag representatives were misleading health professionals about data in relation to glucose monitoring. The Mir and Taylor paper stated that blood glucose monitoring was essential for all patients starting on clozapine or olanzapine. The SPC for Zyprexa stated that appropriate clinical monitoring was advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus. There was no mention of mandatory monthly glucose monitoring. The Panel had considered that all the available evidence had not been reflected. Breaches of Clauses 7.2, 7.9, 8.1 and 15.2 of the Code had been ruled.

Turning to the case now before it, Case AUTH/1361/9/02, the Panel considered that the claims and material at issue were sufficiently different to those considered in Case AUTH/1236/10/01 such that they were not caught by the undertaking given in that case. No breach of Clauses 22 and 2 was ruled.

Complaint received **30 September 2002**

Case completed **14 February 2003**

CASE AUTH/1376/10/02

GALDERMA v LEO

Dovobet journal advertisements

Galderma complained about three advertisements for Dovobet (calcipotriol/betamethasone dipropionate) ointment issued by Leo. Dovobet was indicated for the treatment of stable plaque psoriasis.

Galderma alleged that the claim 'New Dovobet has changed psoriasis therapy for good' was an overstatement which could not be substantiated, since one could not claim that no future therapies would be developed to surpass current treatments for psoriasis. Galderma further alleged that it was inaccurate to claim that 'Dovobet has changed psoriasis therapy …' since the therapy was previously available by the use of individual products containing calcipotriol and betamethasone dipropionate.

The Panel considered that the claim at issue was ambiguous. Whilst the combination of calcipotriol and betamethasone in one medicine was an important change in psoriasis therapy, the phrase 'for good' exaggerated the magnitude of that change and the claim was thus misleading about the overall effect Dovobet would have on psoriasis therapy. Breaches of the Code were ruled.

In relation to the claims 'Remarkable results in just one week' and 'Remarkably fast and powerful in psoriasis', Galderma noted that Douglas *et al* had demonstrated a reduction in mean psoriasis area and severity index (PASI), after 1 week, of 40% with betamethasone and 47% with Dovobet. Whilst a reduction of 47% after one week was significant, to describe this as remarkable was, in Galderma's opinion, unacceptable.

The Panel noted the dictionary definition of 'remarkable' and considered that the claims 'Remarkable results in just a week' and 'Remarkably fast and powerful in psoriasis' overstated the Douglas *et al* data. The Panel considered the claims misleading and not capable of substantiation as alleged and ruled a breach of the Code.

Upon appeal by Leo the Appeal Board noted that Douglas *et al* had demonstrated statistically significant advantages in favour of Dovobet in relation to efficacy and speed of response compared with the monotherapies used alone. However, the Appeal Board considered the claims overstated the totality of the data and in that regard were misleading and not capable of substantiation. The Panel's rulings were upheld.

Galderma noted that the claim 'New Dovobet has changed psoriasis therapy for good – 73% of patients can now markedly improve or clear their psoriasis with visible results in just one week' appeared immediately under the strapline 'Remarkable results'. The positioning of these claims in the same visual field implied that 73% of patients' psoriasis cleared in just one week. Whereas the 73% was the mean PASI reduction after 4 weeks of treatment. Galderma alleged that the wording and positioning of these claims was ambiguous and likely to mislead; it was not made clear that the 73% reduction actually referred to the results after 4 weeks.

The Panel noted that the claim continued by referring to 'visible results in just one week'. In the Panel's view it appeared that 'one week' related not only to the 'visible results' but also to the marked improvement or clearance of psoriasis which was not so. The Panel considered that the claim was misleading in that regard and ruled a breach of the Code.

Galderma (UK) Limited complained about the promotion of Dovobet (calcipotriol/betamethasone dipropionate) ointment by Leo Pharmaceuticals. The materials at issue comprised an abbreviated advertisement (ref 4051) and two full advertisements (refs 4054 and 4061). Dovobet was indicated for the treatment of stable plaque psoriasis vulgaris amenable to topical therapy.

Galderma marketed Silkis (calcitriol).

1 Claim 'New Dovobet has changed psoriasis therapy for good'

This claim appeared in two advertisements, 4054 and 4061.

COMPLAINT

Galderma alleged that this was an overstatement which was not capable of substantiation, since one could not claim that no future therapies would be developed to surpass current treatments for psoriasis. Despite Galderma's request, Leo had failed to provide a satisfactory response with regard to the use of the claim.

Furthermore, Dovobet was a combination of two currently available therapies (calcipotriol and betamethasone dipropionate). Galderma therefore alleged that it was inaccurate to claim that 'Dovobet has changed psoriasis therapy …' since the therapy was previously available by the use of individual products containing the above active ingredients. Galderma did not concur with the comments made by Leo in intercompany correspondence, since individual products containing calcipotriol and betamethasone were currently used as combination treatment, applied at differing times in order to negate any risk of degradation effects.

Galderma alleged that the above claim was in breach of Clauses 7.2 and 7.4.

RESPONSE

Leo stated that Dovobet contained calcipotriol 50mcg/g and betamethasone dipropionate 0.5mg/g. Dovobet produced a clinical response significantly greater than either product given as monotherapy, prescribed twice daily, Douglas *et al* 2001 and data on file. Until Dovobet became available it was not possible to co-prescribe the full twice daily dose of the individual products because of their chemical and pharmaceutical incompatibility. Each degraded in the presence of the other. This incompatibility had been

overcome in Dovobet. Dovobet contained aramol E, an excipient found neither in calcipotriol nor betamethasone dipropionate formulations. As excipients could have an effect on the clinical response of the active substances in topical treatments, it was not true to say that this combination treatment was previously available. The treatment was, therefore, not available prior to the introduction of Dovobet and not only had treatment changed for the better it had indeed changed permanently, or 'for good'. The words 'for good' did not imply that Dovobet would be the best treatment ever for psoriasis. The claim referred to past not future treatments.

It might have been common practice amongst dermatologists to prescribe calcipotriol and steroid for separate applications. Leo was not aware of this being consistent with the summary of product characteristics (SPC) of either product – and it would, therefore, constitute off-label use. However, the significant clinical superiority of Dovobet compared to the individual treatments had also changed this less effective, less convenient and off-label practice 'for good'. Leo maintained therefore that there was no breach of Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that the claim at issue 'New Dovobet has changed psoriasis therapy for good' started a sentence which continued ' – 73% of patients can now markedly improve or clear their psoriasis, with visible results in just one week'.

The Panel noted that prior to the introduction of Dovobet it had not been possible to co-prescribe the full twice daily dose of the individual medicines without the risk of degradation of the active ingredients.

The Panel noted that according to The New Shorter Oxford English Dictionary the phrase 'for good (and all)' was defined *inter alia* as 'finally, permanently'. The Panel considered that the claim at issue was ambiguous. The claim implied that the features of Dovobet were such that it marked not just a permanent but also a final change in the way in which psoriasis patients were treated. Whilst the Panel acknowledged that the combination of calcipotriol and betamethasone in one medicine was an important change in psoriasis therapy the phrase 'for good' exaggerated the magnitude of that change and the claim was thus misleading about the overall effect Dovobet would have on psoriasis therapy. Breaches of Clauses 7.2 and 7.4 were ruled.

2 Claims 'Remarkable results in just a week' and 'Remarkably fast and powerful in psoriasis'

The claim 'Remarkable results in just one week' appeared in advertisements 4054 and 4061. The claim 'Remarkably fast and powerful in psoriasis' appeared in advertisement 4051.

COMPLAINT

Galderma noted that extracts from the clinical study report (MCB 9904 INT) provided by Leo depicted a mean psoriasis area and severity index (PASI) reduction after 1 week of 40% with betamethasone and 47% with Dovobet. Whilst Galderma would not dispute that a reduction of 47% after one week was significant, to describe this as remarkable was in its opinion unacceptable.

Galderma alleged that the claims were in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Leo stated that, as far as speed of response was concerned, steroids had been the gold standard in topical treatment of psoriasis for more than 30 years. It might have been predicted that in terms of an overall clinical response the combination of a steroid with calcipotriol would produce a response at least as good as the individual treatments applied separately. There was no reason to expect a better response other than perhaps from improved compliance. The reality, however, was a statistically and clinically significant improvement compared to both calcipotriol and to betamethasone, both overall and even after one week (Douglas *et al*). This was indeed remarkable. Testimonials received from both patients and doctors confirmed this as one of the major benefits of Dovobet. They found this speed of response 'remarkable'. Leo provided a copy of an email from a consultant dermatologist pleased with the way Dovobet had worked on one patient.

PANEL RULING

The Panel noted that Douglas *et al* (2002) compared, *inter alia*, the efficacy of Dovobet with that of its active components used alone. The first month of the study was run double-blind. The primary efficacy criterion was change in PASI from baseline to the end of the double-blind phase. The results showed that the mean decrease in PASI for Dovobet, betamethasone and calcipotriol was 74.4%, 61.3% and 55.3% respectively. The differences between Dovobet and each of the two monotherapies was statistically significant ($p<0.001$) in favour of Dovobet.

The speed of response to each of the three treatments was assessed by the mean decrease in PASI from baseline to week 1. After one week PASI decreased by 47.4%, 39.8% and 31% in the Dovobet, betamethasone and calcipotriol groups respectively. The differences between the Dovobet group and the other two groups were statistically significant ($p<0.001$) in favour of Dovobet.

The Panel noted that The New Shorter Oxford English Dictionary defined remarkable as, *inter alia*, 'worthy of notice or observation, extraordinary, unusual and striking.' The Panel noted that Leo had provided a copy of an email it had received from a consultant dermatologist enthusiastic about the results seen in one patient using Dovobet. The dermatologist had not described the response as 'remarkable'. Even if the dermatologist had used the term, the Panel noted that the patient concerned had 'burnt out psoriatic arthritis but widespread confluent psoriasis predominantly truncal. No topicals worked, phototherapy not practical …'. The Panel questioned

whether such a patient was typical of those for whom Dovobet was licensed and whether the positive results seen in that patient were also typical. Descriptions of clinical responses had to comply with the Code; they had to be balanced, fair, objective etc and represent the response that doctors would expect to see in the majority of patients.

The Panel noted that Douglas *et al* demonstrated statistically significant advantages in favour of Dovobet in relation to efficacy and speed of response compared with the monotherapies used alone. Nonetheless the Panel considered that the claims 'Remarkable results in just a week' and 'Remarkably fast and powerful in psoriasis' overstated the totality of the data. The Panel considered the claims misleading and not capable of substantiation as alleged and ruled breaches of Clauses 7.2, 7.3 and 7.4 of the Code.

APPEAL BY LEO

Leo appealed on the grounds that the construction put upon the meaning, and the judgement of the Panel as to the appropriateness, of the word 'remarkable' as used in the circumstances quoted, was mistaken.

The facts about Dovobet, the results obtained, and the references to the publications upon which Leo's statements were based, were set out in its response to the complaint. What was at issue was not what the results were, but whether those results were remarkable.

The definitions of 'remarkable' were as follows: Concise Oxford English Dictionary: worthy of notice, exceptional, extraordinary, striking, conspicuous; Chambers: noteworthy, unusual, singular, strange, distinguished; Chambers – 21st C online: worth mentioning or commenting on, unusual, extraordinary. Clearly, no usage would be expected to represent all those definitions.

The data from formal studies, and the observations and experience of clinicians and patients, supported the assertion that the effect produced by Dovobet in one week, and after up to four weeks, was worthy of notice, exceptional in that it was often visibly more rapid and/or complete than was generally the case with pre-existing treatment, and thus both unusual and not ordinary, ie extraordinary. Patients and clinicians had found that fact striking, and thus conspicuous.

Leo had received many unsolicited communications from patients, dermatologists and general practitioners about Dovobet, and in particular about the rapidity of the onset of its action and the degree of improvement (ie the result) after up to four weeks. Several included the word 'remarkable'. It was unnecessary to point out that the writers had thought the results worth mentioning. Indeed, had the response produced by the product been unremarkable, unworthy of notice, unexceptional or ordinary it was highly improbable that such communications would have been sent. Leo stated that it would make these available, not as data supporting the statement but as evidence of the appropriateness in the circumstance of the words used.

COMMENTS FROM GALDERMA

Galderma noted Leo's submission that, in terms of speed of response, 'steroids had been the gold standard in topical treatment of psoriasis for more than 30 years. It might have been predicted that in terms of an overall clinical response the combination of a steroid with calcipotriol would produce a response at least as good as the individual treatments applied separately. There was no reason to expect a better response other than perhaps from improved compliance. The reality, however, was a statistically and clinically significant improvement compared to both calcipotriol and betamethasone, both overall and even after one week'. If Galderma's interpretation of this was correct, Leo was claiming that it did not expect the response to be any better than the individual treatments used alone, and because the results were not as predicted this made it remarkable?

Surely, a pharmaceutical company would not invest a great deal of money and time combining two available treatments if it only believed that the response would be equivalent to the individual treatments applied separately? In reality, it would not be unreasonable to have expected the response of the combination product to have been in a range between the responses from betamethasone to the sum of betamethasone and calcipotriol treatments. The effect produced by Dovobet in one week, and after up to four weeks, fell within this predicted range and was only marginally better than the pre-existing treatments, therefore in Galderma's opinion was not exceptional or extraordinary.

Galderma added that its complaint was not with regards to the definition of the word 'remarkable' but with the use of the word in the context of the claims. There was no disputing the fact that the PASI reductions observed with Dovobet after one week were statistically significant, however, in Galderma's opinion to describe the increase observed over a comparator product as remarkable, exaggerated the magnitude of the actual clinical response, and thus was both misleading and not capable of being substantiated by the clinical evidence available, as was agreed by the Panel.

Galderma considered the email from a consultant dermatologist provided in support of the word 'remarkable' was rather baffling, particularly since not only was the word remarkable not used but the product was also used off licence. It seemed rather naïve for Leo to claim that it had received many unsolicited communications about the response to Dovobet, and yet supplied the above email as evidence of the appropriateness of the word used.

Galderma did not dispute that Leo might well have received testimonials from patients and doctors praising Dovobet, but in reality it was sure Leo would have also received unfavourable testimonials from the same group. Galderma did not need to reiterate that patients were different and responded differently to treatments. Descriptions of clinical responses had to comply with the Code ie be balanced, fair and objective, as a result Galderma did not believe that such correspondence could be used either as supporting data or as evidence of the appropriateness of the claims made.

Galderma continued to maintain that these promotional pieces and any other materials carrying the same wording or promotional activity that communicated these messages were in breach of Clauses 7.2, 7.3 and 7.4 as ruled by the Panel.

APPEAL BOARD RULING

The Appeal Board noted that Douglas *et al* had demonstrated statistically significant advantages in favour of Dovobet in relation to efficacy and speed of response compared with the monotherapies used alone. However, the Appeal Board considered the claims 'Remarkable results in just a week' and 'Remarkably fast and powerful in psoriasis' overstated the totality of the data. The Appeal Board considered the claims misleading and not capable of substantiation and upheld the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.4. The appeal on this point was unsuccessful.

3 Claims 'Remarkable results in just a week', 'New Dovobet has changed psoriasis therapy for good – 73% of patients can now markedly improve or clear their psoriasis, with visible results in just one week'

These claims appeared in advertisements 4054 and 4061.

