NUMBER 71 FEBRUARY 2011

CODE OF PRACTICE REVIEW

PMCPA Prescription Medicines Code of Practice Authority

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

COMPLAINTS IN 2010 DOWN ON 2009

In 2010 the PMCPA received 86 complaints as compared with 92 in 2009. There were 112 complaints in 2008, 127 complaints in 2007, 134 complaints in 2006 and 101 in 2005.

There were 79 cases to be considered in 2010, as compared with 87 in 2009. The number of cases usually differs from the number of complaints because some complaints involve more than one company and others do not become cases at all, often because they do not show that there may have been a breach of the Code.

The number of complaints from health professionals in 2010 (21) was less than the number from pharmaceutical companies (both members and non-members of the ABPI) (23). In addition there were four complaints from anonymous health professionals. Complaints made by pharmaceutical companies are generally more complex than those from outside the industry, usually raising a number of issues.

Four complaints were made by members of the public, seven by pharmaceutical company employees, one from a journalist and two complaints were made by organisations.

There were seventeen anonymous complaints in addition to the four from anonymous health professionals.

The remaining seven complaints were nominally made by the Director and arose from media criticism, voluntary admissions by companies and alleged breaches of undertakings.

COMPLIANCE WITH INTER-COMPANY UNDERTAKINGS

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

It is equally important that companies comply with undertakings given during the course of inter-company dialogue. Although such undertakings are not specifically referred to in the Code or the 2011 Constitution and Procedure breaching an inter-company undertaking may indicate that previous inter-company dialogue has ultimately been unsuccessful.

A formal complaint about a matter which was the subject of the inter-company undertaking can be submitted without the need for further detailed inter-company dialogue. Before submitting a complaint to the Authority companies should, however, ensure that the passage of time or the publication of new data etc is not such as to impact on previous inter-company undertakings.

Guidance on inter-company dialogue is available on the Authority's website (www.pmcpa.org.uk).

SUBMISSION OF AUDIO DATA

It is sometimes the case that a company submits audio or audio-visual material to be considered by the Code of Practice Panel or the Code of Practice Appeal Board. Companies are reminded that their submission should be in writing and if audio or audio-visual material is to be relied upon, a transcript must be provided.

CODE AWARENESS WEEK 2011

Awareness of the ABPI Code of Practice for the Pharmaceutical Industry amongst health professionals has increased significantly during the last five years as a result of Code awareness activities first launched in 2006.

To build on the success of previous activities to support the Code and reinforce the role of health professionals in maintaining high standards, Code Awareness Week 2011 will run from 4 April to 8 April 2011.

To help engage health professionals in learning about the Code and self regulation by the pharmaceutical industry, the PMPCA is developing an e-learning module which is certified as conforming to continuing professional development (CPD) guidelines. It will be launched during Code Awareness Week 2011. This will be one of the free resources available from the PMCPA to help companies run their own Code awareness activities. It will be available from the PMCPA website.

Companies are requested to please support Code Awareness Week 2011 by allocating time for sales representatives and others who have contact with external stakeholders to promote the Code and the e-learning module to doctors, pharmacists, nurses and NHS management as part of their regular programme of calls.

Please contact Vicky Edgecombe (vedgecombe@pmcpa.org.uk) to register your support.

CODE OF PRACTICE TRAINING

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

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

The next Code of Practice seminar date on which places remain available is:
Monday, 16 May 2011

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

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

HOW TO CONTACT THE AUTHORITY

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

www.pmcpa.org.uk

Telephone: 020 7747 8880
Facsimile: 020 7747 8881

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

Direct lines can be used to contact members of the Authority.
Heather Simmonds: 020 7747 1438
Etta Logan: 020 7747 1405
Jane Landles: 020 7747 1415

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

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

CASE AUTH/2335/7/10

MERZ/DIRECTOR v ALLERGAN

Breach of undertaking

Merz alleged that at the FACE (facial aesthetic conference and exhibition) congress, a meeting of aesthetic practitioners held in early July 2010, Allergan had breached the undertaking given in Case AUTH/2183/11/08 by implying that Botox/Vistabel (botulinum toxin) was more potent than Merz's products Xeomin/Bocouture (also botulinum toxin). Bocouture was launched at that meeting and the summary of product characteristics (SPC) was available on Merz's stand from the beginning of the congress.

As the complaint involved an alleged breach of undertaking, it was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

Merz explained that the congress organisers had asked Merz, Allergan and Ipsen [all of which marketed forms of botulinum toxin] to deliver a non-promotional presentation entitled 'Scientific Workshop on Pharmacology, Diffusion and Potency of Available Botulinum Toxins'.

Merz noted that Allergan's presentation, by one of its employees, included a series of efficacy comparisons which favoured the Allergan product, Vistabel (sometimes described as Botox), when compared with the two competitor products and a number of slides showed only the efficacy for Vistabel. The first slide featured a statement that Vistabel prescribing information was available and the last slide was of the prescribing information. All of this together with a misleading presentation of potency data made the presentation promotional; it therefore fell within the scope of the Code.

Data from Hunt *et al* (2009) was presented on two slides. In the first slide the data was presented next to data from Dressler *et al* (2008) which demonstrated that Botox and Xeomin had approximately the same potency using the Merz assay for botulinum toxin. The speaker obliquely criticised this assay as being a gelatine-based assay whereas the Botox assay used a more 'clinically relevant diluent' (saline). The speaker then went on to show the data by Hunt *et al* in a table headed 'Corrected potency units' which implied that these data, in fact, were the correct potency for Xeomin. The speaker described the potency of Xeomin as being 'up to 30% lower' when measured with the Allergan 'standard'. Further data on the potency of Xeomin was boxed in red on the next slide and was again shown as considerably less than 100 units. The data for Botox, as measured by this assay, was not shown. The speaker stated that this demonstrated that different assays gave different results and that it: 'Calls into question any claims that the Xeomin unit, or Bocouture unit, is exactly the same as the Botox unit – that they are interchangeable, that they are 1:1 because if they were you would expect to see 100 unit Xeomin coming up on the Botox reference standard'.

When Case AUTH/2183/11/08 was considered the data from Hunt *et al* had only been presented in poster form however it had now been published as a scientific paper. Merz stated that this was clearly a reference to the extrapolation of this *in vitro* data to the clinical situation and a promotional message. This went against the ruling in Case AUTH/2183/11/08 in which the Panel ruled that the direct relevance or significance of this data to the clinical situation had not been demonstrated and that this was inconsistent with the SPCs which had similar dosing regimens for the products. In addition, Section 4.2 of the Bocouture SPC (Bocouture was the same product as Xeomin but marketed under a different name for the treatment of glabellar lines) stated that: 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency'.

At the end of the presentation the chairman of the session asked for the Botox data as a comparator for the Xeomin potency data presented but the presenter did not directly answer this question which further reinforced the argument that this was not a scientific debate as full data was not provided even when requested, or that there was no comparator in the study which raised questions about the study itself and thus made any conclusions even more misleading.

Merz explained that, following the outcome of Case AUTH/2183/11/08, it became aware that the Hunt *et al* data was still used by Allergan. Following extensive inter-company dialogue, Allergan agreed only to use this data in response to specific requests for information.

Given the inter-company agreement and the undertaking given in the previous case, Merz alleged that the continued use of Hunt *et al* was likely to bring discredit upon or reduce confidence in the industry in breach of Clause 2.

The detailed response from Allergan is given below.

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

companies complied with undertakings.

The Panel noted that the congress organisers had invited speakers from interested companies to present for 20 minutes each at the scientific workshop on pharmacology, diffusion and potency of botulinum toxins. A letter from FACE to Merz referred to presenting on the differences in pharmacology of available toxins. The FACE guidelines for presentation stated the presentation should not be used as an opportunity to market any single product or device.

The Panel considered that it was difficult to view Allergan's presentation as anything other than promotional given its title and its delivery by an employee. It would promote the use of, *inter alia*, Allergan's medicines. The Panel thus considered that the presentation needed to comply with the Code.

The Panel noted that slide 12 compared the potency of Xeomin and Botox according to results obtained using the Merz 'gelatin-like' LD_{50} assay. The mean potency of Xeomin was given as 103 and that of Botox as 101.7. Although not entirely clear from the slide, this data was from Dressler *et al* (poster). The Dressler abstract concluded that the potencies of Xeomin and Botox were equivalent. To the right of the table of data from Dressler *et al* was another table reporting the results for Xeomin from the Allergan saline-based LD_{50} assay (Hunt *et al*). The authors reported the corrected potency of three lots of Xeomin to be 75U/vial, 69U/vial and 78U/vial. No corresponding data was given for Botox. The Panel considered that the audience would inevitably compare the figures from the two tables of data and conclude that Xeomin was less potent than Botox. The following slide (slide 13) also featured a table of data which showed that the potency of Xeomin was less than 100 units (potency reported ranged from 61 to 78 units). Again, no corresponding data for Botox was reported. Although not stated on the slides, both assays (Hunt *et al* and Dressler *et al*) were performed in mice.