COMPLAINT

Galderma noted that the claim 'New Dovobet has changed …with visible results in just one week' appeared immediately under the strapline 'Remarkable results'. The positioning of these claims in the same field of vision implied that 73% of patients' psoriasis cleared in just one week. Whereas the 73% was in fact the mean PASI reduction after 4 weeks of treatment. Galderma believed the wording and positioning of these claims to be both ambiguous and likely to mislead. Leo had not tried to address this issue, instead advising that this claim was clearly and correctly referenced, unambiguous and did not mislead in any way.

Galderma continued to maintain that this claim was misleading and ambiguous, since it was not made clear that the 73% reduction actually referred to the results after 4 weeks. The reader would only be aware that this was the case if they requested and reviewed the references (one of which was data on file). Galderma alleged a breach of Clause 7.2.

RESPONSE

Leo considered that it had sufficiently separated the claim around the efficacy at four weeks both in language ('markedly improve or clear' compared to 'visible results') and in syntax with the use of a comma and the preposition 'with' between the two clauses, from the claim around the rapidity of response at one week. Leo believed that in line with Clause 7.2 this was unambiguous.

PANEL RULING

The claim '73% of patients can now markedly improve or clear their psoriasis, with visible results in just one week' was referenced in one advertisement (ref 4054) to a poster, Douglas *et al* (2001) and data on file and in the other advertisement (ref 4061) to Douglas *et al* (2002) and data on file.

The Panel noted that the Douglas *et al* (2002) paper defined responders as those patients whose psoriasis showed 'marked improvement' or 'clearance' ie the parameters referred to in the claim at issue, at the end of the double-blind period ie after 4 weeks' treatment. The results showed that 68% of patients in the Dovobet group were classified as responders by the investigators. According to patients' own assessments 67.2% were classified as responders.

The claim in question referred to 73% of patients showing a marked improvement or clearance of psoriasis. In the Panel's view this figure was inaccurate. A breach of Clause 7.2 was ruled. This ruling was appealed.

The Panel noted that the claim continued by referring to 'visible results in just one week'. In the Panel's view it appeared that 'one week' related not only to the 'visible results' but also to the marked improvement or clearance of psoriasis which was not so. The Panel did not accept that the two components of the claim, efficacy and speed of response, had been sufficiently separated. The Panel considered that the claim was misleading in that regard and ruled a breach of Clause 7.2.

APPEAL BY LEO

Leo noted that the Panel in its ruling had stated that it had not understood where the figure of 73% had arisen. Leo stated that this was not a complaint made by Galderma and it had not been asked to support this figure.

COMMENTS FROM GALDERMA

Galderma confirmed that this was not a matter disputed in its original correspondence to the Authority.

APPEAL BOARD CONSIDERATION

The Director had referred the appeal on this point to the Chairman of the Appeal Board.

The Chairman considered that the Panel's ruling was outside the scope of the original complaint. The Chairman thus recommended to the Appeal Board that it nullify the ruling by the Panel on this point. This recommendation was accepted by the Appeal Board. The appeal on this point thus no longer stood.

Complaint received **15 October 2002**

Case completed **11 February 2003**

MEDICAL WRITER v CENTOCOR

Retavase email

A medical writer queried whether it was illegal for him to have received, from Medicine Direct, an unsolicited email promoting Retavase (reteplase). The email began 'Announcing the relaunch of RETAVASE.com. Learn about the #1 fibrinolytic used to treat AMI in the U.S.' and discussed its efficacy and safety profile. The email concluded with links to, *inter alia*, the US prescribing information, clinical information and slide presentations. Retavase was referred to as a trade mark of Centocor Inc. The complainant noted that the email appeared to be authorised by the manufacturer and did not originate from a dodgy online pharmacy.

The Panel noted that Retavase was marketed in the US by Centocor BV's parent company, Centocor Inc, which was based in the US. Centocor had no role in the marketing of the product in Europe. It was an established principle under the Code that companies were responsible for the acts or omissions of their overseas affiliates. Centocor BV was thus responsible for acts or omissions of Centocor Inc which came within the scope of the Code.

The Panel noted that Centocor Inc had issued the email concerning the relaunch of www.Retavase.com and disseminated it via six separate third party websites each of which sent email publicity to registered users on an opt-in basis in accordance with the privacy policy of each website. The complainant had received the email from Medicine Direct. The Panel noted Centocor's submission that Medicine Direct sent email publicity via a subcontractor to users who had opted in to receive information from an associated website: www.Cardiosource.com. The Panel also noted Centocor's submission regarding the Cardiosource website privacy policy and content of the registration pages. Centocor did not have access to the third party mailing lists.

The complainant had stated that he was a registered user of various US medical websites, although to the best of his knowledge he had not opted in to receive email from any of them. In any event Centocor Inc had issued and arranged the dissemination of the Retavase email and Centocor BV was thus responsible for it under the Code.

The Panel considered that this was a complex matter. In effect a US company (Centocor Inc) had sent the complainant, who was not a health professional, a promotional email for a medicine, albeit indirectly. Reteplase was marketed in the UK as Rapilysin by another company which held the UK marketing authorization. The Panel considered that the email had not promoted a UK prescription only medicine to the public. It therefore ruled no breach of the Code.

A medical writer complained about an unsolicited email he had received about Retavase (reteplase) from Medicine Direct. The email began 'Announcing the relaunch of RETAVASE.com. Learn about the #1 fibrinolytic used to treat AMI in the U.S.' and discussed its efficacy and safety profile. The email concluded with links to, *inter alia*, the US prescribing information, clinical information and slide presentations. Retavase was referred to as a trade mark of Centocor Inc.

COMPLAINT

The complainant, who was not a medical practitioner, stated that he had received the unsolicited email advertising Retavase and queried whether this was illegal. The complainant noted that the email appeared to be authorised by the manufacturer, and did not originate from some dodgy online pharmacy.

The Authority asked Centocor BV to respond in relation to Clauses 9.8, 20.1 and 20.2 of the Code.

RESPONSE

Centocor BV stated that reteplase was originally developed by Boehringer Mannheim GmbH. In the US, the product was marketed under the trade name Retavase by the parent company Centocor Inc. Centocor's rights on the commercialisation of the product were limited to the US only. In Europe, the product was marketed under the trade name of Rapilysin by Roche. Centocor was not involved in the commercialisation of the product in Europe.

At the occasion of the relaunch of the website www.Retavase.com, an electronic mailing was sent. The website www.Retavase.com was owned by Centocor Inc, the marketing authorisation holder for Retavase in the US. The website was focussed to a US audience only. This was reflected, amongst others, by the fact that Centocor Inc was clearly identified as the owner of the site, only US prescribing information was posted and only US contact addresses were provided.

It was difficult to determine how the complainant received the email. Centocor suspected that it was likely that he was a registered user of one or more US-based, medically-orientated websites whose users opted-in to receive email concerning products that might be of interest to them. Centocor Inc contracted with several of these websites which, in turn, sent publicity concerning Retavase or www.Retavase.com, to those of their registered users who had opted in to receive such information. Publicity concerning the relaunch of www.Retavase.com website had been disseminated through six separate third party websites over the past several months. Each of the websites sent emails to registered users, on an opt-in basis, in accordance with the particular privacy policy of each website.

Centocor Inc did not have access to third party mailing lists compiled by these websites. Therefore it could not determine the target audience or geographic spread of the email received by the complainant.

Centocor Inc would be contacting the third party websites which had disseminated information concerning www.Retavase.com and ask them to remove the name of the complainant from any future Retavase or www.Retavase.com communications.

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The Panel decided to send part of the response to the complainant for further comment.

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FURTHER COMMENTS FROM THE COMPLAINANT

The complainant found it staggering that Centocor was unable to determine how he received the email. He appreciated that Centocor did not have access to the mailing lists of its partner websites, but it really ought to know which website sent the email by looking at the sender's email address – or was this forged, as was commonly done by those sending spam emails? If Centocor had so little control over how emails were sent then that was worrying in itself.

The complainant confirmed that he was a registered user of various US medical websites, although to the best of his knowledge he had not opted-in to receive emails from any of them. If he knew which website had sent the email he could check his status with that site and make sure, but would be very surprised if he had agreed to receive the email. In any case, there were certainly no US medical websites that sent him emails with his permission on a regular basis. The offending email did not give any information about which website sent it or how to unsubscribe from future email, which was generally considered an essential requirement of reputable email marketing.

The complainant noted that his email address had been harvested without his consent and found its way into many lists used by spammers. He suspected that the Retavase email was sent to him in this way, and Centocor's inability (or unwillingness) to say how he got the email only confirmed this suspicion.

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The complainant's additional comments were sent to Centocor BV for its comment.

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FURTHER COMMENTS FROM CENTOCOR

Centocor stated that its US affiliate Centocor Inc did disseminate the announcement of the relaunch of the www.Retavase.com website through six separate third party websites over several months. Some of these websites also performed a mailing by email.

Based on the information provided by the complainant, it appeared that he had received the www.Retavase.com email announcement from the website www.MedicineDirect.com, through its subcontractor www.Bluestreak.com.

Medicine Direct was a US-based medical website operated by Elsevier Science Inc. Elsevier also owned and operated the website www.Cardiosource.com.

Centocor Inc had contacted Elsevier regarding this matter and had determined that Elsevier employed its Medicine Direct website to send email publicity to users who had opted-in to receive information from its Cardiosource website. In turn, www.MedicineDirect.com employed www.Bluestreak.com (through its entity www.ProcessRequest.com) as the actual entity that sent email publicity to registered users of Cardiosource.com. Thus, registered users of www.Cardiosource.com could receive email publicity from Medicine Direct through www.ProcessRequest.com entity.

Registered users of the Cardiosource website could opt-in to receive 'CardioSource announcements' or 'Third party special offers and information relevant to my profession and expertise'. The privacy policy for the Cardiosource.com. website provided that users who opted-in agreed to the certain disclosure of data to third parties.

The registration pages of the website MedicineDirect.com. also provided opt-in tick boxes for users who wished to receive additional information from third parties.

Centocor Inc did not have access to third party mailing lists such as those from www.MedicineDirect.com or www.Cardiosource.com and thus had no means to determine whether the complainant opted-in to receive 'special offers and information of interest [to his] speciality'. Nevertheless, Centocor Inc instructed Elsevier that the complainant, if he was indeed a registered user, should not receive any further publicity regarding www.Retavase.com.

PANEL RULING

The Panel noted that Retavase was marketed in the US by Centocor BV's parent company, Centocor Inc, which was based in the US. Centocor had no role in the marketing of the product in Europe. The Panel noted that it was an established principle under the Code that companies, including non-member companies such as Centocor which had nonetheless agreed to comply with the Code, were responsible for the acts or omissions of their overseas affiliates. Centocor BV was thus responsible for acts of omissions of Centocor Inc which came within the scope of the Code.

The Panel noted that Centocor Inc had issued the email concerning the relaunch of www.Retavase.com and disseminated it via six separate third party websites each of which sent email publicity to registered users on an opt-in basis in accordance with the privacy policy of each website.

The complainant had received the email from Medicine Direct. The Panel noted Centocor's submission that Medicine Direct sent email publicity via a subcontractor to users who had opted-in to receive information from an associated website: www.Cardiosource.com. The Panel also noted Centocor's submission regarding the Cardiosource website privacy policy and content of the registration pages. Centocor did not have access to the third party mailing lists.

The Panel noted the complainant's submission that he was a registered user of various US medical websites, although to the best of his knowledge he had not opted in to receive email from any of them. In any event Centocor Inc had issued and arranged the dissemination of the Retavase email and Centocor BV was thus responsible for it under the Code.

The Panel considered that this was a complex matter. In effect a US company (Centocor Inc) had sent the complainant, who was not a health professional, a promotional email for a medicine, albeit indirectly.

Reteplase was marketed in the UK as Rapilysin by another company with the UK marketing authorization being held by Roche Registration Limited. The Panel considered that the email had not promoted a UK prescription only medicine to the public. It therefore ruled no breach of Clause 20.1 of the Code.

Clause 9.8 of the Code stated that, *inter alia*, email must not be used for promotional purposes except with the prior permission of the recipients. The Panel considered that whether or not the complainant had registered with Medicine Direct, its privacy policy 'Disclosure of data to third parties' and opt-in tick boxes as described by Centocor were insufficiently precise about the nature of the information to be distributed such that registration or opting-in might not constitute prior permission to receive promotional material as required by Clause 9.8 of the Code. However noting its ruling above, the Panel decided that there could be no breach of Clause 9.8 of the Code and ruled accordingly.

Complaint received **21 October 2002**

Case completed **5 February 2003**

PRESCRIBING ADVISER v ASTRAZENECA

Conduct of representative

The prescribing adviser to a primary care trust (PCT) complained that an AstraZeneca representative was advising local practices that the PCT was approving a range of swaps and had suggested that they switched patients receiving certain therapies to others produced by AstraZeneca. The complainant stated that none of the swaps had been approved by any individual or group within the PCT. Differences between the products' licensed indications could lead to use for unauthorised indications and possible harm to patients through adverse effects or inequivalent doses. The changes would cause a significant and unplanned workload for the practices and the appearance that these came from the PCT potentially undermined working relationships.

The Panel noted that the complainant alleged that the representative had referred to the PCT in question endorsing switching patients to certain AstraZeneca products. AstraZeneca had submitted that the representative had only discussed the possible cost benefits of using these products according to the sales aids. The representative denied claiming that the PCT at issue endorsed swapping certain patients to AstraZeneca products and had no knowledge of the PCT's policies. The representative did, however, mention that one product was on the formulary of a local hospital trust and two other local PCTs were endorsing a switch to that product based on cost. The Panel queried whether, when referring to switches made by other local PCTs, the representative had made it sufficiently clear to which PCT he was referring. It was important in such discussions to be abundantly clear to avoid confusion.

The Panel noted that the parties' accounts of what took place differed; it was difficult in such cases to know exactly what had transpired. A judgement had to be made on the evidence which was available, bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint. Given the parties' differing accounts, the Panel was not in a position to determine what had happened. No breach of the Code was therefore ruled.

The prescribing adviser to a primary care trust (PCT) complained about the activities of a representative from AstraZeneca UK Limited.

COMPLAINT

The complainant was writing following information received by her PCT from local practices that a named representative of AstraZeneca had approached them 'to pass on to GPs that the PCT are approving a range of swaps'. By this the representative suggested that they switched patients currently receiving certain therapies to others (all produced by AstraZeneca). The proposed swaps which had been reported were: from Istin to Plendil (one third cheaper); from Cozaar to Amias (one third cheaper); from Serevent plus a steroid/Serevent plus Flixotide/Seretide to Symbicort and all patients on high doses of omeprazole and lansoprazole to Nexium 20mg. It appeared that in no case was a summary of product characteristics (SPC) left with the practice.

The complainant's concerns were that:

- None of the proposed swaps had been approved by any individual or group within the PCT.
- Differences between the products in terms of licensed indications could mean that if a swap went ahead a patient would be receiving treatment for an unlicensed indication, which raised further concerns about efficacy, informed consent and liability.
- If, after a swap from their current therapy, a patient subsequently came to any harm – through an adverse effect or due to receiving an inequivalent dose, that patient might then seek to litigate against the PCT.
- The changes would cause a significant and unplanned workload for the practices, the appearance that these changes came from the PCT potentially undermined working relationships forged with GPs and practice staff.
- The representative gave nothing in writing. Messages were given to practice staff to pass on to their GPs.

The complainant alleged that these activities amounted to unprofessional conduct.

When writing to AstraZeneca the Authority asked it to respond in relation to Clauses 3.2, 7.2 and 15.2 of the Code.

RESPONSE

AstraZeneca stated that the representative in question had visited a number of practices within the PCT. During these visits the need for cost containment was often identified as a major issue and the representative had discussed the possible cost advantages of AstraZeneca's products Symbicort, Plendil, Amias and Nexium with GPs and practice managers. These discussions were supported by the current sales materials with the exception of Plendil which was no longer a promoted product.

AstraZeneca stated that the representative had had little contact with the PCT and therefore was unaware of its policies regarding prescribing recommendations. The representative had consequently not discussed the PCT's prescribing recommendations with customers, or given the impression that this was the case. Similarly he stated that he had never claimed that the PCT was endorsing the alleged treatment switches.

The representative mentioned to a number of practices that Symbicort was on the hospital formulary across the local NHS Trust and that two other PCTs in the area were endorsing changing appropriate patients to Symbicort based on cost savings. At no time did the representative claim that the complainant's PCT was also endorsing such changes.

AstraZeneca did not consider that the representative involved failed to maintain a high level of conduct when discussing the possibilities of changing certain patients to AstraZeneca products or indeed that false information was used to support these discussions.

AstraZeneca reiterated that the representative only ever discussed the possible cost benefits of using AstraZeneca products according to specific sales aids and briefing documents. All of these materials were subjected to the AstraZeneca approval process and did not contain any false or misleading information that would encourage health professionals to change a patient's current treatment to an inappropriate AstraZeneca product or dose.

AstraZeneca therefore denied that the representative in question failed to maintain a high standard of conduct or that the material he used to discuss the possibility of changing particular patient treatments was misleading and could therefore lead to prescribing in a manner inconsistent with the product licence.

AstraZeneca noted that when trying to arrange an appointment to see a GP, practice manager or practice nurse it was often necessary to provide administrative staff with an indication of the nature of the call eg which products or topics were to be discussed. This, in AstraZeneca's opinion, did not constitute promoting to inappropriate staff.

AstraZeneca did not consider the representative involved acted in any way which could be deemed as having failed to maintain high standards.

The complainant mentioned that in no case did the representative leave an SPC for any of the products he was discussing. Clause 15.8 of the Code stated that representatives must provide, or have available to provide if requested, a copy of the SPC for each medicine that they were promoting. The representative in question confirmed that he always carried up-to-date copies of the SPCs for all products he planned to discuss with customers. He could not recall refusing or not being able to provide any of his customers with a copy of a particular SPC.

AstraZeneca stated that the representative in question had passed the ABPI Medical Representatives Examination.

In response to a request for copies of the promotional material used by the representative in question AstraZeneca stated that he was provided with material to promote Symbicort and Nexium only.

In summary, AstraZeneca did not consider the representative in question had acted in any way that constituted a failure to maintain high standards through use of inaccurate information. Nor did AstraZeneca consider that the discussion he held with prescribers in the area would lead to, or encourage, the inappropriate usage of AstraZeneca's products. AstraZeneca therefore did not consider Clauses 3.2, 7.2, 15.2 to have been breached.

FURTHER COMMENTS FROM THE COMPLAINANT

AstraZeneca agreed that its response could be sent to the complainant for comment prior to the Panel making a ruling.

The complainant stated that she did not believe that practice staff and GPs of many years experience would have brought this matter to her attention if they did not believe, or had not been given the clear impression that the PCT was apparently endorsing a range of treatment switches.

PANEL RULING

The Panel noted that the complainant alleged that the representative had referred to the PCT endorsing switching patients to AstraZeneca's products Plendil, Amias, Symbicort and Nexium. The Panel noted AstraZeneca's submission that the representative had discussed with GPs and practice managers the possible cost advantages of Plendil, Amias, Symbicort and Nexium and that these discussions were supported by the current sales materials with the exception of Plendil which was no longer a promoted product. AstraZeneca further submitted that the representative was provided with material to promote Symbicort and Nexium only. The Panel queried whether AstraZeneca's response was consistent on this point.

The Panel noted that the promotional material provided featured comparative clinical data and cost claims. None of the material referred to the PCT at issue.

The Panel noted AstraZeneca's submission that the representative had only discussed the possible cost benefits of using AstraZeneca products according to the AstraZeneca sales aids. Further the representative denied claiming that the PCT at issue endorsed swapping certain patients to AstraZeneca products and had no knowledge of the PCT's policies. AstraZeneca stated that the representative did mention that Symbicort was on the formulary of a local hospital trust and two other local PCTs were endorsing a switch to Symbicort based on cost. The Panel queried whether when referring to switches made by other local PCTs the representative had made it sufficiently clear to which PCT he was referring. It was important in such discussions to be abundantly clear to avoid confusion.

The Panel noted that the parties' accounts of what took place differed. The Panel observed that it was difficult in such cases to know exactly what had transpired. A judgement had to be made on the evidence which was available, bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint. Given the parties differing accounts, the Panel was not in a position to determine what had happened. The Panel therefore ruled no breach of Clauses 3.2, 7.2 and 15.2 of the Code.

Complaint received **2 December 2002**

Case completed **3 February 2003**

CASE AUTH/1395/12/02

JANSSEN-CILAG/DIRECTOR v LILLY

Zyprexa leavepiece

Janssen Cilag complained about the promotion of Zyprexa (olanzapine) by Lilly. As the complaint also involved an alleged breach of undertaking this part of it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given previously by the Appeal Board. The material at issue was a leavepiece consisting of a folder containing an insert. Each was headed 'A Pharmacoepidemiological Study of Diabetes Mellitus and Antipsychotic Treatment in the United States', Cavazzoni *et al*, and included prescribing information. Lilly stated that the insert was a reproduction of a poster presentation. The folder also referred to the study findings.

Both the insert and the folder included a bar chart headed 'Annualized Incidence of DM [diabetes mellitus] in Specific Antipsychotic Treatment Cohorts' which showed the incidence per 1000 patient years for haloperidol, thioridazine, olanzapine, risperidone (Janssen-Cilag's product, Risperdal), clozapine, quetiapine and the general patient population. Beneath the bar chart in the folder it was stated that a direct comparison of the three largest individual antipsychotic treatment cohorts found with regard to the comparative risk of diabetes that haloperidol = olanzapine, risperidone = olanzapine and risperidone > haloperidol.

Janssen-Cilag assumed from the layout that the leavepiece referred to the results of one study, Cavazzoni *et al*. The claims for the comparative risk of diabetes cited reference number 2. No references were listed on the folder. The only reference list was on the insert where reference 2 was cited as Braceland *et al* (1945). Janssen-Cilag alleged that as there were no references on the folder and the reference from the insert was published before the introduction of antipsychotic medications, the leavepiece was not clearly referenced, in breach of the Code.

The Panel noted that the folder did not mention that the data was from a published study and under the clause cited by Janssen-Cilag the data did not need a reference. The Panel ruled no breach of the Code.

Janssen-Cilag alleged that the claim 'Comparative risk of diabetes mellitus' 'risperidone = olanzapine' did not reflect the totality of the data. Numerous publications (Koro *et al*, 2002; Gianfrancesco *et al*, 2002; Lambert *et al*, 2002) in addition to the number of case reports of new incidence of diabetes as a result of treatment with each of these atypical antipsychotics, supported that there was an increased risk of diabetes associated with olanzapine than with risperidone. The claim was alleged to be misleading, unbalanced, not based on an up-to-date evaluation of all the evidence and disparaging of risperidone.

The Panel noted that both the folder and insert were dated February 2002. The additional data referred to by Janssen-Cilag had been published in 2002, for example, Koro *et al* had been published in August 2002. The Panel noted that the WHO data had also recently been published and changes had been made to the Risperdal summary of product characteristics.

The Panel noted that the leavepiece had been used until September 2002. The Panel considered that given the emerging opinion the leavepiece was not an up-to-date evaluation of all the evidence. The data in the leavepiece had not been set in the context of all the available data. Breaches of the Code were ruled. The Panel considered that it was disparaging to state that risperidone = olanzapine given the emerging data. A breach of the Code was ruled.

Janssen-Cilag stated that Lilly had provided a clear undertaking that it would withdraw the piece by 16 September 2002. Janssen-Cilag stated that a representative from Lilly presented this material to health professionals at a meeting in October 2002. Janssen-Cilag alleged a breach of the Code since Lilly had failed to maintain high standards.

The Panel noted that Lilly disputed that the alleged meeting in October had taken place. The Panel considered that in the circumstances it was not possible to determine where the truth lay and it had no option but to rule no breach of the Code.

Janssen-Cilag stated that in a previous case, Case AUTH/1325/5/02, which concerned a medical information letter referring to Zyprexa, diabetes and hyperglycaemia, the Panel had ruled that the way in which Lilly had used the phrase '… the accruing evidence (on diabetes and hyperglycaemia) is relevant to all antipsychotics…' was disparaging. Lilly had accepted the ruling and undertook not to repeat the breach. As presented above, Janssen-Cilag alleged that Lilly continued to disparage Risperdal in the same manner in breach of its undertaking.

Turning to the present case the Panel considered that the leavepiece was sufficiently different to the medical information letter previously at issue in Case AUTH1325/5/02. The Panel considered that the leavepiece was not in breach of the undertaking given in Case AUTH1325/5/02 and no breach of the Code was ruled.

Janssen-Cilag alleged that Lilly's continued use of claims disparaging Risperdal, despite having given an undertaking to the Authority to the contrary, and its continued use of the leavepiece brought discredit upon the industry in breach of Clause 2.

The Panel noted its ruling with regard to the alleged continued use of the leavepiece and the alleged breach of undertaking above and consequently ruled no breach of Clause 2 of the Code.

Janssen Cilag Ltd complained about the promotion of Zyprexa (olanzapine) by Eli Lilly and Company Limited. The material at issue was a leavepiece consisting of a four page folder (ref ZY1101) containing a six page insert (ref ZY1102). Each was headed 'A Pharmacoepidemiological Study of

Diabetes Mellitus and Antipsychotic Treatment in the United States', Cavazzoni *et al*, and included prescribing information. Lilly stated that the insert was a reproduction of a poster presentation. The folder also referred to the study findings.

Both the insert and the folder included a bar chart headed 'Annualized Incidence of DM [diabetes mellitus] in Specific Antipsychotic Treatment Cohorts' which showed the incidence per 1000 patient years for haloperidol, thioridazine, olanzapine, risperidone (Janssen-Cilag's product, Risperdal), clozapine, quetiapine and the general patient population. Beneath the bar chart in the folder, ZY1101, it was stated that a direct comparison of the three largest individual antipsychotic treatment cohorts found with regard to the comparative risk of diabetes mellitus that haloperidol = olanzapine, risperidone = olanzapine and risperidone > haloperidol.

1 References

COMPLAINT

Janssen-Cilag stated that from the layout of the leavepiece it must be assumed that the whole piece was referring to the results of one study, Cavazzoni *et al*. The comparative risk claims (ie haloperidol = olanzapine; risperidone = olanzapine; risperidone > haloperidol) cited reference number 2. No references were listed on the folder ZY1101. The only reference list was on the insert, ZY1102, where reference 2 was cited as Braceland *et al* (1945).

As there were no references on ZY1101 and clearly the reference from ZY1102 could not support claims comparing the risk of diabetes mellitus for antipsychotics (as it was published before the introduction of antipsychotic medications), the piece was not clearly referenced. A breach of Clause 7.6 of the Code was alleged.

RESPONSE

Lilly stated that since it had, and had at the time of the alleged incident, agreed to withdraw the piece, it did not wish to submit a detailed defence of the leavepiece itself, however Lilly refuted most of the alleged breaches.

The alleged breach of the Code relating to references was accepted by Lilly. The references should have appeared after the prescribing information on the back page of the folder but were omitted. Lilly accepted this was a breach of Clause 7.6.

PANEL RULING

The Panel noted that Clause 7.6 of the Code required clear references to be given when promotional material referred to published studies. The Panel noted that the folder did not mention that the data was from a published study. Therefore under Clause 7.6 the data did not need a reference and consequently there was no breach of Clause 7.6 of the Code. The Panel ruled accordingly.

During its consideration of this allegation, the Panel considered that it was misleading to cite a reference in promotional material and not to list that reference on the material at issue. Such material failed to meet the requirements of Clause 7.2 of the Code. There was no allegation of a breach of Clause 7.2. The Panel requested that its views be drawn to Lilly's attention.

2 Claim 'Comparative risk of diabetes mellitus' 'risperidone = olanzapine'

COMPLAINT

Janssen-Cilag alleged that the claim did not reflect the totality of the data. Numerous publications (Koro *et al*, 2002; Gianfrancesco *et al*, 2002; Lambert *et al*, 2002) in addition to the number of case reports of new incidence of diabetes mellitus as a result of treatment with each of these atypical antipsychotics, supported that there was an increased risk of diabetes mellitus associated with olanzapine treatment than with risperidone treatment. The claim was alleged to be misleading, unbalanced and not based on an up-to-date evaluation of all the evidence in breach of Clauses 7.2 and 7.3. Furthermore it was alleged to be disparaging of risperidone in breach of Clause 8.1.

RESPONSE

Lilly pointed out that the allegation that the leavepiece, a folder designed to summarise and display the results of one piece of research, failed to reflect the totality of the data was self-evident. The leavepiece was clearly designed to give the results of just one piece of research in an emerging and contentious field. But if this were found to be in breach of the Code that finding would have implications for all distribution of individual pieces of research, which was surely not the intention. Lilly therefore maintained that the production of an item showcasing an individual piece of research could not possibly reflect the totality of the data and thus the requirements of the Code were not applicable and no breach should be ruled.

The Code did mention the problems of deciding what was a balanced view of the data in fields where scientific opinion was emerging (supplementary information to Clause 7.2) and this was clearly true for the emerging picture regarding the diabetogenic potential of various antipsychotic drugs. In this context Janssen-Cilag had maintained that its product, risperidone, was free from diabetogenic potential and had taken issue with Lilly on several occasions over Lilly's view that diabetogenic potential was a class effect. At the time Lilly agreed to withdraw the leavepiece it appeared that the balance of evidence (as referred to by Janssen-Cilag) was moving in a direction which favoured its point of view, however the very recent publication by the WHO Drug Surveillance Centre showing that there was a definite statistically significant signal that risperidone was associated with diabetogenic potential (Hedenmalm 2002) highlighted the problem with the shifting balance of emerging scientific information. Indeed the WHO data showed that the signal implicating risperidone had been present for some years but had gone unnoticed until now.

Although the findings of Cavazzoni *et al* presented in the leavepiece were discordant with some of the other published studies, they were not inconsistent with the WHO data: if risperidone did have diabetogenic potential it would be expected that, due to the variation in population based epidemiology studies, some data would emerge associating the medicine as was found by Cavazzoni *et al*. It would therefore be reasonable for that data to be disseminated as for any of the alternative data.

As a result Lilly did not accept that the leavepiece disparaged risperidone since it accurately reported the finding of a respectable piece of scientific research in a field of emerging scientific opinion and made a point which could have been made some years earlier had the WHO data been available in the public domain. Lilly therefore denied breaches of Clauses 7.2, 7.3 and 8.1.

PANEL RULING

The Panel noted Lilly's comments that the leavepiece was designed to give the results of one piece of research and thus 'could not possibly reflect the totality of the data and thus the requirements of the Code were not applicable…'. The Panel considered that the folder and insert were promotional items and subject to the Code. Although the insert reproduced the poster presentation Lilly had used Cavazzoni *et al* as a basis for drawing up its own promotional material. The leavepiece was produced by the company and each item included prescribing information.