Slides 25 and 26 demonstrated a clinical advantage for Vistabel vs Xeomin (Moers-Carpi) which delegates might assume was due to the favourable potency data given on slides 12 and 13.

Slide 30 was headed 'Are they [botulinum toxins] all the same' followed by 'They are not interchangeable. Difference in: …….. - clinical performance'.

The Panel noted that in Case AUTH/2183/11/08 Allergan had been ruled in breach of the Code; the Panel referred to its ruling in that case.

Case AUTH/2183/11/08

In the Panel's view the data presented in a product monograph and an objection handler which derived from Hunt *et al* implied that there was a difference in potencies between Xeomin and Botox in favour of Botox. This was inconsistent with the summaries of product characteristics (SPCs) which showed similar dosing regimens for the two products. The Panel accepted that there was some animal data that possibly showed a difference. However, the supplementary information to the Code was clear that animal data should not be extrapolated to the clinical situation unless there was data to show that it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the comparison could not be substantiated and did not reflect all of the evidence. Breaches of the Code were ruled.

Case AUTH/2335/7/10

The Panel noted that since it had considered Case AUTH/2183/11/08 Merz had launched Bocouture – which was the same as Xeomin but was only indicated for the temporary improvement in the appearance of moderate to severe glabellar frown lines in adults below 65 years when the severity of those lines had an important psychological impact for the patient. The Bocouture SPC stated in Section 4.2 that 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) [i.e. Botox] are of equal potency'. The Panel noted that Allergan had only recently obtained a copy of the Merz data-on-file document to support the grant of the Bocouture licence and, the Panel assumed, the statement in Section 4.2 of the Bocouture SPC. In contrast to that statement, Allergan had submitted clinical data which demonstrated a statistically significant clinical advantage for Vistabel vs Bocouture (Moers-Carpi).

The Panel considered that the comparative data shown in the presentation was sufficiently different to the material considered in Case AUTH/2183/11/08 for it not to be caught by the undertaking given in that case. The previous material had not referred to Dressler *et al* or the Moers-Carpi data as shown later in the presentation. The Panel did not consider that the presentation was in breach of the undertaking given in Case AUTH/2183/11/08 and in that regard high standards had been maintained. No breaches of the Code were ruled.

The Panel considered that as there had been no breach of the undertaking there could be no breach of Clause 2. No breach of that clause was ruled.

Upon appeal by Merz the Appeal Board noted that the title of Allergan's presentation was 'Pharmacology, diffusion and potency of Botulinum Toxins'. Slide 1 listed the various botulinum toxins available from the three manufacturers. Slide 3 of the presentation showed a number of vials of different sizes and was headed 'Are they all the same?'. Beneath the picture of the vials was the second question 'Are they non-interchangeable – Structure? Unit potency? Stability? Diffusion

characteristics? Clinical performance?'. The last slide had the same heading and picture of vials below which was now the statement 'They are non-interchangeable. Differences in: Structure, Unit potency, Stability, Diffusion characteristics, Clinical performance'.

The Appeal Board noted that Merz had drawn attention to slides 12 and 13 of the presentation. These were headed 'Differences in LD_{50} assays' and 'Xeomin potency'. Slide 10 made it clear that the products were different '… and non-interchangeable potency units are specific'. Slide 11 was headed 'Reasons for potency differences' with the sub headings 'Intrinsic differences in product characteristics' and 'Differences in LD_{50} assays'.

The Appeal Board noted that the presentation had included data from the small (n=12) Moers-Carpi study which was a split-face comparison of Vistabel and Xeomin in the forehead region of healthy volunteers. The results presented were those which showed a statistically significant advantage for Vistabel [Botox] vs Xeomin when brow position was assessed by digital photography. The results of the patients' own evaluation of therapy, however, were not included; these showed no difference between the products.

The Appeal Board noted that the Bocouture [Xeomin] SPC stated in Section 4.2 that 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900KD) [ie Botox] are of equal potency'. The Appeal Board noted that the relevant data was an unpublished non-inferiority study which Allergan had received from Merz after the meeting in question.

The Appeal Board did not accept Allergan's submission that the inclusion of the Dressler *et al* and Moers-Carpi studies meant that the presentation was substantially different to the product monograph and objection handler at issue in Case AUTH/2183/11/08.

Overall, the Appeal Board considered that the presentation had implied that Xeomin was less potent than Botox using, *inter alia*, the same data, ie Hunt *et al*, as that at issue in Case AUTH/2183/11/08. The Appeal Board considered that the presentation breached the undertaking and in that regard high standards had not been maintained. Breaches of the Code were ruled. The appeal on both points was successful.
The Appeal Board noted that an undertaking was an important document. The Appeal Board considered that Allergan's conduct was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Appeal Board ruled a breach of Clause 2. The appeal on this point was successful.

Merz alleged that at the FACE (facial aesthetic conference and exhibition) congress, a meeting of aesthetic practitioners held at the Royal College of Physicians 2-4 July 2010, Allergan had breached the undertaking given in Case AUTH/2183/11/08 by implying that Botox/Vistabel (botulinum toxin) was more potent than Merz's products Xeomin/Bocouture (also botulinum toxin). Merz explained that it launched Bocouture at this meeting having been granted a marketing authorization on Tuesday, 29 June 2010. The promotional stand made it clear that a marketing authorization had been granted and the summary of product characteristics (SPC) was available on the stand from the beginning of the congress.

As the complaint involved an alleged breach of undertaking, it was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

COMPLAINT

Merz referred to a presentation delivered by an Allergan employee at the congress on 2 July and provided photographs of the slides taken at the event. Merz, Allergan and Ipsen [all of which marketed forms of botulinum toxin] were asked to present at the congress. It had been made clear to the Merz speaker that the presentation should not be promotional and that the presentation was a 'Scientific Workshop on Pharmacology, Diffusion and Potency of Available Botulinum Toxins'.

Merz believed that the same brief was sent to all companies. Allergan's opening slide stated that it was an invited talk and thus non-promotional. Had it remained true to the original brief of 'Pharmacology, Diffusion and Potency', as indicated by the title and requested by the event organisers, it would have been non-promotional. However, a series of efficacy comparisons favoured the Allergan product, Vistabel (sometimes described as Botox), when compared with the two competitor products (slides 25-32), a number of slides showed only the efficacy for Vistabel (slides 21-24), the first slide featured a statement that prescribing information for Vistabel was available and the last slide was of the prescribing information. All of this together with a misleading presentation of potency data made the presentation promotional; it therefore fell within the scope of the Code.

Data from Hunt *et al* (2009) was presented on two slides. In the first slide the data was presented next to data from Dressler *et al* (2008) which demonstrated that Botox and Xeomin had approximately the same potency using the Merz assay for botulinum toxin. Allergan's speaker obliquely criticised this assay as being a gelatine-based assay whereas the Botox assay used a more 'clinically relevant diluent' (saline) and went on to show the data by Hunt *et al* in a table headed 'Corrected potency units' which implied that these data, in fact, were the correct potency for Xeomin. The speaker described the potency of Xeomin as being 'up to 30% lower' when measured with the Allergan 'standard'. Further data on the potency of

Xeomin was boxed in red on the next slide and was again shown as considerably less than 100 units. The data for Botox, as measured by this assay, was not shown. The speaker stated that this demonstrated that different assays gave different results and that it:

> 'Calls into question any claims that the Xeomin unit, or Bocouture unit, is exactly the same as the Botox unit – that they are interchangeable, that they are 1:1 because if they were you would expect to see 100 unit Xeomin coming up on the Botox reference standard'. [An audio recording of the presentation was provided].

When Case AUTH/2183/11/08 was considered the data from Hunt *et al* had only been presented in poster form however it had now been published as a scientific paper.

Merz stated that this was clearly a reference to the extrapolation of this *in vitro* data to the clinical situation and a promotional message. This went against Case AUTH/2183/11/08 in which the Panel ruled that the direct relevance or significance of this data to the clinical situation had not been demonstrated and that this was inconsistent with the SPCs which had similar dosing regimens for the products. In addition, Section 4.2 of the Bocouture SPC (Bocouture was the same product as Xeomin but marketed under a different name for the treatment of glabellar lines) stated that: 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency'.

Merz submitted that the presentation was not exempt from the Code because:

- Clause 1.2 required that responses to individual enquiries could only relate solely to the subject matter in the enquiry, were accurate and did not mislead. The subject matter requested was exceeded in this presentation as efficacy data was presented in addition to potency data.
- The efficacy data presented clearly positioned Allergan's product as superior.
- The presentation was misleading as it presented data that contradicted Section 4.2 of the Bocouture SPC. In addition the speaker's words directly contradicted Section 4.2 of the Bocouture SPC.
- The presentation of the potency data from Hunt *et al* was also misleading as both Xeomin (Bocouture) and Botox (Vistabel) had similar dosing regimens. This was commented upon for Xeomin and Botox in Case AUTH/2183/11/08 and cited as a reason why the data was misleading. This was no less true now than it was then.
- It was not 'scientific debate' as it was misleading and contained promotional messages.

At the end of the presentation the chairman asked for the Botox data as a comparator for the Xeomin potency data presented but the presenter avoided directly answering this question which further reinforced the argument that this was not a scientific debate as full data was not provided even when requested, or that there was no comparator in the study which raised questions about the study itself and thus made any conclusions even more misleading.

Merz explained that, following the outcome of Case AUTH/2183/11/08, it became aware that the data was still being used in that a medical liaison executive, accompanied by a sales representative, had presented this data proactively at a meeting in May 2009 at a teaching hospital. Merz contacted Allergan about this and, following extensive inter-company dialogue, the two companies agreed that Allergan would not use this data at all except in response to specific requests for information. Directors of Merz and Allergan signed a letter to cement this agreement.

This activity represented a breach of undertaking and thus Clause 25. Merz alleged that Allergan had failed to maintain high standards in breach of Clause 9.1. Furthermore, Allergan's action in that it entered into an undertaking to the PMCPA which it later did not honour, was given a 'second chance' by Merz which it flouted by breaching the undertaking again, was likely to bring discredit upon or reduce confidence in the industry in breach of Clause 2.

RESPONSE

Allergan disagreed that it had breached its undertaking given in Case AUTH/2183/11/08 or that the presentation was promotional. Given that Merz, Allergan and Ipsen were all invited to provide speakers for the scientific workshop at issue, and given the nature of the topic provided by the conference organisers, Allergan rigorously scrutinised the presenter's presentation to ensure full compliance with the Code, specifically in relation to content, its non-promotional nature and previous PMCPA rulings. The company ensured that it was a stand alone presentation, that it was non-promotional i.e. scientifically accurate and balanced and addressed the topic requested 'Pharmacology, Diffusion and Potency of Botulinum Toxins'.

Allergan noted that the congress was organised by Wigmore, suppliers of Dysport/Azzalure and Xeomin/Bocouture to the UK market.

Allergan agreed with Merz that this was a non-promotional scientific workshop. The presentations were delivered within the congress rather than a company sponsored workshop. In order to provide balance, representatives from all three UK manufacturers of botulinum toxins were invited to present on 'Pharmacology, Diffusion and Potency of Botulinum Toxins'. This title was set by the FACE organisers. Allergan engaged in extensive dialogue with the organisers of FACE to establish the non-promotional nature of the workshop.

The presentation in question was discussed in depth with the FACE conference organiser to ensure that its content met the requirements for a non-promotional scientific debate. In particular, the conference organiser confirmed that it was appropriate to include clinical and comparative data in order that the clinical relevance of the pre-clinical data could be presented in clinical context. This was confirmed in correspondence in which the conference organiser, *inter alia*, reassured Allergan that the content was as requested.

Allergan strongly disagreed that the presentation was promotional or indeed that it breached either its undertaking or the inter-company dialogue agreement with Merz.

Allergan noted that Merz made much of the launch of Bocouture at FACE. Allergan provided some context around statements made by Merz on this matter although ultimately did not believe the availability of the Bocouture marketing authorization was germane to this complaint.

The presenter was not aware of the imminent launch of Bocouture or indeed the content of the Bocouture SPC, when the presentation was prepared. In order to ensure full compliance with the Code and Allergan's processes, the presentation was examined in advance of the workshop which was held on 2 July, the first day of the congress. Allergan was not aware of any press release or publicity activities to announce the grant of the Bocouture marketing authorization before or on 2 July 2010. Furthermore, the Bocouture SPC was not available on the electronic Medicines Compendium (eMC) on 2 July.

Allergan noted that following its presentation, Merz's presenter stated that he would only refer to Xeomin, as Bocouture was not yet approved for cosmetic use in the UK. Clearly, Merz's own speaker did not know that the company had just gained the marketing authorization for Bocouture.

As stated in the declaration on the first slide, Allergan's presenter had been invited to participate in a scientific debate and the presentation was examined to ensure it was non-promotional. The fact that the presentation referred to clinical data on Vistabel (or Botox where relevant in the context of the data being discussed) did not *per se* make it promotional, although it did provide clinical context.

Allergan abided by the brief given and provided a scientifically accurate, balanced, non-promotional presentation for the reasons discussed below.

Balance was provided within the presentation through the data from Dressler *et al*, Lowe *et al* (2010) and Kerscher *et al* (2009) (all of which provided a contrary view to Allergan's position), and also due to the fact that the three companies each presented their view on the same topic. Allergan did not have an audio recording or photographs of the presentation made by Merz or Ipsen as the conference organisers prohibited the use of audio or video recording at the conference. A clear notice to this effect was given at the start of the session. The photographs of the slides submitted by Merz were of a poor quality and so Allergan assumed they were taken with a hidden camera/phone.

However, Allergan provided abstracts of the two other presentations and requested that Merz provided its presentation for context and the FACE conference organisers should be asked to supply the Ipsen presentation. It was only when all three presentations were viewed together that Allergan's presentation could be fairly assessed for balance.

On viewing the full presentation and listening to the audio provided by Merz, Allergan believed it would be clear that this was a fair and balanced presentation of the available scientific data on the topic requested by the conference organisers.

Slide 3 set the scene by looking at the differences between the products and the fact, as stated in the SPCs for all the botulinum toxins, that unit doses of the various products were not interchangeable.

Slides 4-9 discussed the pharmacology of the botulinum toxins.

Slides 10-13 covered the topic of potency – as requested by the conference organisers. Again this information was contextualised by the slide entitled 'BoNT products are different AND non-interchangeable potency units are specific' (slide 10). In the US new non-proprietary (generic) names had been established to reinforce the lack of interchangeability of the unit doses. This slide was considered to be relevant to the audience in the context of a scientific debate on the potency of botulinum toxins as US speakers frequently presented at EU congresses.

There were two slides which detailed data from Hunt *et al* (slides 12 and 13). As acknowledged by Merz, the data were balanced by the inclusion of data on slide 12 from Dressler *et al*, which demonstrated similar numbers of potency units for Botox and Xeomin when tested using the Merz reference LD_{50} assay. Allergan believed there were genuine criticisms of the data from Dressler *et al* and that a scientific forum was an appropriate place to raise these concerns. The data from Hunt *et al* showed that in the Allergan LD_{50} assay, with Botox as the reference standard, Xeomin units were not equivalent to Botox units. The presenter used this data to support the fact that unit doses of the botulinum toxins were not interchangeable.

Aside from two slides on stability (slides 14 and 15) and a summary slide (slide 30), the remaining slides looked at the topic of diffusion, as requested by the conference organisers, and which clearly related to both the safety and efficacy profiles of all three botulinum toxins. The presenter's presentation

reviewed the available data on clinical models of diffusion using anhidrosis halos and supporting clinical data to illustrate what was found from the clinical models. This was done in a balanced way including studies sponsored by Merz and Allergan.

Allergan acknowledged that the presentation referred to the location of prescribing information and contained prescribing information at the end. The addition of prescribing information was a 'belt and braces' approach to demonstrate the level of scrutiny applied to this presentation. Whilst the inclusion of the prescribing information might have been incorrect and given the wrong impression, Allergan stood completely by the fact that this was a balanced, scientifically accurate, non-promotional presentation.

Regarding Merz's specific comments/allegations about the data itself, Allergan stated that it believed that the data from Hunt *et al* were relevant in the context of a non-promotional presentation, as they supported the fact that the botulinum toxin units were not interchangeable due to differences in LD_{50} assay techniques between different manufacturers. Furthermore the data were supported by recently available clinical data from Moers-Carpi (2010) (slides 25 and 26) which demonstrated that in a clinical split-face comparison of Vistabel (12 units) and Xeomin (12 units), the two products were not equivalent. Therefore, these data were relevant to the clinical situation and use in a non-promotional setting did not go against the ruling in Case AUTH/2183/11/08.