The Panel noted that Clause 7.2 required, *inter alia*, that information was balanced, fair, objective and based on an up-to-date evaluation of all the evidence. Promotional material reflecting one piece of evidence was not necessarily a breach of the Code providing that the requirements of the Code, particularly Clause 7.2, were met. The supplementary information to Clause 7.2, emerging clinical or scientific opinion, stated that where a clinical opinion existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material.

Promotional materials had to comply with the Code at the time they were used.

Both the folder and insert were dated February 2002. The additional data referred to by Janssen-Cilag had been published in 2002; for example Koro *et al* had been published in the BMJ, 3 August 2002. The Panel noted that the WHO data had also recently been published and changes had been made to the Risperdal SPC.

In this instance the leavepiece might have been acceptable at the time it was first used but did not reflect all the available evidence as the further studies were published. It might be that the WHO study counterbalanced the studies referred to by Janssen-Cilag. In the Panel's view the leavepiece did not treat the matter in a balanced manner as referred to in the supplementary information to Clause 7.2 regarding emerging clinical or scientific opinion.

The Panel noted that the leavepiece had been used until September 2002. The Panel considered that given the emerging opinion the leavepiece was not an up-to-date evaluation of all the evidence. The data in the leavepiece had not been set in the context of all the available data. Breaches of Clauses 7.2 and 7.3 were ruled. The Panel considered that it was disparaging to state that risperidone = olanzapine given the emerging data. A breach of Clause 8.1 was ruled.

During its consideration of this case the Panel was concerned that Lilly had agreed on 13 August that the leavepiece was in breach of the Code but had taken over a month to withdraw it from use. The Panel requested that Lilly be advised of its views in this regard.

3 Alleged failure of Lilly to comply with an undertaking given to Janssen-Cilag

COMPLAINT

Janssen-Cilag stated that it had sought to rectify the situation through intercompany communication. Lilly was in agreement that the piece no longer reflected an up-to-date evaluation of the published literature and as a result provided a clear undertaking that it would withdraw the piece by 16 September 2002.

Janssen-Cilag stated that Lilly had failed to comply with its undertaking, as the leavepiece had remained in circulation. A representative from Lilly presented this material to health professionals at a hospital meeting on 24 October 2002. Janssen-Cilag had expected that Lilly would have instituted its standard operating procedure to withdraw the item accepted by then to be in breach of Clause 7.2 (by virtue of it not being an up-to-date evaluation of the literature). This should have meant all representatives would have returned all copies of the item for destruction. Janssen-Cilag alleged Lilly had failed to maintain the high standards expected of the industry.

RESPONSE

Lilly stated that it had agreed with Janssen-Cilag on 13 August to cease using the leavepiece by 16 September 2002. Consequently at a face-to-face meeting on 11 September, Lilly briefed the sales managers to stop using the Cavazzoni paper and to use another publication. Detailed training was given.

During the course of a 4-day training meeting, 16-19 September, the sales managers then briefed the Lilly sales force. On 16 September the Cavazzoni paper was officially withdrawn. The following day the sales force was officially briefed to cease using the Cavazzoni leavepiece and instead use another publication.

As a final check, so as to ensure the full compliance with withdrawal of non-approved promotional materials, the Zyprexa Brand Manager sent an e-mail to all the sales representatives, the day after the training session had been completed (20 September), giving a completed list of approved and non-approved materials for use in the promotion of Zyprexa.

Janssen-Cilag stated that on 24 October, a representative from Lilly presented the Cavazzoni data to health professionals at a hospital. Lilly requested that Janssen-Cilag provide further information regarding this incident, not least as the sales representatives who covered this area stated that they were not at the hospital on that day. Janssen-Cilag has declined to do this. Consequently in the absence of any substantiated information, Lilly was unable to comment on this alleged meeting, and furthermore surprised by the fact the Janssen-Cilag had decided to refer the matter to the Authority directly rather than at an intercompany level.

Consequently Lilly denied a breach of Clause 9.1.

PANEL RULING

The Panel noted that Lilly disputed that the alleged meeting on 24 October referred to by Janssen-Cilag had taken place. The Panel considered that in the circumstances it was not possible to determine where the truth lay and it had no option but to rule no breach of Clause 9.1 of the Code.

4 Alleged breach of undertaking

COMPLAINT

Janssen-Cilag stated that in a previous complaint it had made, Case AUTH/1325/5/02, which concerned a medical information letter referring to Zyprexa, diabetes and hyperglycaemia, one of the Panel's rulings referred to the use by Lilly of the phrase '… the accruing evidence (on diabetes and hyperglycaemia) is relevant to all antipsychotics…'. The Panel had ruled that the way in which Lilly had used this phrase was in breach of Clause 8.1 of the Code. Lilly had accepted that ruling and undertook not to repeat that breach. Unfortunately, as presented above, the evidence showed that Lilly continued to disparage Risperdal in the same manner (that was by claiming that the risk of developing diabetes mellitus for Risperdal equalled that of olanzapine). Accordingly Janssen-Cilag alleged a breach of Clause 22.

RESPONSE

Lilly stated that in Case AUTH/1325/5/02 the Panel had ruled that Lilly's medical information letter was in breach of Clause 8.1. The statement at issue was:

'The following statement is included in the Zyprexa Summary of Product Characteristics.

Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

In view of the body of evidence presented above, this advice may be relevant for all patients receiving antipsychotics.'

The Panel had found that Lilly's medical information letter suggested that the above statement, which had been added to the Zyprexa SPC, should be similarly added to the SPCs of all antipsychotics. However the Panel had accepted that the data had some relevance to other antipsychotics, although it was the degree to which it applied, that varied.

Lilly pointed out that there was no statement to this effect in the leavepiece now at issue. Lilly had not breached its undertaking as alleged.

PANEL RULING

The Panel considered that the leavepiece was sufficiently different to the medical information letter previously at issue in Case AUTH1325/5/02. The Panel considered that the leavepiece was not in breach of the undertaking given in Case AUTH1325/5/02 as alleged and no breach of Clause 22 of the Code was ruled.

5 Alleged breach of Clause 2

COMPLAINT

Janssen-Cilag contended that Lilly's continued use of claims disparaging Risperdal, despite having given an undertaking to the Authority to the contrary, and its continued use of the leavepiece after having given a separate undertaking to Janssen-Cilag to withdraw it since it was no longer up-to-date, showed a lack of respect for the Code and industry standards bringing discredit on the industry. Janssen-Cilag alleged a breach of Clause 2.

RESPONSE

Lilly stated that given the action it had taken in withdrawing the leavepiece in September when it would not have been unreasonable to continue with its use, any suggestion that the incident alleged to have taken place in October had brought the pharmaceutical industry into disrepute was unreasonable and not supported by the facts.

PANEL RULING

The Panel noted its rulings in points 3 and 4 above and consequently ruled no breach of Clause 2 of the Code.

Complaint received **2 December 2002**

Case completed **28 January 2003**

MEDIA/DIRECTOR v SCHERING PLOUGH

Promotion of NeoClarityn

An article in Prescriber by a general practitioner was critical of the promotion of NeoClarityn (desloratadine) by Schering-Plough. In accordance with established practice the matter was taken up by the Director as a complaint under the Code.

The article referred to a conversation with a Schering-Plough representative about NeoClarityn and the detail aid used by the representative. The author gained the impression that NeoClarityn was so non-sedating that it was the only antihistamine that RAF pilots could take without failing some sort of drug test. The representative was reported as saying the medicine never caused sedation. The author considered that in medicine the words 'always' or 'never' were invariably false because there would always be a patient, or an atypical presentation of a disease, that would prove you wrong.

The Authority drew attention to the fact that a similar issue had led to breaches of the Code being ruled in Cases AUTH/1172/3/01 and AUTH/1304/6/02 and Schering-Plough might thus have failed to comply with the undertaking given in those cases. It was the Authority's responsibility to ensure compliance with undertakings. This was in accordance with advice given by the Code of Practice Appeal Board.

Turning to the present case, Case AUTH/1397/12/02, the Panel noted Schering-Plough's submission that it was unable to identify any specific representative who could have made the alleged claims.

The Panel noted that the original article was based on a conversation with a representative. The author was however unable to provide sufficient information to enable the representative or detail aid to be identified or to provide further details about precisely what was said and when. In such circumstances the company was not able to fully investigate the matter. The Panel was unable to determine precisely what was said by the representative or which detail aid had been used. The Panel was thus obliged to rule no breach of the Code.

An article in Prescriber, 19 November 2002, by a general practitioner, was critical of the promotion of NeoClarityn (desloratadine) by Schering-Plough Ltd. In accordance with established practice the matter was taken up by the Director as a complaint under the Code.

COMPLAINT

The article referred to a conversation with a Schering-Plough representative about NeoClarityn and the detail aid used by the representative. The author gained the impression that NeoClarityn was, apparently, so non-sedating that it was the only antihistamine that RAF pilots could take without failing some sort of drug test. The representative was reported as saying that this was because the medicine never caused sedation. As a medical student, the author had often been reminded that in medicine the words 'always' or 'never' were invariably false because there would always be a patient, or an atypical presentation of a disease, that would prove you wrong.

When writing to Schering-Plough, the Authority asked it to bear in mind the requirements of Clauses 2, 9.1 and 22 of the Code. The Authority drew attention to the fact that a similar issue had led to breaches of the Code being ruled in Cases AUTH/1172/3/01 and AUTH/1304/6/02 and Schering-Plough might thus have failed to comply with the undertaking given in those cases. It was the Authority's responsibility to ensure compliance with undertakings. This was in accordance with advice previously given by the Code of Practice Appeal Board.

RESPONSE

Schering-Plough noted that the Authority suggested that NeoClarityn was being promoted as having no impairment of performance, a claim it considered to be inconsistent with the summary of product characteristics (SPC).

Schering-Plough shared the Authority's concern and had taken this matter extremely seriously. It used its best endeavours to investigate this matter thoroughly, with the intention of both addressing the Authority's concerns and taking decisive disciplinary action against any employee found to have breached the Code. This investigation included, but was not restricted to reviewing: all detail aids that might have been relevant; the general training of the representatives and their specific training in relation to the issues the Authority raised; the company's overall management of promotional claims and investigating any discussions any of Schering-Plough's representatives could have had with the general practitioner.

Despite these efforts, the lack of pertinent information had made it difficult to address the concerns. The Authority's letter did not state, nor was Schering-Plough able to establish from the author, when the alleged meeting took place, who the relevant sales representative was, or even which detail aid was used.

1 The article as a basis for complaint

Schering-Plough was unable to identify the representative who could have made the alleged claims. Schering-Plough had telephoned the author and learned that the article had been written several months after the relevant meeting had occurred. Because of the length of time that had elapsed since the meeting, he was understandably unable to inform Schering-Plough when the call had taken place, who the relevant representative was, or identify the detail

aid that was used, let alone confirm the specific wording of the conversations that might have occurred. The author confirmed this in an email in which he stated:

'The article is part of a diary page, which is, by its very nature, meant to be a 'tongue-in-cheek' perspective on prescribing issues, and therefore is hopefully light-hearted and humorous. Although the story is based on a conversation with a representative from Schering-Plough, it's impossible for me to recall who the representative was, and when the contact took place.

The comical side of the conversation was the idea of testing any medication that could cause sedation out on pilots while they were engaged in 'real-life' flying, and I'm sure that there was no intent to flout or breach acceptable marketing practices by the representative during the conversation. For that reason I would not have expected that an article such as this would have resulted in a complaint under the ABPI Code.'

The author's email confirmed Schering-Plough's overriding impression of the Prescriber article; it was clearly a light-hearted, anecdotal piece, to amuse rather than criticise the marketing practices of any pharmaceutical company. With this in mind, the author might justifiably have been less than precise, and used some artistic licence, when relating the relevant events.

In discussing the idea of testing any medication that could cause sedation on pilots whilst they were engaged in 'real-life flying', the author had been successful in amusing readers. However, as the author confirmed, it was clearly not his intention to produce an accurate transcript of his meeting with a sales representative, and should not be taken as such.

Both the author and Schering-Plough believed that there was little basis for the use of such a light-hearted tongue-in-cheek, article as grounds for a complaint under the Code. Schering-Plough also did not believe its contents could be justifiably relied on as evidence of any action or statement by Schering-Plough or its employees. In any event, the author concluded that: 'I'm sure there was no intent to flout or breach acceptable marketing practices by the representative during the conversation'.

2 Acceptability of the alleged claims

The Authority referred to two previous cases: Case AUTH/1172/3/02 and Case AUTH/1304/6/02. In the former, Schwarz Pharma had complained that a Schering-Plough detail aid indicated that NeoClarityn had 'No sedation or impairment of performance'. The Authority had addressed each of these points separately.

Section 5.1 of NeoClarityn's SPC made it clear that desloratadine was non-sedating, did not readily penetrate the central nervous system and, at the recommended daily dose, resulted in no excess incidence of somnolence as compared to placebo. On this basis, the Panel had ruled that 'it was not misleading to claim that NeoClarityn caused no sedation and ruled no breach'.

In respect of the claim that NeoClarityn caused no impairment of performance, the Panel had considered this to be inconsistent with section 4.7 of the SPC, which stated that 'NeoClarityn has no or negligible influence on the ability to drive and use machines'. On that basis, it had ruled that absolute claims that NeoClarityn caused no impairment of performance were both misleading and exaggerated.

In Case AUTH/1304/4/02, the Panel had expanded this objection to the claim 'without impairing performance.' The emergence of new data confirming the lack of performance impairment by desloratadine was irrelevant because the product's SPC still stated that 'NeoClarityn has no or negligible influence on the ability to drive or use machines'.

a) The non-sedation claim

Schering-Plough stated that it seemed from these two decisions that claims relating to the lack of sedative effect of NeoClarityn were acceptable.

Schering-Plough noted that, as part of its investigations, it had reviewed all of its detail aids that the author might have seen. Nowhere in any aid, other promotional material, or any of the representatives' briefing and training materials did Schering-Plough make or recommend a claim suggesting that NeoClarityn 'never caused sedation'.

b) The flight performance claim

The next claim to which the Authority objected was that NeoClarityn was so non-sedating that it was the only antihistamine RAF pilots could take without failing some kind of drug test. While it was unclear as to whether such a claim was ever made, if it were, Schering-Plough believed it would be consistent with NeoClarityn's SPC.

Section 5.1 of the SPC stated that 'NeoClarityn given at a single daily dose of 7.5mg did not affect psychomotor performance in clinical trials. In a single dose study performed in adults, desloratadine 5mg did not affect standard measures of flight performance including exacerbation of subjective sleepiness or tasks related to flying'. The Committee for Proprietary Medicinal Product's (CPMP) Scientific Discussion published as part of the European Public Assessment Report (EPAR) for NeoClarityn made the basis of this statement clear:

'The influence of desloratadine on the ability to fly was investigated in a single dose, 3-way crossover study in 21 healthy volunteers. Desloratadine 5mg produced no detrimental effects related to flying ability, including those tasks addressing vigilance, tracking, and complex task performance or on subjective sleepiness for the measured period of 1 to 6 hours after drug administration… While the sedative effects of multiple dose treatment were not evaluated in this study, the data from this study are predictive of long-term desloratadine as:

1 desloratadine exhibits linear pharmacokinetics, as a result no unexpected accumulation has been observed after 28 days

2 the clinical experience with treatment periods up

to six weeks has shown a somnolence rate no different from placebo, and

3 there were no reports of sedation following administration of desloratadine 45mg (nine-fold the clinical dose)'.