As stated above, the presenter did not know about the imminent launch of Bocouture, or the content of the Bocouture SPC, when the presentation was prepared. The presentation was prepared in good faith; the Xeomin SPC was used as a reference. Given that the Bocouture marketing authorization was only announced on the day of the FACE conference and that even the Merz speaker was unaware of this, Allergan did not believe it was misleading for it to present only the Moers-Carpi data without referring to the new SPC statement 'Comparative clinical study results *suggest* that Bocouture and the comparator product containing conventional botulinum toxin type A complex (900 kD) are of equal potency' (emphasis added by Allergan). This statement was based on an unpublished non-inferiority study. As established in Case AUTH/2270/10/09, all that could be claimed from a non-inferiority study was that one product was no worse than another by the pre-specified margin in the study. Allergan had just received the Merz data-on-file document to support the grant of the licence and would ensure that any future scientific presentations reflected this unpublished non-inferiority data.

Allergan was unaware of any other comparative data publically available and therefore believed the presentation was a fair and accurate representation of the available data.

In summary Allergan submitted that:

- The presentation was examined by a Code signatory and confirmed to be balanced, scientifically accurate and therefore non-promotional; it was not certified as it was not considered promotional.
- The presentation clearly addressed the subject requested by the conference organisers, who confirmed that it was entirely appropriate to present clinical and comparative data to provide context. The reference to efficacy data did not make this a promotional presentation if presented in a balanced way and in the context of the diffusion of the products. Balance was also provided by the presentations of the two other company speakers, as was the nature of a debate.
- The presentation was prepared in good faith, prior to the public availability of the Bocouture SPC. That said the presentation did not contradict the SPC which only *suggested* the products were of equal potency based on a non-inferiority study. Case AUTH/2270/10/09 established that equivalence or equal potency could not be claimed from a non-inferiority study.
- The presentation of the Hunt *et al* data was not misleading. It was fully contextualised with comparative data (Dressler *et al*) and the pre-clinical findings had recently been confirmed in a clinical study (Moers-Carpi).
- This was a non-promotional presentation within a scientific debate.

Allergan submitted that if every presentation made at a scientific congress was now to be assessed as potentially promotional it would limit future legitimate scientific exchange.

Allergan disagreed that the presentation had breached its inter-company agreement with Merz. Allergan continued to abide by the letter and spirit of its part of the agreement despite the recent case about claims based on non-inferiority studies (Case AUTH/2270/10/09) which were contrary to Merz's part of the agreement.

Finally, scientific debates by their nature involved different parties, typically with opposing views, stating their case in order that the audience could assess the balance of evidence and draw their own conclusions. Although these scientific debates presented pharmaceutical companies with significant challenges they remained of particular interest to clinicians attending such conferences. Allergan considered that it was legitimate, in the context of a scientific debate, balanced not only with opposing data but also contextualised with recently available clinical data from Moers-Carpi, to present the two slides containing the Hunt *et al* data.

Allergan refuted any allegation of a breach of undertaking and thus Clause 25 of the Code. Similarly it denied a breach of Clause 9.1 or 2. Allergan also denied the alleged breaches of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings. The Panel considered that given the Authority's responsibility in ensuring compliance with undertakings, inter-company dialogue as set out in Paragraph 5.2 of the Constitution and Procedure was not required in this regard before a complaint could be accepted.

The Panel noted that the organisers of the FACE congress had invited speakers from interested companies to present for 20 minutes each at the scientific workshop on pharmacology, diffusion and potency of botulinum toxins. A letter from FACE to Merz referred to presenting on the differences in pharmacology of available toxins. The FACE guidelines for presentation stated the presentation should not be used as an opportunity to market any single product or device.

The Panel considered that it was difficult to view the presentation as anything other than promotional given its title and its delivery by an Allergan employee. It would promote the use of, *inter alia*, Allergan's medicines. The Panel thus considered that the presentation, given by an Allergan employee and including information about Allergan's product Botox/Vistabel, needed to comply with the Code. The Panel disagreed with Allergan's submission that the presentation at issue should be viewed in the context of the other two presentations. In the Panel's view, each presentation had to stand alone under the Code; none could rely on any of the others for balance.

The Panel noted that slide 12 compared the potency of Xeomin and Botox according to results obtained using the Merz 'gelatin-like' LD_{50} assay. The mean potency of Xeomin was given as 103 and that of Botox as 101.7. Although not entirely clear from the slide, this data was from Dressler *et al* (poster). The Dressler abstract concluded that the potencies of Xeomin and Botox were equivalent. To the right of the table of data from Dressler *et al* was another table reporting the results for Xeomin from the Allergan saline-based LD_{50} assay (Hunt *et al*). The authors reported the corrected potency of three lots of Xeomin to be 75U/vial, 69U/vial and 78U/vial. No corresponding data was given for Botox. The Panel considered that the audience would inevitably compare the figures from the two tables of data and conclude that Xeomin was less potent than Botox. The following slide (slide 13) also featured a table of data which showed that the potency of Xeomin was less than 100 units (potency reported ranged from 61 to 78 units). Again, no corresponding data for Botox was reported. Although not stated on the slides, both assays (Hunt *et al* and Dressler *et al*) were performed in mice.

Slides 25 and 26 demonstrated a clinical advantage for Vistabel vs Xeomin (Moers-Carpi) which delegates might assume was due to the favourable potency data given on slides 12 and 13.

Slide 30 was headed 'Are they [botulinum toxins] all the same' followed by 'They are not interchangeable. Difference in: …….. - clinical performance'.

The Panel noted that in Case AUTH/2183/11/08 Allergan had been ruled in breach of the Code; the Panel referred to its ruling in that case.

Case AUTH/2183/11/08

In the Panel's view the data presented in a product monograph and an objection handler which derived from Hunt *et al* implied that there was a difference in potencies between Xeomin and Botox in favour of Botox. This was inconsistent with the summaries of product characteristics (SPCs) which showed similar dosing regimens for the two products. The Panel accepted that there was some animal data that possibly showed a difference. However, the supplementary information to the Code was clear that animal data should not be extrapolated to the clinical situation unless there was data to show that it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the comparison could not be substantiated and did not reflect all of the evidence. Breaches of, *inter alia*, Clauses 7.2, 7.3 and 7.10 of the Code were ruled.

Case AUTH/2335/7/10

The Panel noted that since it had considered Case AUTH/2183/11/08 Merz had launched Bocouture – which was the same as Xeomin but was only indicated for the temporary improvement in the appearance of moderate to severe glabellar frown lines in adults below 65 years when the severity of those lines had an important psychological impact for the patient. The Bocouture SPC stated in Section 4.2 that 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) [i.e. Botox] are of equal potency'. The Panel noted that Allergan had only recently obtained a copy of the Merz data-on-file document to support the grant of the Bocouture licence and, the Panel assumed, the statement in Section 4.2 of the Bocouture SPC. In contrast to that statement, Allergan had submitted clinical data which demonstrated a statistically significant clinical advantage for Vistabel vs Bocouture (Moers-Carpi).

The Panel considered that the comparative data shown in the presenter's presentation was sufficiently different to the material considered in Case AUTH/2183/11/08 for it not to be caught by the undertaking given in that case. The previous material had not referred to Dressler *et al* or the Moers-Carpi data as shown later in the presentation. The Panel did not consider that the presentation was in breach of the undertaking given in Case AUTH/2183/11/08 and so it ruled no breach

of Clause 25. In that regard high standards had been maintained. No breach of Clause 9.1 was ruled.

The Panel considered that as there had been no breach of the undertaking there could be no breach of Clause 2. No breach of that clause was ruled.

During the consideration of this case the Panel noted Allergan's submission that the presentation given by the presenter referred to all the data of which Allergan was aware. Clinical data was presented which appeared to support the *in vivo* potency data. Contrary clinical data was referred to in the Bocouture SPC but the SPC gave the date of first authorization as 29 June 2010 ie three working days before the presentation was given. (The Panel had not been given a copy of that data). The Panel noted Allergan's submission that it had only recently obtained a copy of the data referred to in the Bocouture SPC and that future presentations would reflect that data. Nonetheless, the Panel considered that the presentation had not referred to the totality of the clinical efficacy data and in that regard it queried whether by only referring to Moers-Carpi, the presenter's presentation was misleading and unbalanced. It appeared that the comparative clinical efficacy of Vistabel and Bocouture had not been resolved clearly in favour of one product or the other. Where a clinical or scientific issue existed which had not been clearly resolved in favour of one generally accepted viewpoint, the Code required particular care to be taken to ensure that the issue was treated in a balanced manner in promotional material. The Panel requested that Allergan be advised of its concerns in this regard.

APPEAL BY MERZ

Merz alleged that Allergan had breached the undertaking given in Case AUTH/2183/11/08 by seeking to convince medical practitioners that Xeomin was less potent than Botox using the same data. This claim was inconsistent with the respective product SPCs and head-to-head clinical comparisons. The use of this data to create this argument was found to be unsubstantiated and not to encourage the rational use of a medicine in Case AUTH/2183/11/08. The inclusion of additional data that did not support this claim did not prevent the presenter from concluding that Xeomin was less potent than Botox. Further animal data was cited to reinforce this point and the presenter summarised with the unambiguous claim that the presence of these data 'Calls into questions any claims that the Xeomin unit, or Bocouture unit, is exactly the same as the Botox unit – that they are interchangeable, that they are 1:1 because if they were you could expect to see 100 unit Xeomin coming up on the Botox reference standard'. The Panel acknowledged that the data, as presented, would lead the audience to conclude that Xeomin was significantly [sic] less potent than Botox. The Panel was also clear, as was Merz, that the presentation was promotional in tone and context and so fell under the Code. In Case AUTH/2183/11/08 the Panel drew the same conclusion from the same data when it concluded: '…that on the balance of probabilities the Allergan representative had claimed there was a difference in potency for the products. This was inconsistent with the SPCs which had similar dosing regimens for the products'. In that case, the Panel further stated that 'The comparison could not be substantiated and did not reflect all the evidence'. Merz alleged that the Panel's ruling in Case AUTH/2183/11/08 clearly applied to Allergan's presentation delivered at the FACE congress. It was as true now as it was then and the very large data set which showed clinical non-inferiority of Xeomin to Botox remained unchallenged.

Merz alleged that the comparative potencies of the Allergan (Botox/Vistabel) and Merz (Xeomin/Bocouture) toxins was further reinforced in the Bocouture SPC (which was available on the Merz stand that clearly launched Bocouture at the FACE conference) where the regulators concluded that all the data suggested that the two products were equipotent. For such a statement to appear in an SPC meant that this was not a matter of scientific debate but had been clearly positioned by the regulator. Merz noted that the medicine in Botox was identical to that in Vistabel and Xeomin was identical to that in Bocouture.

Merz noted Allergan's reference to Moers-Carpi. This data was presented 12 slides after the potency tables in question. Merz noted that this study was in a small patient population (n=12) in an indication that was outside the licensed indications for Bocouture and Vistabel.

Merz alleged that Allergan omitted to convey the comparison was outside of the product licenses for both products and consequently not relevant. Allergan went on to present data that highlighted a technical difference in the results for the two products rather than the clinically relevant outcome in this therapeutic area, of patient subjective evaluation, for which there was no difference. Allergan could not therefore use this off label data to show that Hunt *et al* was of clinical reference or significance.

Allergan, however, was aware of the very large data set which compared Xeomin and Botox and clearly and unambiguously showed that Xeomin was not inferior to Botox in the clinical setting (Benecke *et al* 2005, Roggenkämper *et al* 2006, Merz data on file). Allergan also knew that, based upon these data the regulator very deliberately adopted the same dosage schedule for Xeomin as adopted for Botox, and subsequently Bocouture as for Vistabel. Allergan should also have known, as the information was available before the presentation, that the regulators clearly viewed Vistabel and Bocouture as equipotent, a fact that was unambiguously articulated in the Bocouture SPC.

Merz alleged that this represented a breach of undertaking as:

- Allergan sought to convince the audience in a clearly promotional presentation that Xeomin was less potent than Botox by presenting animal data which conflicted with all relevant clinical evaluations
- The animal data from which the speaker's conclusion was drawn were exactly the same data subject to the undertaking in Case AUTH/2183/11/08
- The Panel accepted that this presentation of the same data in Case AUTH/2183/11/08 would lead the audience to the same conclusion, namely that Xeomin was less potent than Botox
- The presentation of the data would go against the Panel's view in Case AUTH/2183/11/08 and it remained inconsistent with the identical dosing
- That the much later presentation of partial results of a small study outside the license of either product, whilst not referring to a very large relevant clinical data set, did not detract from the clear intention to present misleading argument and not promote the rational use of a medicine.

Merz questioned the value of undertakings if they allowed a company to present data ruled in breach of the Code in a slightly different way but draw the same conclusion. Merz alleged that Allergan intended the presentation to circumvent the undertaking given following Case AUTH/2183/11/08 whilst ensuring that the same message was communicated. This eroded the purpose of undertakings. The presentation of the data and the conclusions drawn were clearly in breach of the undertaking given in Case AUTH/2183/11/08 and therefore in breach of Clauses 2, 9.1 and 25.

COMMENTS FROM ALLERGAN

Allergan disagreed that it had breached the undertaking given in Case AUTH/2335/7/10. Allergan was well aware of that case ruling and the undertaking it had given and had rigorously scrutinized the presentation at issue to ensure that it had fully taken into account its undertaking; it was confident that the presentation did not constitute a breach of undertaking.

Allergan submitted that the presentation was reviewed for compliance with the Code as a stand alone presentation. Specifically it was reviewed to ensure that it was scientifically accurate and balanced and addressed the topic requested; 'Pharmacology, Diffusion and Potency of Botulinum Toxins'. At the time of preparation and approval it took into account all the publically available information. The presentation was given by a senior employee.

Allergan submitted that the appeal rested on Merz's assertion that Allergan breached the undertaking in respect of Case AUTH/2183/11/08. The case report ensured the full context was provided but the key concluding section of the Panel ruling was (*asterisked clarification added by Allergan):

'The Panel considered that given the comparative potency information in the product monograph and objection handler [*derived from Hunt *et al* (2006) – now available as a full publication] it was not unrealistic that representatives might have used this information when promoting Botox to health professionals. There was no instruction about how to use the information comparing the potency of Xeomin and Botox. The Panel considered on the balance of probabilities the Allergan representative had claimed there was a difference in potency for the products. This was inconsistent with the summaries of product characteristics (SPCs) which showed similar dosing regimens for the two products. The Panel accepted that there was some animal data that possibly showed a difference. However, the supplementary information to Clause 7.2 was clear that animal data should not be extrapolated to the clinical situation unless there was data to show that it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the product monograph and objection handler were misleading with regard to the information about potency. The comparison could not be substantiated and did not reflect all of the evidence. The material would not encourage the rational use of a medicine. Thus the Panel ruled breaches of Clauses 7.2, 7.3 and 7.10.'

Allergan submitted that it would be clear from the evidence placed below that it had taken into account the requirement for balance, reflection of all the available data (at the time of the presentation) and the care required when presenting and extrapolating animal data. Allergan submitted that it had not breached its undertaking or attempted to circumvent the undertaking as alleged by Merz, and it had complied with both the letter and spirit of the Code.

Allergan reiterated some of the information provided previously to give appropriate context to address the points raised by Merz:

Allergan submitted that the FACE congress took place on the 2-4 July 2010, in London, UK. This conference was organised by Wigmore, suppliers of Dysport/Azzalure and Xeomin/Bocouture to the UK market.

Allergan understood this was a non-promotional scientific workshop. The presentations were delivered within the congress rather than a company sponsored workshop. In order to provide balance, representatives from all three manufacturers of botulinum toxins in the UK were invited by the FACE organisers to present on the pharmacology, diffusion and potency of botulinum toxins. Allergan engaged in extensive dialogue with the organisers of FACE to establish the non-promotional nature of the workshop.

The presentation in question was discussed in depth with the FACE conference organiser to ensure

that the content met the organiser's requirements for a non-promotional scientific debate. In particular, the organiser confirmed that it was entirely appropriate to include clinical and comparative data in order that the clinical relevance of the pre-clinical data could be presented in clinical context. This was confirmed in correspondence in which Allergan was reassured that the content was as requested. As stated in the declaration on the first slide, the presenter was an invited speaker, participating in a scientific debate. Allergan had abided by the brief given and provided a scientifically accurate, balanced, non-promotional presentation for the reasons discussed below.

Allergan noted that in its ruling the Panel considered it difficult to view the presentation as anything other than promotional given its title and delivery by an Allergan employee. Allergan had previously outlined why the presentation was non-promotional. However, even when considered as a promotional presentation it did not breach the undertaking. It provided a balanced overview of all the available data on the requested topics as outlined below and as recommended in the ruling with respect to Case AUTH/2183/11/08.