The CPMP was sufficiently comfortable with the validity and implication of these results to allow a Type II variation of its marketing authorization to allow them to be 'reflected in the SPC section 5.1'. Even though it was doubtful that this specific claim was made, any claim that NeoClarityn did not affect the standard measures of flight performance was nevertheless consistent with the NeoClarityn's SPC and was neither misleading nor exaggerated.

Again, Schering-Plough was unable to identify any detail aid that bore a flight-related endorsement such as the one cited in the article. It was, however, possible that the author was referring to a detail aid that cited a study by the UK Government's Defence Evaluation and Research Agency ('DERA') (now the Defence Science and Technology Laboratory (DSTL)), part of the Ministry of Defence. A copy of this detail aid was provided. The study showed that desloratadine had no effect on the ability to fly and, in DERA's own words, the results of this study demonstrated that 'NeoClarityn could prove to be suitable for those involved in skilled activity and transportation'. Schering-Plough's claim was therefore consistent with the study, and therefore the SPC.

Nowhere in this detail aid or any other promotional material did Schering-Plough make a claim that RAF pilots were permitted to take NeoClarityn while on active duty. No Schering-Plough detail aid bore any endorsement similar to the advertising campaign described in the article, namely 'As used by NASA'.

One possible explanation for the Authority's view was a belief that these two claims, taken together suggested that NeoClarityn caused no impairment of performance. However, the claims were quite distinct, and Schering-Plough did not believe it was possible to draw any such inference from them. This would also be inconsistent with the Panel's analysis on Case AUTH/1172/3/01, in which sedation and performance claims were analysed separately.

Schering-Plough believed that there were strong arguments that both these claims, even in the form the Authority alleged would have been substantiated, were consistent with NeoClarityn's SPC, and were neither misleading nor exaggerated.

3 Processes to ensure compliance with the Code, and undertakings

a Training on the Code

Representatives were trained in the Code on their initial training course, and it was a condition of their continuing employment that they passed the ABPI Medical Representatives Examination and continued to work within the Code at all times. While Schering-Plough had been unable to identify the representative mentioned in the article, it could state that the representative had either passed the ABPI examination, or was in the process of training to take it.

Schering-Plough's compliance programme and corporate policy required ongoing training and testing on the Code. Schering-Plough was reassured that its representatives were effectively trained on the principles of the Code and any representative who spoke to the author of the article would have a sound knowledge of his/her responsibilities to the Code.

b Training on the adverse event profile of NeoClarityn, especially its effect on sedation

Schering-Plough provided copies of the relevant training slides and briefing documents, all of which made it clear that there was no mention of the claims referred to in the Authority's letter. The claims the representatives were trained on were in line with the SPC for NeoClarityn and complied with the Code, in particular Clause 7.

c Training of the organisation on rulings of the Authority

A synopsis of all relevant rulings of the Authority was transmitted to the sales and marketing teams to help ensure they were kept up-to-date with rulings related to Schering-Plough's products (including undertakings with regard to claims made about NeoClarityn) as well as the other rulings made by the Authority to ensure that they were well educated about the evolving framework within which they operated.

It was a condition of continued employment that representatives (and all members of sales and marketing teams) attested to, and signed, yearly, a copy of Schering-Plough's Business Conduct Policy which outlined their responsibility to abide by the local UK regulations and codes, including the ABPI Code.

d Control of promotional claims made

To ensure that neither Schering-Plough nor its employees breached the Code, and particularly that they did not breach any undertaking to the Authority, all promotional material for NeoClarityn, including representative training and briefing material, was reviewed against a list of approved and unapproved claims which Schering-Plough had provided. The unapproved claims list included every claim that Schering-Plough had undertaken to the Authority not to use. All Schering-Plough materials were checked against these lists to ensure that they were compliant with its undertakings.

Additionally, Schering-Plough had changed its arrangements for promotional material approval, which it submitted enhanced its ability to ensure that all materials complied with the Code.

4 Conclusions

Schering-Plough did not accept that the article in question demonstrated that it had, either in the letter or the spirit, breached Clauses 22, 9.1 and 2 of the Code.

The author's letter to Schering-Plough demonstrated emphatically that he did not believe that its representative caused him offence, or that it deviated from the quality standards it aspired to. It could not agree therefore that it was in breach of Clause 9.1.

Schering-Plough strongly believed that neither its activities nor its materials had brought discredit upon, or reduced confidence in, the pharmaceutical industry and there was no breach of Clause 2.

This light-hearted article by a GP writer should not be taken as a basis to reduce the confidence of the Authority, or Schering-Plough's customers, in its commitment to quality.

PANEL RULING

The Panel noted that the original article discussed 'a routine run through a detail aid about NeoClarityn'. The author noted an endorsement in the detail aid which, in the view of the author, gave the impression that 'NeoClarityn is, apparently, so non-sedating that it is the only antihistamine that RAF pilots can take without failing some sort of drug test'. Further the representative stated that NeoClarityn '… never caused sedation'.

The Panel noted that in Case AUTH/1172/3/01 the claim 'No sedation or impairment of performance' was alleged to be an all-embracing claim. The Panel noted that the NeoClarityn SPC stated that desloratadine was non-sedating. It did not readily penetrate the central nervous system and at the recommended daily dose there was no excess incidence of somnolence as compared to placebo. The SPC also stated that in some patients concentrations of desloratadine might be higher than expected; in some individuals maximum desloratadine concentration was about 3-fold higher. The safety profile of these subjects was not different to that of the general population. The Panel had considered that it was not misleading to claim that NeoClarityn caused no sedation and had ruled no breach of the Code in that regard. Turning to impairment of performance however, the Panel noted that the SPC stated 'NeoClarityn has no or negligible influence on the ability to drive or use machines'. The Panel had considered, therefore, that the claim that NeoClarityn caused no impairment of performance was misleading and exaggerated and could not be substantiated. Breaches of Clauses 7.2, 7.3 and 7.8 of the Code had been ruled.

In Case AUTH/1304/4/02 the claim 'without impairing performance' had been considered sufficiently similar to the claim 'no sedation or impairment of performance' for it to be covered by the undertaking given in the Case/AUTH/1172/3/01. A breach of Clause 22 had been ruled.

Turning to the present case, Case AUTH/1397/12/02, the Panel noted Schering-Plough's submission that it was unable to identify any specific representative who could have made the alleged claims. Schering-Plough submitted that it had been advised by the author that he had written the article several months after the relevant meeting had occurred. A letter written by the author to the company stated that the article by its very nature (a diary page) was meant to be a 'tongue-in-cheek' perspective on prescribing issues and was described as 'light-hearted and humorous'. The author stated that it was impossible for him to recall who the representative was and when the contact took place.

The Panel noted the comments made by the author including his letter to the Authority. The author stated that the article was written in September 2002 and it was possible that the interview took place several months before the article was written in the first few months of 2002. The author was unable to give any specifics about the conversation.

The Panel noted that a detail aid ref NCL/02 285 featured the claim 'Two studies including one by DERA (the Defence Evaluation and Research Agency) have confirmed that NeoClarityn could be suitable for those involved in skilled activity and transportation' above a photograph of a fighter plane taking off. The Panel queried whether the image of a fighter plane taking off was consistent with the company's submission that the detail aid did not claim that RAF pilots were permitted to take NeoClarityn while on active duty.

The Panel noted that the original article was based on a conversation with a representative. The diary page was described by its author as light-hearted and humorous. The author was however unable to provide sufficient information to enable the representative or detail aid to be identified or to provide further details about precisely what was said and when. In such circumstances the company was not able to fully investigate the matter. The Panel was unable to determine precisely what was said by the representative or which detail aid had been used. The Panel was thus obliged to rule no breach of Clauses 2, 9.1 and 22 of the Code.

Proceedings commenced **5 December 2002**

Case completed **28 January 2003**

CASE AUTH/1400/12/02

NOVARTIS v ASTRAZENECA

Promotion of Arimidex

Novartis complained about the promotion of Arimidex (anastrozole) by AstraZeneca. At issue were a journal advertisement, a leavepiece and a mailing each of which referred to the use of Arimidex in early breast cancer. Reference was made to the ATAC (Arimidex, Tamoxifen Alone or in Combination) study. The first results had been published in June 2002.

The Arimidex summary of product characteristics (SPC) stated that the product was indicated for the treatment of advanced breast cancer in postmenopausal women and that efficacy had not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen. An indication for adjuvant treatment of postmenopausal women with oestrogen receptor positive early invasive breast cancer who were unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities had recently been added. The ATAC study had been used by AstraZeneca in applying for this new indication.

Novartis stated that the patients with early breast cancer in the ATAC study were different from those for whom Arimidex was licensed. Postmenopausal women were eligible for inclusion in the study if they had histologically proven operable invasive breast cancer, had completed primary surgery and chemotherapy, and were candidates to receive hormonal adjuvant therapy; there was no suggestion that they were selected on the basis of inability to take tamoxifen. Indeed, in two out of the three study arms tamoxifen was included as a trial medicine. In contrast, the SPC for Arimidex specifically excluded patients able to take tamoxifen. Therefore whilst a small percentage of patients in the ATAC study might have coincidentally received Arimidex in compliance with the licence, the vast majority had not. As such it was inappropriate to use this data to promote the efficacy of Arimidex. The promotional material included a claim of '22% risk reduction versus tamoxifen for disease-free survival'. Novartis alleged that AstraZeneca was misleading the prescriber and promoting outside the marketing authorization.

The Panel noted from the Arimidex SPC that the indication for treatment of early breast cancer was limited to patients who were unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities. These limitations needed to be reflected in the promotional material. The journal advertisement, the leaflet and the mailing all referred to the new indication.

The Panel noted that the ATAC study compared tamoxifen (established adjuvant treatment) with anastrozole alone and in combination with tamoxifen as adjuvant treatment for postmenopausal women with early invasive operable breast cancer. The study was designed to answer three questions: Was anastrozole at least as effective as tamoxifen?; Did anastrozole offer any safety or side effect benefits over tamoxifen? and Could a combination of anastrozole plus tamoxifen offer additional efficacy or safety benefits over tamoxifen alone? Disease-free survival estimates at 3 years were 89.4% for patients on anastrozole and 87.4% for patients on tamoxifen (p=0.013). Results with the combination were not significantly different from those with tamoxifen alone. The improvement in disease-free survival with anastrozole was seen in the subgroup of hormone receptor positive patients but not the receptor negative patients. Overall survival was a secondary endpoint but there were insufficient events at the time of publication of the first results for formal analysis.

The Panel considered that the ATAC study protocol was not designed to select breast cancer patients who were unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities. There was no specific data on this set of patients.

In the journal advertisement the headline claims were '22% risk reduction versus tamoxifen for disease-free survival' and 'It's about time'. The product logo appeared with the strapline 'in early breast cancer'. The statement 'Adjuvant treatment of postmenopausal women with oestrogen receptor positive early invasive breast cancer who are unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities' appeared in small print across the bottom of the advertisement just below the product logo.

The Panel considered that the advertisement implied that in the treatment of postmenopausal women with early breast cancer, prescribers had a simple choice between tamoxifen and Arimidex. This was not so. Arimidex could only be used in patients with oestrogen receptor positive early invasive breast cancer who were unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities. The Panel considered that the advertisement was inconsistent with the SPC. A breach of the Code was ruled.

The Panel considered that it was misleading to claim '22% risk reduction versus tamoxifen for disease-free survival' as there was no way of knowing if the 22% risk reduction, which was based on all receptor positive patients, would also apply to the high-risk group of receptor positive patients with early breast cancer for whom Arimidex was licensed. The Panel ruled a breach of the Code.

Page 2 of the leavepiece included the three claims '22% risk reduction versus tamoxifen for disease-free survival (p=0.005)', '58% reduction in the odds of developing contralateral breast cancer versus tamoxifen (p=0.007)' and 'Significant tolerability benefits compared with tamoxifen'. The statement 'New licence for adjuvant treatment of postmenopausal women with oestrogen receptor positive early invasive breast cancer who are unable to take tamoxifen therapy because of high risk of

thromboembolism or endometrial abnormalities' appeared in a highlighted box at the bottom of the same page. Beneath this statement a footnote to the claim '22% risk reduction versus tamoxifen for disease-free survival (p=0.005)' read 'in hormone-receptor-positive patients'.

The Panel considered that its rulings above were relevant here; in relation to each claim it was not known whether the benefits seen would apply to the subset of high-risk patients for whom Arimidex was licensed. The Panel ruled breaches of the Code.

The mailing consisted of a letter, a reply paid card for requesting additional information and a leaflet. The leaflet claimed that Arimidex was superior to tamoxifen in adjuvant treatment of early breast cancer. Both the letter and the leavepiece included similar claims to those in the leavepiece.

The Panel considered that the claim in the leaflet that Arimidex was 'Superior to tamoxifen' added further weight to the impression that prescribers had a simple choice between the two agents and would encourage doctors to prescribe Arimidex in preference to tamoxifen and not just for those high-risk patients unable to take tamoxifen in line with the SPC. The Panel considered that its comments and rulings above were relevant here; breaches of the Code were ruled.

Novartis Pharmaceuticals UK Ltd complained about the promotion of Arimidex (anastrozole) by AstraZeneca UK Limited.

The Arimidex summary of product characteristics (SPC) stated that it was indicated for the treatment of advanced breast cancer in postmenopausal women and that efficacy had not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen. Recently, an indication for adjuvant treatment of postmenopausal women with oestrogen receptor positive early invasive breast cancer who were unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities had been added to the SPC.

The material at issue was a journal advertisement (ref ARI 02/11578), a leavepiece (ref ARI 02/11349) and a mailing which consisted, *inter alia*, of a letter (ref ARI 02/11352b), and a leaflet (ref ARI 02/11352a). All the materials referred to the use of Arimidex in early breast cancer. Reference was made to the ATAC (Arimidex, Tamoxifen Alone or in Combination) study. The first results had been published in June 2002.

COMPLAINT

Novartis stated that the promotional materials placed emphasis on the results of the ATAC study to support claims made in relation to the recently revised licensed indication. Novartis stated that the population of patients represented in the ATAC study was different from the population represented by the licensed indication statement.

The current SPC for Arimidex included a very specific approved licensed indication, 'Adjuvant treatment of postmenopausal women with oestrogen receptor positive early invasive breast cancer who are unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities'.

The selection of promotional materials for Arimidex included a claim of '22% risk reduction versus tamoxifen for disease-free survival'.

Novartis stated that in contrast to the SPC statement, postmenopausal women were eligible for inclusion in the study if they had histologically proven operable invasive breast cancer, had completed primary surgery and chemotherapy, and were candidates to receive hormonal adjuvant therapy. There was no suggestion that patients enrolled in the study were selected on the basis of inability to take tamoxifen. Indeed, in two out of the three study arms tamoxifen was included as a trial medicine. In contrast, the SPC for Arimidex specifically excluded patients able to take tamoxifen.

Novartis' opinion therefore was that whilst a small percentage of patients in the ATAC study might have coincidentally received Arimidex in compliance with the licence, the vast majority had not. As such it was inappropriate that AstraZeneca should be using this data to promote the efficacy of Arimidex. By doing so AstraZeneca was misleading the prescriber in breach of Clause 7.2 and promoting outside the marketing authorization in breach of Clause 3.2 of the Code.

RESPONSE

AstraZeneca stated that, on the basis of the first protocolled analysis of the ATAC trial, the Arimidex licence had recently been varied to include the following indication: 'Adjuvant treatment of postmenopausal women with oestrogen receptor positive early invasive breast cancer who are unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities'.