Allergan noted that on viewing the presentation, and listening to the audio provided by Merz to the PMCPA (copy supplied to Allergan via the PMCPA), it submitted that it would be clear that this was a fair and balanced presentation of the available scientific data on the topic requested by the conference organisers. Slide 3 set the scene and looked at the differences between the products and the fact, as stated in the SPCs for all the botulinum toxins, that unit doses of the various toxins were not interchangeable. Slides 4 – 9 discussed the pharmacology of the botulinum toxins. Slides 10 - 13 covered the topic of potency – as requested by the conference organisers. Again this information was contextualised by the slide entitled 'BoNT products are different AND non-interchangeable potency units are specific' (slide 10). In the US new non-proprietary (generic) names had been established to reinforce the lack of interchangeability of the unit doses. Slide 11 was relevant to the audience in the context of a scientific debate on potency of the botulinum toxins as US speakers frequently presented in EU congresses.

Allergan noted that slides 12 and 13 referred to Hunt *et al*. As acknowledged by Merz, the data were balanced by the inclusion on slide 12 of Dressler *et al* which demonstrated a similar number of potency units for Botox and Xeomin when tested using the Merz reference LD_{50} assay. Allergan submitted there were genuine criticisms of the Dressler data and that a scientific forum was an appropriate place to raise these concerns. The data by Hunt *et al* showed that in the Allergan LD_{50} assay, with Botox set as the reference standard, Xeomin units were not equivalent to Botox units. The presenter used this data to support the fact that unit doses of the botulinum toxins were not interchangeable.

Allergan noted that the relevant section of the audio recording provided by Merz (minutes 9 through to 12) was heard with the context of the accompanying slides (slides10-13) the isolated quotation, 'Calls into question any claims that the Xeomin unit, or Bocouture unit, is exactly the same as the Botox unit – that they are interchangeable. That they are 1:1 because if they were you would expect to see 100 units Xeomin coming up on the reference standard', could be seen as a balanced summary of the preceding data and a clear message that the products were not interchangeable. It was not, as Merz suggested, a conclusion by Allergan that Xeomin had was less potent than Botox, only that the two were not interchangeable.

Allergan submitted that aside from slides 14 and 15 on stability and a summary slide, the remaining slides referred to diffusion, as requested by the conference organisers, which clearly related to the safety and efficacy profiles of all three botulinum toxins. The presentation reviewed the available data on clinical models of diffusion using anhidrosis halos and supporting clinical data to illustrate what was found from the clinical models. This was done in a balanced way including studies sponsored by Merz and Allergan.

Aside from the balance provided around the issue of lack of interchangeability with the inclusion of Dressler *et al* the presentation did not contradict the Xeomin SPC and continued to reflect the Xeomin non-inferiority data cited by Merz (Benecke *et al*; Roggenkämper *et al*). It was well established (Case AUTH/2270/10/09) that equivalence or equal potency could not be claimed from a non-inferiority study.

Allergan submitted that Merz made much of the launch of Bocouture at FACE; Allergan provided some context around statements made by Merz on this matter although ultimately Allergan did not believe the availability of the Bocouture marketing authorization was germane to this complaint. The presenter was not aware of the imminent launch of Bocouture or indeed the content of the Bocouture SPC, when the presentation was prepared. In order to ensure full compliance with the Code and Allergan's processes, the presentation was examined in advance of the workshop which was held on the 2 July, the first day of the congress. Allergan were not aware of any press release or publicity activities to announce the grant of the Bocouture marketing authorization prior to or indeed on the 2 July 2010. Furthermore, the Bocouture SPC was not available on the electronic medicines compendium (eMC) on the 2 July. Allergan noted that a presenter, who presented after the presenter on behalf of Merz at the scientific workshop under discussion, stated at the outset that he would only refer to Xeomin, as Bocouture was not yet approved for cosmetic use in the UK. Clearly, Merz's own speaker was not aware that Merz UK had just gained the marketing authorization.

Allergan submitted that the presenter's presentation

was prepared in good faith with reference to the existing Xeomin SPC. Given that the Bocouture marketing authorization was only announced on the day of the FACE conference and that even the Merz speaker was unaware of this, Allergan did not believe it was misleading to present only the Moers-Carpi data without reference to the Bocouture SPC statement below.

> '4.2 Posology and method of administration
>
> **Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.** [in bold in the SPC]
>
> Comparative clinical study results *suggest* that Bocouture and the comparator product containing conventional botulinum toxin type A complex (900 kD) are of equal potency'. (emphasis added).

Allergan submitted that the statement above was based on an unpublished non-inferiority study. As had been well established in Case AUTH/2270/10/09, all that could be claimed from a non-inferiority study was that one product was no worse than another by the pre-specified margin in the study.

Allergan had requested the Merz data on file to support the grant of the licence on 22 July and received it on 27 July. This data was not available in the public domain. Allergan could only request it once promotional material citing it became available. In future, as previously stated, Allergan would ensure that any future scientific presentations reflected this unpublished non-inferiority data.

Allergan noted that recently available clinical data from Moers-Carpi (slides 25 and 26) was presented which demonstrated that in a clinical split-face comparison of Vistabel (12 units) and Xeomin (12 units), the two products were not equivalent. Therefore, these data were relevant to the clinical situation and their use in a non-promotional setting (as Allergan understood the context of the presentation to be) did not go against the ruling of Case AUTH/2183/11/08.

In conclusion, Allergan submitted that the presentation, with contextualised reference to Hunt *et al* did not constitute a breach of undertaking because:

- The data presented was substantially different to the materials considered in Case AUTH/2183/11/08.
- The presentation was balanced and scientifically accurate and evaluated all the reasonably available evidence at the time of preparation and presentation.
- The presentation of Hunt *et al* was fully contextualised with comparative data (Dressler *et al*) and the pre-clinical findings had recently been confirmed in a clinical study (Moers-Carpi).
- The presentation was prepared in good faith, before the Bocouture SPC was publicly available. That said the presentation did not contradict the SPC which stated that unit doses recommended for Bocouture were not interchangeable with those for other botulinum toxins and only suggested the products were of equal potency, based on a non-inferiority study. Case AUTH/2270/10/09 had established that equivalence or equal potency could not be claimed from a non-inferiority study.

Finally, scientific debates by their nature involved different parties, typically with opposing views, stating their case in order that the audience could assess the balance of evidence and draw their own conclusions. Although these scientific debates presented pharmaceutical companies with significant challenges they remained of particular interest to clinicians attending such conferences. Allergan submitted that it was legitimate, in the context of a scientific debate, balanced not only with opposing data but also contextualised with recently available clinical data from Moers-Carpi, to present the two slides containing the Hunt data. Allergan denied that it had breached its undertaking and thus Clause 25 of the Code. It also denied breaches of Clauses 2 and 9.1.

FINAL COMMENTS BY MERZ

Merz stated that whilst Allergan might have sought approval by the FACE congress organiser for its presentation, Merz was sure that the organiser did not have the necessary Code expertise to determine the promotional or non-promotional nature of any activity undertaken by a pharmaceutical company. Merz would be disappointed to learn that Allergan had abdicated responsibility for this decision to the FACE organiser. Merz noted that Allergan had stated that it believed that its presentation was fair and balanced. Merz alleged that data from Hunt *et al* was presented that supposedly directly compared Xeomin with Botox. However, it did not include a very large data set showing non-inferiority of Xeomin to Botox in over 700 patients and did not mention the statement in section 4.2 of the Bocouture SPC that suggested equal potency of the two products.

Merz alleged that the slide which cited Hunt *et al* and Dressler *et al* (which was dismissed by the presenter and Allergan) and the subsequent slide of only the Hunt *et al* together with the presenter's words left no doubt that the message was that Xeomin was less potent than Botox. The conclusion from this *in vitro* data was not supported by the large clinical trials that Allergan were aware of at the time of the presentation and therefore its presentation was not a fair and balanced representation of the available data.

Merz noted that promotional material had to be up-to-date and reflect the available data. Bocouture was granted a marketing authorization on 29 June and the Bocouture SPC was available when the presentation was delivered and therefore was of

direct relevance to this case. Allergan's suggestion that it did not know that Bocouture was being launched was difficult to believe as the Merz stand at the conference launched Bocouture and was erected by 8am; one stand separated the Merz stand from the Allergan stand. Materials available on the stand included a Bocouture leavepiece and SPC. The stand was visited by a number of Allergan employees in the morning of 2 July prior to the presentation in the afternoon. That the presenter was not aware of the imminent launch of Bocouture when he prepared the presentation was not relevant as it was licensed when the presentation was given. The Code required all material to be up-to-date. This presentation was not up-to-date when it was delivered.

Merz alleged that the fact that the source of the data behind the Bocouture SPC was not available to Allergan was not relevant as the wording of the SPC was available and represented the regulator's view of the data and should have been represented.

Merz alleged that again Allergan mentioned the Moers-Carpi data which was a very small off-label study the conclusions of which were only partly reported by Allergan. The use of this data in this way was questioned by the Panel in this case as not representing of the totality of clinical data, which it did not, but was selected to support Hunt *et al*.

APPEAL BOARD RULING

The Appeal Board noted from slide 1 that the title of Allergan's presentation was 'Pharmacology, diffusion and potency of Botulinum Toxins'. Slide 1 also listed the various botulinum toxins available from the three manufacturers. Slide 3 of the presentation showed a number of vials of different sizes and was headed 'Are they all the same?'. Beneath the picture of the vials was the second question 'Are they non-interchangeable – Structure? Unit potency? Stability? Diffusion characteristics? Clinical performance?'. The last slide had the same heading and picture of vials below which was now the statement 'They are non-interchangeable. Differences in: Structure, Unit potency, Stability, Diffusion characteristics, Clinical performance'.

The Appeal Board noted that Merz had drawn attention to slides 12 and 13 of the presentation. These were headed 'Differences in LD_{50} assays' and 'Xeomin potency'. Slide 10 made it clear that the products were different '… and non-interchangeable potency units are specific'. Slide 11 was headed 'Reasons for potency differences' with the sub headings 'Intrinsic differences in product characteristics' and 'Differences in LD_{50} assays'.

The Appeal Board noted that the presentation had included data from the small (n=12) Moers-Carpi study which was a split-face comparison of Vistabel and Xeomin in the forehead region of healthy volunteers. The results presented were those which showed a statistically significant advantage for Vistabel [Botox] vs Xeomin when brow position was assessed by digital photography. The results of the patients' own evaluation of therapy, however, were not included; these showed no difference between the products.

The Appeal Board noted that the Bocouture [Xeomin] SPC stated in Section 4.2 that 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900KD) [ie Botox] are of equal potency'. The Appeal Board noted that the relevant data was an unpublished non-inferiority study which Allergan had received from Merz on 27 July after the meeting in question.

The Appeal Board did not accept Allergan's submission that the inclusion of the Dressler *et al* and Moers-Carpi studies meant that the presentation was substantially different to the materials (a product monograph and an objection handler) at issue in Case AUTH/2183/11/08.

Overall, the Appeal Board considered that the presentation had implied that Xeomin was less potent than Botox using, *inter alia*, the same data, ie Hunt *et al*, as that at issue in Case AUTH/2183/11/08. The Appeal Board considered that the presentation breached the undertaking given in that case and ruled a breach of Clause 25. In that regard high standards had not been maintained. A breach of Clause 9.1 was ruled. The appeal on both points was successful.

The Appeal Board noted that an undertaking was an important document. The Appeal Board considered that Allergan's conduct was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Appeal Board ruled a breach of Clause 2. The appeal on this point was successful.

The Appeal Board noted that Allergan had initially considered that the presentation was not promotional and had reviewed it in that context. That the presentation was non-promotional had been rejected by the Panel. The Appeal Board was concerned that Allergan's initial view regarding the status of the presentation showed a lack of understanding although at the appeal hearing the company made it clear that it now accepted that the presentation was promotional.

Complaint received	**21 July 2010**
Case completed	**6 December 2010**

CASE AUTH/2346/8/10

MERZ/DIRECTOR v ALLERGAN

Breach of undertaking

In Case AUTH/2335/7/10, Merz alleged that a presentation given by Allergan at a meeting had breached the undertaking given in Case AUTH/2183/11/08 by implying that Botox/Vistabel (botulinum toxin) was more potent than Merz's product Xeomin/Bocouture (also botulinum toxin). Merz submitted further evidence to support its allegation which, because it related to a different meeting, was taken up as a separate case, Case AUTH/2346/8/10.

As the complaint involved an alleged breach of undertaking, it was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

Merz referred to a meeting in July 2010 at which Merz and Allergan had been invited to present to a group of health professionals who were trying to decide which botulinum to purchase. Merz noted that the invitation asked for five topics to be covered in the presentation ie product information; evidence base for licence usage; equivalence; head-to-head studies and stability.

Merz stated that the presentation given by Allergan's employees consisted of, amongst other topics, the data from Hunt and Clarke (2009) that was the subject of Case AUTH/2183/11/08 and the subsequent allegation of breach of undertaking in Case AUTH/2335/7/10. Merz submitted that some of the audience had asked if Allergan's data was accurate as Allergan had emphasised the supposed relative lack of potency of Xeomin. Merz was unaware of whether this was in the context of clinical head-to-head studies as requested by the organisers.

Merz noted that the meeting took place after Allergan knew about Merz's allegation of a breach of undertaking and as the meeting was clearly promotional, further demonstrated the lack of respect Allergan had for its undertakings to either Merz or the PMCPA and therefore continued to breach the Code including Clause 2.

The detailed response from Allergan is given below.

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

The Panel noted that Allergan had been invited to a Botulinum Toxin Information Day to present information about Botox to a selected group of health professionals and managers. The invitation defined the scope and content of the presentation. The Panel considered that it was difficult to view Allergan's presentation as anything other than promotional given its delivery by a senior employee.

The Panel further noted Allergan's submission that its presentation should be viewed together with the presentation from Merz so that the Allergan presentation could be fairly assessed for balance. In the Panel's view, each presentation had to stand alone under the Code; neither could rely on the other for balance.

The Panel noted that slide 19 of the presentation referred to Hunt and Clarke and stated that in an Allergan saline based LD_{50} assay Botox and Xeomin were found to have different potencies with the potency of three Xeomin 100U vials ranging from 69U/vial to 78U/vial. No comparable data for Botox was reported. It was stated that the saline-based assay reflected 'real world' clinical usage. Immediately below the Hunt and Clarke data was data from Dressler *et al* in which, using a Merz non saline-based LD_{50} assay, Botox and Xeomin were found to be equipotent. The mean potency of Botox was reported as 101.7U/vial whereas that for Xeomin was 103U/vial. Beneath the two tables of data from Hunt and Clarke and Dressler *et al* was the claim 'By using stabilizing agents for the bioassay, it was shown that 100 unit vials of Botox (Allergan, Irving, CA) containing complexing proteins, and 100 unit vials of Xeomin, a preparation free from complexing proteins, show equipotency in the mouse LD_{50} bioassay' referenced to Mander (2009).

The Panel noted that the summary slide (slide 34) did not refer to the comparative potencies of Botox and Xeomin. Slide 13 referred to the non-interchangeability of units of Xeomin, Dysport and Allergan (Vistabel) by reference to the products' SPCs.

The Panel noted that in Case AUTH/2183/11/08, Allergan had been ruled in breach of the Code; the Panel referred to its ruling in that case.

Case AUTH/2183/11/08

In the Panel's view the data presented in a product monograph and an objection handler which derived from Hunt *et al* implied that there was a difference in potencies between Xeomin and Botox in favour of Botox. This was inconsistent with the summaries of product characteristics (SPCs) which showed similar dosing regimens for the two

products. The Panel accepted that there was some animal data that possibly showed a difference. However, the supplementary information to the Code was clear that animal data should not be extrapolated to the clinical situation unless there was data to show that it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the comparison could not be substantiated and did not reflect all of the evidence. Breaches of the Code were ruled.

Case AUTH/2346/8/10

The Panel considered that the comparative data shown in the presentation was sufficiently different to the material considered in Case AUTH/2183/11/08 for it not to be caught by the undertaking given in that case. The previous material had not referred to Dressler *et al* or the Mander data. The Panel did not consider that the presentation was in breach of the undertaking given in Case AUTH/2183/11/08 and so in that regard high standards had been maintained. No breach of the Code was ruled.

The Panel considered that as there had been no breach of the undertaking there could be no breach of Clause 2. No breach of that clause was ruled.

Upon appeal by Merz the Appeal Board noted that slide 19 of the presentation referred to Hunt and Clarke and stated that in an Allergan *saline-based* LD_{50} assay Botox and Xeomin were found to have different potencies. An adjacent table of data showed the potency of three Xeomin 100U vials, as tested in 2006, ranging from 69U/vial to 78U/vial. The same three lots were tested again in 2007, with recorded potencies of 61-67U/vial (Hunt and Clarke). The 2007 potency data was linked to a statement 'Avg potency of 2 batches tested just before/after expiry'. The Appeal Board questioned the relevance of testing the potency just after expiry of the product. Text to the right of the data from Hunt and Clarke stated '- Allergan 100U BOTOX Reference Standard (regulatory release)' and '- Saline-based assay reflects "real world" clinical usage.'

Below the Hunt and Clarke data was data from Dressler *et al* in which, using a Merz non saline-based LD_{50} assay, Botox and Xeomin were found to be equipotent. The mean potency of Botox was reported as 101.7U/vial whereas that for Xeomin was 103U/vial. Beneath the two tables of data from Hunt and Clarke and Dressler *et al* was the claim 'By using stabilizing agents for the bioassay, it was shown that 100 unit vials of Botox (Allergan, Irving, CA) containing complexing proteins, and 100 unit vials of Xeomin, a preparation free from complexing proteins, show equipotency in the mouse LD_{50} bioassay' referenced to Mander *et al*.