The primary objective of the ATAC trial was to compare the efficacy and tolerability of Arimidex and combined Arimidex and tamoxifen versus tamoxifen alone in the adjuvant treatment of early breast cancer.

The ATAC trial was conducted in women with hormone receptor positive (or unknown) breast cancer tumours. The protocol was not designed to select breast cancer patients who were at high risk of thromboembolism or endometrial abnormalities. Instead, the selection criterion used was whether patients were eligible candidates for hormonal treatment of their breast cancer, having completed primary therapy (surgery and chemotherapy where given). Observations were therefore, and still continued to be, made on a more general population.

On first analysis of the ATAC results, superior efficacy, in terms of disease-free survival, against tamoxifen alone was demonstrated. Further efficacy analysis at 47 months (thus extending the medical follow-up for the primary endpoint) provided additional confirmation. However it also became obvious that in the Arimidex arm there was a lower incidence of both thromboembolism and endometrial abnormalities compared with tamoxifen alone. The ATAC steering committee would have been unable to

predict such events with any certainty prior to the study being conducted.

The resulting licence for Arimidex therefore reflected the results of the ATAC trial.

AstraZeneca disagreed with Novartis' comments that the patient population in the ATAC trial was different to that represented by the licensed indication. The population represented by the licence was part of the population represented in the ATAC trial. Indeed it was unfair of Novartis to state that only a small proportion of patients in the ATAC trial might have received Arimidex in accordance with the new licence. As mentioned before, the ATAC trial was not designed to specifically stratify out a high-risk population. A retrospective analysis could not provide such data. The exact number was therefore unknown. However given the mean age of the ATAC trial population (64.1 years for both the Arimidex and tamoxifen arms and 64.3 years in the combination arm) and the nature of the disease it was unlikely to be a small proportion of patients who were at high risk from thromboembolism or endometrial abnormalities.

Novartis also commented on the fact that two out of the three treatment arms in the ATAC trial included tamoxifen, while the new licence for Arimidex was for those patients not able to take tamoxifen.

For the treatment of early breast cancer, tamoxifen had been the most established and used medicine in the adjuvant setting for almost 20 years. Therefore in order to accurately assess the efficacy of Arimidex in this particular setting the comparison with tamoxifen was essential. Without this comparison in the ATAC trial, there would have been no grounds from which a licence extension could have been based.

The claim '22% risk reduction versus tamoxifen for disease-free survival' which featured in the journal advertisement was supported by the published report of the ATAC trial. Disease-free survival was a well established and recognised efficacy measure of early breast cancer treatment and was one of the primary endpoints for the ATAC trial.

In addition to this, section 5.1 of the Arimidex SPC included the wording:

'In a large phase III study conducted in 9366 postmenopausal women with early invasive breast cancer, adjuvant treatment with anastrozole following surgery showed statistical superiority over tamoxifen for the primary endpoint time to disease recurrence.'

The advertisement also featured the wording of the new licence as in the SPC.

In summary, the results of the ATAC trial had satisfied the regulatory authorities sufficiently to grant AstraZeneca a licence for Arimidex in the adjuvant treatment of early breast cancer in women who were unable to take tamoxifen because of high risk of thromboembolism or endometrial abnormalities. Consequently AstraZeneca did not consider using the results of a pivotal regulatory trial that formed the basis of a licence approval in promotional material inappropriate. All promotional material included the exact wording of the new indication with no implication that Arimidex should be prescribed in all patients with early disease.

AstraZeneca did not consider that the use of the ATAC trial data would result in a health professional being misled as to how Arimidex should be prescribed in the adjuvant breast cancer setting. Nor did AstraZeneca consider that it had promoted outside the current licence.

PANEL RULING

The Panel noted that the change in the Arimidex SPC was such that the product was now indicated for use as adjuvant treatment in early postmenopausal invasive breast cancer as well as in advanced breast cancer. The indication for treatment of early breast cancer was limited to patients who were unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities. These limitations needed to be reflected in the promotional material. The journal advertisement, the leaflet and the mailing all referred to the new indication.

The Panel noted that the ATAC study compared tamoxifen (established adjuvant treatment) with anastrozole alone and in combination with tamoxifen as adjuvant treatment for postmenopausal women with early invasive operable breast cancer. The study was designed to answer three questions:

a Was anastrozole at least as effective as tamoxifen?

b Did anastrozole offer any safety or side effect benefits over tamoxifen?

c Could a combination of anastrozole plus tamoxifen offer additional efficacy or safety benefits over tamoxifen alone?

Disease-free survival estimates at 3 years were 89.4% for patients on anastrozole and 87.4% for patients on tamoxifen (p=0.013). Results with the combination were not significantly different from those with tamoxifen alone. The improvement in disease-free survival with anastrozole was seen in the subgroup of hormone receptor positive patients but not the receptor negative patients. Overall survival was a secondary endpoint but there were insufficient events at the time of publication of the first results for formal analysis. Anastrozole was significantly better tolerated than tamoxifen with respect to endometrial cancer, vaginal bleeding and discharge, cerebrovascular events, venous thromboembolic events and hot flushes. Tamoxifen was significantly better tolerated than anastrozole with respect to musculoskeletal disorders and fractures.

The authors stated that although tamoxifen was relatively well tolerated about 30% of women complained of hot flushes, vaginal discharge or vaginal bleeding. Less common although much more serious were the long-term risks of endometrial cancer and thromboembolic disease. For these reasons, in addition to the potential in the adjuvant setting for improved efficacy, the study was undertaken.

The Panel noted AstraZeneca's submission that it did not consider that the use of a pivotal regulatory trial

that formed the basis of a licence approval in promotional material was inappropriate. The Panel noted that such use must of course comply with the Code. The Panel considered that this was a difficult matter. The ATAC study protocol was not designed to select breast cancer patients who were unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities. There was no specific data on this set of patients. The Panel further noted that the ATAC study had been used by AstraZeneca in applying for the change in indication.

1 Journal advertisement

The headline claims were '22% risk reduction versus tamoxifen for disease-free survival' and 'It's about time'. The product name appeared in logo format with the strapline 'in early breast cancer'. The statement 'Adjuvant treatment of postmenopausal women with oestrogen receptor positive early invasive breast cancer who are unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities' appeared in small print across the bottom of the advertisement just below the product logo.

The Panel considered that the licensed indication for the use of Arimidex in preference to tamoxifen had not been made sufficiently clear. The advertisement implied that in the treatment of postmenopausal women with early breast cancer, prescribers had a simple choice between tamoxifen and Arimidex. This was not so. Arimidex could only be used in patients with oestrogen receptor positive early invasive breast cancer who were unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities. The Panel considered that the advertisement was inconsistent with the SPC. The Panel noted the statement included at the bottom of the advertisement but considered that this did not negate the overall impression given by the advertisement. The Panel ruled a breach of Clause 3.2 of the Code.

The Panel considered that it was misleading to claim '22% risk reduction versus tamoxifen for disease-free survival' as there was no way of knowing if the 22% risk reduction, which was based on all receptor positive patients, would also apply to the high-risk group of receptor positive patients with early breast cancer for whom Arimidex was licensed. The Panel ruled a breach of Clause 7.2 of the Code.

2 Leavepiece

Page 2 of the leavepiece included the three claims '22% risk reduction versus tamoxifen for disease-free survival (p=0.005)', '58% reduction in the odds of developing contralateral breast cancer versus tamoxifen (p=0.007)' and 'Significant tolerability benefits compared with tamoxifen'. The statement '**New licence for** adjuvant treatment of postmenopausal women with oestrogen receptor positive early invasive breast cancer who are unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities' appeared in a highlighted box at the bottom of the same page. Beneath this statement a footnote to the claim '22% risk reduction versus tamoxifen for disease-free survival (p=0.005)' read 'in hormone-receptor-positive patients'.

The Panel noted that there were differences between the advertisement at issue at point 1 and the leavepiece. The licensed indication was given greater prominence. The patient population in whom the 22% risk reduction was obtained was described as hormone receptor positive. Nonetheless the Panel considered that its rulings at point 1 were relevant here; in relation to each claim it was not known whether the benefits seen would apply to the subset of high-risk patients for whom Arimidex was licensed.

The Panel ruled breaches of Clauses 3.2 and 7.2 of the Code.

3 Mailing

The mailing consisted of a letter, a reply paid card for requesting additional information and a leaflet. The letter included similar claims to the leavepiece. The leaflet claimed that Arimidex was superior to tamoxifen in adjuvant treatment of early breast cancer. It included similar claims to those in the leavepiece.

The Panel considered that the claim in the leaflet that Arimidex was 'Superior to tamoxifen' added further weight to the impression that prescribers had a simple choice between the two agents and would encourage doctors to prescribe Arimidex in preference to tamoxifen and not just for those high-risk patients unable to take tamoxifen in line with the SPC.

The Panel considered that its comments and rulings at points 1 and 2 above were relevant here; breaches of Clauses 3.2 and 7.2 were ruled.

Complaint received **16 December 2002**

Case completed **20 February 2003**

CASE AUTH/1404/12/02

WYETH v NOVO NORDISK

Meeting and local treatment guidelines

Wyeth complained about the involvement of Novo Nordisk in a meeting on hormone replacement therapy (HRT) and in the preparation of local NHS trust treatment guidelines on the menopause. Wyeth stated that the meeting 'Hormone Replacement Therapy – What a Year! So, where are we now?' was organised by Novo Nordisk's representative whose mobile telephone number and address were given on the programme. This clearly constituted sponsorship which should have been stated on the programme, together with the company name.

The Panel noted that the meeting had been arranged to launch local treatment guidelines. Four companies had sponsored the meeting; three with donations and the fourth, Novo Nordisk, with administrative support. None of the companies had had any role in the selection of speakers, topics or delegates. The Panel noted the submission that the doctors who had organised the meeting wished it to be seen to be independent of pharmaceutical company influence. The Panel considered that a statement to reflect the companies' involvement should have been on the invitation; such a statement did not preclude an assurance regarding the independence of the meeting content. The Panel considered that the failure to declare Novo Nordisk's role meant that the company had failed to declare its sponsorship of the meeting on the invitation and a breach of the Code was ruled.

Wyeth noted that at the bottom of the second page of the local treatment guidelines was the statement 'Facilitated by [the name of a Novo Nordisk representative]'. There were no details as to whom the person was. This constituted sponsorship. The guidelines were clearly derived from the local formulary which had a similar flowchart structure but contained no brand names. Product names had been added to the guidelines at issue and this was alleged to be disguised promotion. There was also no date of preparation or reference number, and no prescribing information. There was a selective listing of HRT products, mostly those from Novo Nordisk, which notably excluded all of Wyeth's products. This was neither balanced nor fair. Wyeth stated that the guidelines were given out at meetings etc.

The Panel noted that the only reference on the guidelines to Novo Nordisk's involvement was the statement 'Facilitated by [name]'. The Panel considered that this was insufficient to meet the requirements of the Code; readers of the guidelines would be unaware of Novo Nordisk's involvement. The Panel considered that a statement acknowledging the company's administrative help with guidelines should have been included; such a statement did not preclude an assurance of the independence of the guidelines. The Panel considered that the failure to declare Novo Nordisk's role meant that the company had failed to declare its sponsorship of the guidelines and a breach of the Code was ruled.

The Panel noted that Novo Nordisk's only involvement had been the provision of administrative support; the company had not influenced the content of the guidelines. Novo Nordisk had not used the guidelines promotionally. The Panel thus did not consider that the company was liable under the Code for the content of the guidelines and in that regard the Director determined that there was no *prima facie* case to answer.

Wyeth Pharmaceuticals complained about the involvement of Novo Nordisk Limited in a meeting on hormone replacement therapy (HRT) and in the preparation of guidelines on the menopause. Correspondence between the parties had failed to resolve the issues.

1 Meeting entitled 'Hormone Replacement Therapy – What a Year! So, where are we now?'

COMPLAINT

Wyeth stated that this meeting was organised by a Novo Nordisk representative whose mobile telephone number and address were given on the programme. This clearly constituted sponsorship which should have been stated on the programme, together with the company name. Wyeth alleged that the absence of such a statement constituted a breach of Clause 9.9 of the Code.

RESPONSE

Novo Nordisk noted that Clause 9.9 stated that 'Material relating to medicines and their uses, whether promotional in nature or not, which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company'. This was a safeguard to make readers of such sponsored material aware of sponsorship at the outset. It was not a specific requirement of Clause 19 to declare sponsorship of meetings in advance though under Clause 10 promotional activities must not be disguised. Clearly any material produced as a result of the meeting would have to declare sponsorship as required by the Code. The key point here was that the two local treatment guidelines were developed a priori and independently of any pharmaceutical company. No material was produced/modified as a result of this meeting and therefore Novo Nordisk believed there was no breach of Clause 9.9.

Novo Nordisk explained that the purpose of the meeting was to launch the local HRT and menopause clinic guidelines, to encourage discussion on the recent controversy surrounding HRT, and to see how this might affect local clinical practice. The meeting was hosted by a local doctor and was of considerable educational value. The key point was that the meeting, but not the guidelines, was 'sponsored' by four named pharmaceutical companies. This sponsorship allowed each company to have a stand at the meeting. No company had any involvement in the selection of topics, speakers or delegates. The meeting was open to all GPs and practice nurses in the region. Each of the four companies donated

approximately £150. Novo Nordisk's representative provided administrative support for the meeting including the application for postgraduate approval. As was common practice in this area, the representative acted as a contact for the invitees to confirm their attendance and in order to do this, a mobile telephone number was given on the invitation and the representative's address was used for invitees to respond to. This was done because of a lack of resource within the NHS and at the express wish of one of the doctors organising the meeting who had previously used the services of the representative. In addition there was a cost saving in applying for postgraduate education allowance (PGEA) since the representative had a 'season ticket' and the doctor applying would have had to pay the full application fee. As a result of the representative donating her administrative skills, Novo Nordisk was allowed to have a stand at the meeting although it did not actually donate any money. The invitation did not indicate that the telephone number and address belonged to a Novo Nordisk employee and the representative's answer-phone message had been changed and did not state that she had any connection with Novo Nordisk. The purpose of this arrangement was to be in accordance with the wishes of the organisers that the meeting should be seen to be independent of any pharmaceutical company influence. The Wyeth employee who telephoned the representative asked expressly if she was a Novo Nordisk employee and she answered truthfully. It was clear to Novo Nordisk that the invitees would not have associated this meeting with Novo Nordisk, or any other company which, considering that no company influenced the meeting, was not misleading and it was hard to see how its representative could have behaved more professionally.

Novo Nordisk stated that the reason for the meeting organisers not wanting to name companies on the invitations to meetings was disappointing though completely understandable. It had been their past experience that some companies initially declared an intention to support a meeting but subsequently changed their minds. If this change of heart took place after the printing of the invitations those companies effectively received credit for something they did not do.

PANEL RULING

The Panel noted that Novo Nordisk had tried to meet the wishes of the organisers. The first priority for pharmaceutical companies in such situations must be to ensure that their activities complied with the Code.

The Panel noted that two clauses of the Code referred to declaration of sponsorship; Clause 9.9 as alleged by the complainant and also Clause 19.3 which related specifically to the sponsorship of meetings. Wyeth had not alleged a breach of Clause 19.3. Nevertheless the Panel noted that Clause 19.3 stated that 'When meetings are sponsored by pharmaceutical companies, that fact must be disclosed in all of the papers relating to the meetings and in any published proceedings. The declarations of sponsorship must be sufficiently prominent to ensure that readers are aware of it at the outset'. The supplementary information to Clause 19.3, *inter alia*, referred the reader to the requirements of Clause 9.9.

The meeting in question had been arranged to launch local treatment guidelines on the use of HRT. Four companies had sponsored the meeting; three with donations of approximately £150 each and the fourth, Novo Nordisk, with administrative support. None of the companies had had any role in the selection of speakers, topics or delegates. The Panel noted the submission that the doctors who had organised the meeting wished the event to be seen to be independent of pharmaceutical company influence. Four companies had, however, provided financial support or administrative support which had enabled the meeting to take place. The Panel considered that a statement to reflect the companies' involvement should have been on the invitation; such a statement did not preclude an assurance regarding the independence of the meeting content. Regardless of the organisers' wishes, the Panel considered that the failure to declare Novo Nordisk's role meant that the company had failed to declare its sponsorship of the meeting on the invitation. The Panel therefore ruled a breach of Clause 9.9 of the Code as alleged.

During its consideration of this matter the Panel was concerned that, at the meeting organisers' request, the Novo Nordisk representative had changed her answer-phone message so that when delegates telephoned to confirm their attendance they heard no reference to the company name. The Panel considered that delegates should have been aware that the meeting administrator was in fact a Novo Nordisk representative. In that regard the Panel noted the principle behind Clause 15.5 of the Code that representatives should not mislead as to their identity or that the company they represented. The Panel requested that Novo Nordisk be advised of its concerns in this regard.

2 Local NHS trust guidelines

COMPLAINT

Wyeth noted that at the bottom of the second page of the guidelines was the statement 'Facilitated by [name]'. This constituted sponsorship as in point 1 above and was alleged to be in breach of Clause 9.9. The guidelines were clearly derived from the local formulary which had a similar flowchart structure but contained no brand names. Product names had been added to the guidelines at issue and this was alleged to be disguised promotion in breach of Clause 10. There was also no date of preparation in breach of Clause 4.9 or reference number, and no prescribing information in breach of Clause 4.1. There was a selective listing of HRT products, mostly those from Novo Nordisk, which notably excluded all of Wyeth's products. This was neither balanced nor fair in breach of Clause 7.2.

Wyeth stated that the guidelines were given out at meetings etc.

RESPONSE

Novo Nordisk stated that the guidelines in question did not arise from the meeting and so it could not see

how a breach of Clause 9.9 could be alleged. Novo Nordisk did not sponsor the guidelines and was not involved in the construction of the flow diagram or the choice of products listed as examples. Novo Nordisk provided a copy of a letter from one of the doctors organising the meeting confirming this. The guidelines were therefore not promotional items of Novo Nordisk and Novo Nordisk could not be accountable for their contents. Therefore Novo Nordisk did not believe that any other of the alleged breaches had occurred since these could de facto only apply to a company's promotional material or promotional aids.

Novo Nordisk explained that the guidelines at issue had recently been updated in view of the recent Women's Health Initiative (WHI) study and the new version was launched at the meeting at issue in point 1 above. It was therefore an old and obsolete version of the guidelines about which Wyeth was complaining and so Novo Nordisk would limit its comments to this previous version, which was no longer circulated, other than to say that the current version contained no reference to Novo Nordisk or to the named representative.

The guidelines were launched in June 2002 at an update day which was sponsored by nine companies each contributing £400 of financial support. These nine companies did not include Novo Nordisk, but did include Wyeth. The meeting was open to all GPs and practice nurses in the region (as per the meeting at point 1 above) but on this occasion the delegates were asked to make a financial contribution. A total of six hours of PGEA was approved. For the reasons stated above none of the companies involved were named on the invitation at the wishes of the organisers. All of the companies had a stand at the meeting and were verbally acknowledged as having made a contribution and so their sponsorship was apparent. It was an important fact that the doctor organising the meeting was not aware of any copies of these guidelines being subsequently made available to anyone not present at the meeting and so anyone in receipt of a copy would have been aware of the participating companies' sponsorship of the meeting. Novo Nordisk stressed that it was the meeting which was sponsored and not the guidelines which were independently prepared in advance by the authors and not modified as a result of the meeting. Novo Nordisk believed that if the industry wished to be involved with facilitating education for GPs then there must be flexibility within the Code to enable companies to meet the needs of the meeting organisers whilst in no way appearing to be disguised promotion. Novo Nordisk firmly believed that this meeting was consistent with both the letter and the spirit of the Code.

The guidelines were compiled by three health professionals who were mentioned as the contributors on the guidelines themselves. The guidelines stated 'Facilitated by [name]', but did not mention Novo Nordisk. This was because the authors wanted to acknowledge the representative's administrative support during the development of the guidelines. However the representative was not aware that her name would appear on the guidelines and neither she nor Novo Nordisk had any influence on the guidelines or the products chosen to be mentioned as examples within them. To suggest otherwise was to call into question the independence of the contributors. Novo Nordisk noted that the products of its competitor companies were mentioned frequently, for example Evorel (five times in different preparations), Femoston, Adgyn Estro, Elleste Solo (twice), FemSeven (three times) and Progynova. It was because of the three contributors' individual preferences that no Wyeth products were chosen as examples but Novo Nordisk noted that these products were given as examples using 'eg' and not as the only product or choice of products available to a GP. At the time that the guidelines were developed, the local formulary, to which Wyeth referred, had not been updated for four years and was in the process of review; the formulary guidelines were only made available online, after the production of the guidelines being complained about, and the latter were not derived from them as Wyeth had alleged. The doctor organising the meeting set out exactly who was involved in the production of each of the guidelines. The guidelines were given in paper copy only to the GPs and nurses who requested them at the meeting in June and were not distributed by anyone after this meeting. They were specifically not a promotional aid of Novo Nordisk and were not used as such by its representative. As such they did not require a date of preparation, reference number or prescribing information. Novo Nordisk clearly could not comment on the use or otherwise of these guidelines by other companies.

Novo Nordisk repeated that it did not have any influence or involvement in the production of these guidelines and that its representative had behaved in a most professional manner in complying with the wishes of the meeting organisers, specifically with their express request to not have the names of the sponsoring companies on the invitations to their meetings for the reason detailed above. Novo Nordisk reiterated that any recipient of the guidelines which had been replaced, would have been present at the meeting on 5 June and been aware of all the companies involved in supporting the study day. Novo Nordisk did not believe therefore that it had breached the Code. Furthermore the company considered that it would be hugely damaging to the relationships between health professionals and the pharmaceutical industry if practical help such as applying for PGEA approval was seen as disguised promotion. Novo Nordisk hoped that the specimen letter referring to the meeting at which the guidelines were launched was testimony to that. No letters were written for the December meeting as it was arranged by telephone but the same principles applied.

PANEL RULING

The Panel noted its comments in point 1 above with regard to companies meeting the wishes of organisers but at the same time being liable under the Code for their own activities.

The Panel noted that Clause 9.9 of the Code stated that 'Material relating to medicines and their uses,

whether promotional in nature or not, which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company'. Supplementary information to Clause 9.9 stated that the declaration of sponsorship must be sufficiently prominent to ensure that readers of sponsored material were aware of it at the outset. The menopause guidelines at issue clearly related to medicines and their uses. Novo Nordisk had sponsored the guidelines in that its representative had provided administrative support. The only reference on the guidelines to Novo Nordisk's involvement was the statement 'Facilitated by [name]'. The Panel considered that this was insufficient to meet the requirements of Clause 9.9 of the Code; readers of the guidelines would be unaware of Novo Nordisk's involvement. The Panel considered that a statement acknowledging the company's administrative help with guidelines should have been included; such a statement did not preclude an assurance of the independence of the guidelines. Regardless of the authors' wishes, the Panel considered that the failure to declare Novo Nordisk's role meant that the company had failed to declare its sponsorship of the guidelines. The Panel therefore ruled a breach of Clause 9.9 of the Code.

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

The Panel noted that although the guidelines mentioned some of Novo Nordisk's products, the company's only involvement had been the provision of administrative support; the company had not influenced the content of the guidelines. Novo Nordisk had not used the guidelines promotionally. One of the authors of the guidelines had confirmed that no company had had any input into the writing of the guidelines and that they were only distributed to GPs at the meeting. The Panel thus did not consider that Novo Nordisk was liable under the Code for the content of the guidelines and in that regard the Director determined that there was no *prima facie* case to answer.

Complaint received **23 December 2002**

Case completed **17 February 2003**

CASE AUTH/1407/1/03

DIRECTOR v PHARMACIA

Zydol journal advertisement

The Panel had previously considered a complaint (Case AUTH/1368/10/02) that a journal advertisement had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one the subject of complaint appeared in the same journal. These were taken up with the companies concerned.

The current case concerned two facing pages. The left-hand page was a typical journal advertisement for Pharmacia's product Zydol (tramadol) which included prescribing information. The right-hand page, presented more in the style of an 'advertorial', was headed 'Advertisement feature chronic pain', with the sub-heading 'The challenge of chronic pain'. The use of Zydol in the treatment of chronic pain was discussed in detail: prescribing information was not included. Both pages included the same reference number. The design of the material was such that it appeared to consist of two one page advertisements and not one two page advertisement.

The Panel considered that the presentation and style of each page was so different that they were designed to be read as two separate pages and not as a double page spread as submitted by Pharmacia. Each page needed prescribing information and so a breach of the Code was ruled with regard to the right-hand page.

The Panel had previously considered a complaint (Case AUTH/1368/10/02) that an advertisement in the NHS Journal of Healthcare Professionals (September 2002) had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one the subject of complaint appeared in the journal. These were taken up with the companies concerned.

Case AUTH/1407/1/03 concerned two facing pages. The left-hand page was a typical journal advertisement for Pharmacia Limited's product Zydol (tramadol) which included prescribing information. The right-hand page, presented more in the style of an 'advertorial', was headed 'Advertisement feature chronic pain', with the sub-heading 'The challenge of chronic pain'. The use of Zydol in the treatment of chronic pain was discussed in detail: prescribing information was not included. Both pages included the same reference number, P8002/07/02.

COMPLAINT

The design of the material was such that it appeared to consist of two one page advertisements and not one two page advertisement. Attention was drawn to Clause 4.1 of the Code.

RESPONSE

Pharmacia stated that the advertisement included prescribing information on the left-hand side of the double page spread, but not on the right-hand side, and the issue was whether the right-hand side was part of the same advertisement or a separate stand-alone item.

The advertisement in question had always been treated as a single advertisement. It was certified as a single item with each page carrying the same unique identifier – P8002/07/02. If necessary Pharmacia could provide confirmation from the agency or journal that the advertisement was set up as a single double page spread. At the first draft stage, when the concept was that of a single page advertorial, it was identified that prescribing information was needed and the left-hand page was added with the sole purpose of fulfilling that requirement.

Pharmacia noted that the prescribing information on the left-hand side filled one third of the page and was adjacent to the advertorial. Pharmacia believed that a statement to the effect that the prescribing information could be found opposite was not necessary for the average reader.

The only possible confusion might arise from the different format of the right- and left-hand pages. The reasons for that were clear. The left-hand side was a light-hearted advertisement using cartoon figures and containing no scientific material. Such a format would not be appropriate for the right-hand side which had serious scientific content. Pharmacia was not aware of any definitions within the Code that helped decide whether this advertisement was in fact two advertisements.

Pharmacia noted the reference to a complaint about an advertisement in the same issue of the journal, and several similar cases within the same issue. Although it did not know which advertisements were at issue, a brief review of the journal indicated several advertorials. Pharmacia listed four of these which it stated were classed as 'Advertisements' yet made no attempt to provide prescribing information within the piece or on adjacent pages. Pharmacia did not wish to lodge complaints regarding these items and merely cited them as advertorials which were not similar to that placed by Pharmacia and therefore should not be used to set precedent.

In summary, Pharmacia maintained that the material at issue was a single advertisement which complied with the Code. The company acknowledged, however, that the different styles of the two halves might create the false impression that these were separate pieces. It would ensure that the confusion did not arise in the future.

PANEL RULING

The Panel had to decide whether the material consisted of two one-page advertisements or one two-page advertisement.

The Panel considered that the advertisement for Zydol on the left-hand page was a typical journal advertisement. Prescribing information was included.

The facing page, headed 'Advertisement feature chronic pain', had the appearance of an article and did not appear to be linked to the advertisement opposite. It was a different colour and style to the advertisement on the facing page. The right-hand page presented a detailed discussion of the use of Zydol in the treatment of chronic pain. The Panel noted that each page included the same reference number but did not consider that this alone was sufficient to support the submission that the material was a two page advertisement.

The Panel considered that the presentation and style of each page was so different that they were designed to be read as two separate pages and not as a double page spread as submitted by Pharmacia. Each page needed prescribing information and so a breach of Clause 4.1 of the Code was ruled with regard to the right-hand page headed 'Advertisement feature chronic pain'.

Proceedings commenced 10 January 2003

Case completed 20 February 2003

CASE AUTH/1408/1/03

DIRECTOR v ELAN PHARMA

Actiq journal advertisement

The Panel had previously considered a complaint (Case AUTH/1368/10/02) that a journal advertisement had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one the subject of complaint appeared in the same journal. These were taken up with the companies concerned.

The current case concerned a two page advertisement headed 'Cancer pain relief' and 'Advertisement' which was presented in the style of an 'advertorial' and featured a two page article written by a GP facilitator and entitled 'Breakthrough pain in cancer – a treatment challenge'. One sub-section of the article reviewed the efficacy of Actiq (oral transmucosal fentanyl citrate) which was marketed by Elan Pharma. In the bottom right hand corner of the article, above the list of references, was an abbreviated advertisement for Actiq.

The Panel considered that the two page article was an advertisement for Actiq The two pages (the article plus the abbreviated advertisement) taken together did not meet the requirements for an abbreviated advertisement set out in the Code. The two page article therefore needed prescribing information. A breach of the Code was ruled.

The Panel had previously considered a complaint (Case AUTH/1368/10/02) that an advertisement in the NHS Journal of Healthcare Professionals (September 2002) had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one the subject of complaint appeared in the journal. These were taken up with the companies concerned.

Case AUTH/1408/1/03 concerned a two page advertisement headed 'Cancer pain relief' and 'Advertisement'. The advertisement was presented in the style of an 'advertorial' and featured a two page article written by a GP facilitator and entitled 'Breakthrough pain in cancer – a treatment challenge'. One sub-section of the article reviewed the efficacy of Actiq (oral transmucosal fentanyl citrate) which was marketed by Elan Pharma Limited. In the bottom right hand corner of the article, above the list of references, was an abbreviated advertisement for Actiq.

COMPLAINT

The two page advertisement promoted Actiq and prescribing information was not included as required by Clause 4.1 of the Code. The inclusion of an abbreviated advertisement was not sufficient to meet the requirements of Clause 4.1.

RESPONSE

Elan accepted that the failure to include prescribing information constituted a breach of Clause 4.1 of the Code.

Elan stated that it had robust procedures in place to ensure that all promotional activities complied with the requirements of the Code. 2002 was, however, a year of considerable change in structure and personnel, particularly around the time when the advertisement in question was placed. Unfortunately, it would appear that this had resulted in what the company was confident was an isolated mistake.

PANEL RULING

The Panel considered that the two page article was an advertisement for Actiq and thus prescribing information was required. The placing of the abbreviated advertisement immediately following the two page article was not sufficient to meet the requirements for prescribing information.

The two pages (the article plus the abbreviated advertisement) taken together did not meet the requirements for an abbreviated advertisement set out in Clause 5 of the Code. For example two A4 pages was larger than the permitted size. The two page article therefore needed prescribing information. A breach of Clause 4.1 of the Code was ruled.

Proceedings commenced 10 January 2003

Case completed 20 February 2003

CASE AUTH/1409/1/03

DIRECTOR v NOVARTIS

Glivec journal advertisement

The Panel had previously considered a complaint (Case AUTH/1368/10/02) that a journal advertisement had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one the subject of complaint appeared in the same journal. These were taken up with the companies concerned.

The current case concerned two consecutive double page spreads referring to Novartis' product Glivec (imatinib). The first double page spread was headed 'Clinical' and featured an article entitled 'Imatinib for chronic myeloid leukaemia guidance' which was an edited version of guidance on the subject from the National Institute for Clinical Excellence. The first page of the second double page spread was headed 'advertisement'; both pages were headed 'Chronic myeloid leukaemia' and featured an article entitled 'Taking aim on cancer' written by an employee of Novartis. The article was about Glivec and included the product and company logos. The role of Novartis with regard to the article entitled 'Imatinib for chronic myeloid leukaemia guidance' was unclear. The second double page spread, headed 'Taking aim on cancer', could be considered to be an advertisement for Glivec which did not include prescribing information.

The Panel noted that Novartis had no involvement with the article entitled 'Imatinib for chronic myeloid leukaemia guidance'. It had been produced by the journal independently of Novartis. The article was not therefore subject to the Code and the Director decided that there was no *prima facie* case to answer.

The Panel considered that the article 'Taking aim on cancer', the second double page spread, was an advertisement for Glivec. The advertisement did not include prescribing information and the Panel therefore ruled a breach of the Code.

The Panel had previously considered a complaint (Case AUTH/1368/10/02) that an advertisement in the NHS Journal of Healthcare Professionals (September 2002) had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one the subject of complaint appeared in the journal. These were taken up with the companies concerned.

Case AUTH/1409/1/03 concerned two consecutive double page spreads referring to Novartis Pharmaceuticals UK Ltd's product, Glivec (imatinib). The first double page spread was headed 'Clinical' and featured an article entitled 'Imatinib for chronic myeloid leukaemia guidance' which was an edited version of guidance on the subject from the National Institute for Clinical Excellence (NICE). No author was stated. The first page of the second double page spread was headed 'advertisement'; both pages were headed 'Chronic myeloid leukaemia' and featured an article entitled 'Taking aim on cancer' written by an employee of Novartis. The article was about Glivec and included the product and company logos.

COMPLAINT

The role of Novartis with regard to the article entitled 'Imatinib for chronic myeloid leukaemia guidance' was unclear. It could be an advertisement or a sponsored article. Attention was drawn to Clauses 4.1 and 9.9 of the Code.

The second double page spread, headed 'Taking aim on cancer', could be considered to be an advertisement for Glivec which did not include prescribing information. Attention was drawn to Clause 4.1 of the Code.

RESPONSE

Novartis stated that with regard to the article headed 'Imatinib for chronic myeloid leukaemia guidance', the company was alerted by the editors of the journal to a piece which they intended to write on Glivec and the NICE guidance. Novartis was not involved in the format, content or copy review of this article.

At the same time, Novartis was invited to write a background piece on Glivec and the important development in targeted therapy which Glivec represented. Novartis had not intended to disguise the fact that a company employee had written this article, and this fact was therefore clearly included at the end of the article. At the time that copy text was being formatted and cleared with the editors, it was not apparent that it would appear under the banner 'Advertisement'. Unfortunately, as its proposed function was primarily to act as a background piece to Glivec, it would appear that both Novartis and the journal editors overlooked the fact that prescribing information would be required. Space for the article was purchased by the company and a copy of the invoice was provided. Novartis accepted that a lack of clarification with the editors in their solicitation of the background article meant that it was in breach of Clause 4.1.

PANEL RULING

The Panel noted that Novartis had no involvement with the article entitled 'Imatinib for chronic myeloid leukaemia guidance'. It had been produced by the journal independently of Novartis. The article was not therefore subject to the Code and the Director decided in accordance with Paragraph 6.1 of the Constitution and Procedure that there was no *prima facie* case to answer.

The Panel considered that the article 'Taking aim on cancer', the second double page spread, was an advertisement for Glivec. The article, written by a Novartis employee, appeared beneath the heading 'advertisement', included the product logo and the company had paid for its placement within the journal. The advertisement did not include prescribing information and the Panel therefore ruled a breach of Clause 4.1 of the Code.

Proceedings commenced 10 January 2003

Case completed 24 February 2003

CASE AUTH/1411/1/03

DIRECTOR v GLAXOSMITHKLINE

Promotion of devices in journal advertisement

The Panel had recently considered a complaint (Case AUTH/1368/10/02) that a journal advertisement had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one the subject of complaint appeared in the same journal. These were taken up with the companies concerned.

The current case concerned a three page item; the first page featured in small print the heading 'An advertisement feature supported by an educational grant from Allen & Hanburys', above a corporate logo. The item was entitled 'The importance of appropriate device selection – consistency in asthma management'. The item, *inter alia*, reviewed dry powder inhalers and referred specifically to the Accuhaler and Diskhaler. It was stated that the Accuhaler could be used to administer a wide range of medicines, including short- and long-acting ß$_2$ agonists, inhaled steroids, and combination therapy. No medicines were mentioned with regard to the Diskhaler.

The advertisement referred to a number of different devices and the medicines available in each device. No prescribing information was given.

The Panel noted that the advertisement referred to two devices, the Accuhaler and Diskhaler. Allen & Hanburys marketed Ventolin (short-acting ß$_2$ agonist), Serevent (long-acting ß$_2$ agonist), Flixotide (steroid) and Seretide (combined steroid and long-acting ß$_2$ agonist) each of which were presented in the Accuhaler. The Panel considered that the prescribing information for all of the medicines, and not just one of them as suggested by GlaxoSmithKline, should have been included. The advertisement also referred to the Diskhaler but did not mention any medicine available in it. Allen & Hanburys marketed five different Diskhalers and so the prescribing information for at least one of them needed to be given. In the absence of any prescribing information the Panel ruled a breach of the Code.

The Panel had recently considered a complaint (Case AUTH/1368/10/02) that an advertisement in the NHS Journal of Healthcare Professionals (September 2002) had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one the subject of complaint appeared in the Journal. These were taken up with the companies concerned.

Case AUTH/1411/1/03 concerned a three page item; the first page featured in small print the heading 'An advertisement feature supported by an educational grant from Allen & Hanburys', above a corporate logo.

The item was entitled 'The importance of appropriate device selection – consistency in asthma management'. The item, *inter alia*, reviewed dry powder inhalers and referred specifically to the Accuhaler and Diskhaler. It was stated that the Accuhaler could be used to administer a wide range of medicines, including short- and long-acting ß$_2$ agonists, inhaled steroids, and combination therapy. No medicines were mentioned with regard to the Diskhaler. There were no author details given; at the end of the article details of Allen & Hanburys' Customer Contact Centre were stated. The matter was taken up with GlaxoSmithKline UK Limited.

COMPLAINT

The advertisement referred to a number of different devices and the medicines available in each device. No prescribing information was given which appeared to be a breach of Clause 4.1 of the Code. The supplementary information to Clause 4.1 of the Code, 'Advertisements for Devices', stated that where an advertisement related to the merits of a device which was supplied containing a variety of medicines, the prescribing information for one only needed to be given if the advertisement made no reference to any particular medicine. It further stated that full prescribing information must be included in relation to each particular medicine referred to.

RESPONSE

GlaxoSmithKline accepted that the article should have carried prescribing information for one of the molecules available in the Accuhaler. The company apologised for this unintended omission which was an oversight on the part of its approval team. The company would ensure that this did not happen again.

PANEL RULING

The Panel noted that the advertisement referred to two devices, the Accuhaler and Diskhaler. Allen & Hanburys marketed Ventolin (short-acting ß$_2$ agonist), Serevent (long-acting ß$_2$ agonist), Flixotide (steroid) and Seretide (combined steroid and long-acting ß$_2$ agonist) each of which were presented in the Accuhaler. The Panel considered that given the statement in the advertisement that the Accuhaler could be used to administer a wide range of medicines including short- and long-acting ß$_2$ agonists, inhaled steroids and combination therapy, the prescribing information for all of the medicines, and not just one of them as suggested by GlaxoSmithKline, should have been included. The advertisement also referred to the Diskhaler but did not mention any medicine available in it. Allen & Hanburys marketed five different Diskhalers and so the prescribing information for at least one of them needed to be given. In the absence of any prescribing information the Panel ruled a breach of Clause 4.1 of the Code.

Proceedings commenced 10 January 2003

Case completed 26 February 2003

CASE AUTH/1412/1/03

DIRECTOR v ROSEMONT

Journal advertisement for Rosemont liquid medicines

The Panel had previously considered a complaint (Case AUTH/1368/10/02) that a journal advertisement had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one the subject of complaint appeared in the same journal. These were taken up with the companies concerned.

The current case concerned a two page advertisement referring to Rosemont's products, each page was headed 'Specialists in Oral Liquid Medicines'. The advertisement was presented in the style of an 'advertorial' and featured an article entitled 'Don't rush to crush!' The text referred to the disadvantages of tablet crushing or capsule opening, practices which were widespread in UK nursing homes. The potential dangers to carers from crushing cytotoxic medicines was discussed and Rosemont's product Soltamox (liquid tamoxifen) was referred to as a possible solution to the problem. A photograph of four of Rosemont's liquid preparations was included. No author was stated. The advertisement did not include any prescribing information.

The Panel considered that the material was a two page advertisement. It was paid for by Rosemont and referred to Rosemont products. The advertisement did not include prescribing information for the products mentioned and the Panel therefore ruled a breach of the Code.

The Panel had previously considered a complaint (Case AUTH/1368/10/02) that an advertisement in the NHS Journal of Healthcare Professionals (September 2002) had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one the subject of complaint appeared in the journal. These were taken up with the companies concerned.

Case AUTH/1412/1/03 concerned a two page advertisement referring to Rosemont Pharmaceuticals Ltd's products. Each page was headed 'Specialists in Oral Liquid Medicines'. The advertisement was presented in the style of an 'advertorial' and featured an article entitled 'Don't rush to crush!' The text referred to the disadvantages of tablet crushing or capsule opening, practices which were widespread in UK nursing homes. The potential dangers to carers from crushing cytotoxic medicines was discussed and Rosemont's product Soltamox (liquid tamoxifen) was referred to as a possible solution to the problem. A photograph of some of Rosemont's liquid preparations, Sulpor, Soltamox, Frusol and Syprol was included. A video from Rosemont Pharmaceuticals was offered for sale. No author was stated.

COMPLAINT

The advertisement did not include prescribing information for Soltamox, Sulpor, Frusol and Syprol. Attention was drawn to Clause 4.1 of the Code.

RESPONSE

Rosemont stated that the article was commissioned by the NHS Journal of Healthcare Professionals and was written by a registered general nurse, based on information supplied by Rosemont together with her own research. Rosemont supplied the author with a press release about the medication management video, a copy of a booklet called Medication Management of the Elderly, together with research papers.

The text of the article was forwarded to Rosemont for comment only. The company did not see the visuals and did not know that pack shots without prescribing information would be included. Rosemont did not directly supply the photograph of the products and if it had been asked for the photograph, it would only have been supplied together with the relevant prescribing information.

Rosemont regretted any misunderstanding that might have been caused and would ensure that every possible procedure was in place to prevent this happening again.

Following a request for further information Rosemont stated that it had booked an advertisement and details of the cost were provided. However, it was suggested that an educational piece about the topical subject of tablet crushing would be more relevant to the readers, therefore Rosemont agreed to do this rather than take out an advertisement. The author of the article, who had a special interest in the subject and had published a number of papers, had previously written the text about tablet crushing; she was not paid by Rosemont to write the article. Rosemont received the tablet crushing section from the journal, but only to check for typographical errors. There was no correspondence between Rosemont and the author. The photography for the article was supplied by Rosemont's agency on request of the journal; unfortunately this was not checked by Rosemont in accordance with procedures and therefore a group shot of selected Rosemont products was sent by mistake. Had Rosemont known this pack shot was being supplied it would have been stopped immediately.

PANEL RULING

The Panel noted that Rosemont had paid for the placement of the material and had provided information to the author. The photograph had been supplied by Rosemont's agency without Rosemont's knowledge. The Panel noted that companies must ensure that they knew everything that their agencies were doing on their behalf.

The Panel considered that the material was a two page advertisement. It was paid for by Rosemont and

referred to Rosemont products. The advertisement did not include prescribing information for the products mentioned and the Panel therefore ruled a breach of Clause 4.1 of the Code.

Proceedings commenced **10 January 2003**

Case completed **14 February 2003**

CODE OF PRACTICE REVIEW – MAY 2003

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

1346/7/02	**Pfizer v Lilly**	**Promotion prior to grant of marketing authorization**	**Breaches Clauses 2, 3.1, 15.2 and 15.9** **Public reprimand by ABPI Board**	**Appeal by respondent** **Report from Appeal Board to ABPI Board**	**Page 3**
1354/8/02	**Lilly v Janssen-Cilag**	**Risperdal Consta press release**	**Four breaches Clause 7.2 Two breaches Clause 7.4 Breaches Clauses 7.6 and 7.10**	**Appeal by respondent**	**Page 13**
1361/9/02 & 1390/11/02	**Lilly v Janssen-Cilag and Organon Laboratories**	**Risperdal 'Dear Doctor' letter**	**Three breaches Clause 7.2 Breaches Clauses 7.9, 7.10 and 9.1**	**Appeals by complainant and respondents**	**Page 22**
1376/10/02	**Galderma v Leo**	**Dovobet journal advertisements**	**Three breaches Clause 7.2 Breach Clause 7.3 Two breaches Clause 7.4**	**Appeal by respondent**	**Page 35**
1381/10/02	Medical Writer v Centocor	Retavase email	No breach	No appeal	Page 39
1394/12/02	Prescribing Adviser v AstraZeneca	Conduct of representative	No breach	No appeal	Page 42
1395/12/02	**Janssen-Cilag/Director v Lilly**	**Zyprexa leavepiece**	**Breaches Clauses 7.2, 7.3 and 8.1**	**No appeal**	**Page 44**
1397/12/02	Media/Director v Schering Plough	Promotion of NeoClarityn	No breach	No appeal	Page 48
1400/12/02	**Novartis v AstraZeneca**	**Promotion of Arimidex**	**Three breaches Clause 3.2 Three breaches Clause 7.2**	**No appeal**	**Page 52**
1404/12/02	**Wyeth v Novo Nordisk**	**Meeting and local treatment guidelines**	**Two breaches Clause 9.9**	**No appeal**	**Page 56**
1407/1/03	**Director v Pharmacia**	**Zydol journal advertisement**	**Breach Clause 4.1**	**No appeal**	**Page 60**
1408/1/03	**Director v Elan Pharma**	**Actiq journal advertisement**	**Breach Clause 4.1**	**No appeal**	**Page 61**
1409/1/03	**Director v Novartis**	**Glivec journal advertisement**	**Breach Clause 4.1**	**No appeal**	**Page 62**
1411/1/03	**Director v GlaxoSmithKline**	**Promotion of devices in journal advertisement**	**Breach Clause 4.1**	**No appeal**	**Page 63**
1412/1/03	**Director v Rosemont**	**Journal advertisement for Rosemont liquid medicines**	**Breach Clause 4.1**	**No appeal**	**Page 64**

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, about seventy 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 such medicines made available to the general 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 or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- 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.

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 Nicholas Browne 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 should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).