The Appeal Board considered that presenting the Hunt and Clarke data at the top of the slide gave it more prominence than the Dressler *et al* data below. Further, the use of phrases 'Reference Standard (regulatory release)' and 'real world' implied that the Hunt and Clarke results were more robust than those of Dressler *et al*. The Xeomin assay, as used by Dressler *et al* was referred to as 'non saline-based'. The Appeal Board considered that by emphasising *'non saline-based'* implied that it was not as good. Both assays had been accepted by the regulators for the respective botulinum toxins.

The Appeal Board noted that the summary slide (slide 34) did not refer to the comparative potencies of Botox and Xeomin.

The Appeal Board noted that none of the slides referred to the statement in the Bocouture SPC that 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) [ie Botox] are of equal potency'. Both the Bocouture SPC and the data on file to support this SPC statement were available to Allergan when the presentation was delivered but were nonetheless not included.

Slide 19 was in a section headed 'Non interchangeability of Botulinium Toxins' which also included slide 13 headed, 'Regulatory agencies recognize non-interchangeability' that gave details of non interchangeability statements in the SPCs for Xeomin, Dysport and Vistabel. Slide 18, headed 'What Clinical Data Exist for Xeomin?', gave limited information about some of the clinical data for Xeomin.

The Appeal Board did not accept Allergan's submission that slide 19 was a balanced slide on the Hunt and Clarke data. Nor did it accept Allergan's submission that the presentation was substantially different to the materials at issue in Case AUTH/2193/11/08. The Appeal Board considered that the use of Hunt and Clarke data implied that Botox was more potent than Xeomin which was inconsistent with the product SPCs and the available clinical data. This was sufficiently similar to the point at issue in Case AUTH/2183/11/08 to be caught by the undertaking in that case. The Appeal Board ruled a breach of the Code. In that regard high standards had not been maintained. The Appeal Board ruled a breach of the Code. The appeal on both points was successful.

The Appeal Board noted that an undertaking was an important document. The Appeal Board considered that failing to comply with the undertaking and assurance in this instance had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board ruled a breach of Clause 2. The appeal on this point was successful.

In Case AUTH/2335/7/10 Merz had alleged that a presentation given by Allergan at a meeting had breached the undertaking given in Case AUTH/2183/11/08 by implying that Botox/Vistabel (botulinum toxin) was more potent than Merz's

product Xeomin/Bocouture (also botulinum toxin). Merz submitted further evidence to support its allegation which, because it related to a different meeting, was taken up as a separate case, Case AUTH/2346/8/10.

As the complaint involved an alleged breach of undertaking, it was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

COMPLAINT

Merz referred to a meeting in July 2010 at which Merz and Allergan had been invited to present to a group of consultants, registrars and pharmacists who were trying to decide which botulinum to purchase. Merz noted that the invitation clearly stated that five topics were to be covered in the presentation ie product information; evidence base for licence usage; equivalence; head-to-head studies and stability.

The Allergan presentation, given by commercial employees, immediately followed the Merz presentation. The meeting was clearly promotional as it was intended to convince the audience to prescribe, buy and administer the medicines that were the subject of the presentation and therefore clearly fell into the definition given in Clause 1.2 of the Code.

Merz stated that the presentation given by Allergan employees consisted of, amongst other topics, the data from Hunt and Clarke (2009) that was the subject of Case AUTH/2183/11/08 and the subsequent allegation of breach of undertaking in Case AUTH/2335/7/10. Merz submitted it had been asked by members of the audience if the data presented by Allergan was accurate as Allergan had emphasised the supposed relative lack of potency of Xeomin. Merz was unaware of whether this was in the context of clinical head-to-head studies as requested by the organisers.

Merz noted that the meeting took place after Allergan knew about Merz's allegation of a breach of undertaking and as the meeting was clearly promotional, further demonstrated the lack of respect Allergan had for its undertakings to either Merz or the PMCPA and therefore continued to breach Clauses 25, 9.1 and 2 of the Code.

RESPONSE

Allergan stated that it, along with Merz, was invited to present at a Botulinum Toxin Information Day. Allergan submitted that its presentation was given by a senior medical employee, not a commercial employee, in response to an NHS foundation trust's request for scientific information. As outlined by Merz, both companies were asked to provide information on the five topics listed in the invitation.

Allergan did not agree that the meeting was promotional. It had reviewed, approved and certified its presentation as non-promotional ie as a scientifically accurate and balanced presentation, provided on request and addressing the topics stated in the invitation.

Commercial representatives attended in case the focus of the meeting evolved such as to require the provision of commercial information as it was not clear from the invitation as to the interests of the pharmacists or managers who would be present.

Allergan noted that Merz was specifically concerned about the use of the data by Hunt and Clarke. Allergan disagreed with Merz's allegation that Allergan's use of this data was in breach of the undertaking given in Case AUTH/2183/11/08.

Allergan and Merz were asked to address the topic of equivalence. Allergan covered this in the section of its presentation entitled 'Non-interchangeability of botulinum toxins'. This title was important as Allergan did not believe that the products were equivalent or that equivalence should be claimed.

The summary of product characteristics (SPCs) for the two botulinum toxin type A preparations stated that 'doses are specific to each preparation and are not interchangeable with other preparations of the toxin.'

Allergan noted that Merz had previously been found in breach of the Code for trying to establish equivalence (Cases AUTH/2119/4/08 and AUTH/2270/10/09). However, as established in Case AUTH/2270/10/09, and acknowledged by Merz, there was no data to support the equivalence of the two products and equivalence or equal potency could not be claimed from its non-inferiority studies. The two non-inferiority studies (Benecke *et al* 2005 and Roggenkämper *et al* 2006) demonstrated similar efficacy and safety profiles, not equivalence. Clearly lack of equivalence and non-interchangeability were linked.

Only slide 19 in the 34 slide presentation discussed Hunt and Clark. Allergan considered that these data were relevant in the context of a non-promotional presentation as they supported the fact that the botulinum toxin units were not interchangeable due to differences in LD_{50} assay techniques between different manufacturers.

The data were balanced by the inclusion of data from Dressler *et al* (2008) which demonstrated similar number of potency units for Botox and Xeomin when tested using the Merz reference LD_{50} assay. Hunt and Clarke showed that in the Allergan LD_{50} assay, with Botox set as the reference standard, Xeomin units were not equivalent to Botox units. In its presentation, Allergan used this data to support the fact that unit doses of the botulinum toxins were not interchangeable. This data was not used, as suggested by Merz, to demonstrate a lack of potency, only to confirm, as stated in the product SPCs, and established by case precedent, that botulinum toxin A units were not interchangeable.

Allergan suggested that Merz provided its presentation to the PMCPA for context. It was only when both presentations were viewed together that the Allergan presentation could be fairly assessed for balance.

Allergan considered that the use of one balanced slide on Hunt and Clarke was relevant in the context of a non-promotional scientific presentation. The data supported the fact that the botulinum toxin units were not interchangeable due to differences in LD_{50} assay techniques between different manufacturers. Therefore, these data were relevant to the clinical situation and its use in a non-promotional setting did not go against the ruling of Case AUTH/2183/11/08.

Allergan denied breaches of Clauses 25, 9.1 and 2 of the Code.

PANEL RULING

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future.

It was very important for the reputation of the industry that companies complied with undertakings. The Panel considered that given the Authority's responsibility in ensuring compliance with undertakings, inter-company dialogue as set out in Paragraph 5.2 of the Constitution and Procedure was not required in this regard before a complaint could be accepted.

The Panel noted that Allergan had been invited to a Botulinum Toxin Information Day to present information about Botox to a selected group of consultants, clinicians, pharmacists and managers. The invitation defined the scope and content of the presentation. The speaker from Allergan was a senior medical employee. The Panel considered that it was difficult to view the presentation as anything other than promotional given its delivery by an Allergan employee.

It appeared that, because the presentation had been given in response to a request for information, Allergan considered that it was non-promotional. The Panel noted, however, that the exemption in Clause 1.2 to the term promotion, was for replies 'made in response to *individual* enquiries'. Such requests had to be unsolicited. The Panel was not certain that this was so or that each member of the audience had individually asked for the information. The Panel decided that the presentation could not take the benefit of this exemption to the definition of promotion.

The Panel further noted Allergan's submission that its presentation should be viewed together with the presentation from Merz so that the Allergan presentation could be fairly assessed for balance. In the Panel's view, each presentation had to stand alone under the Code; neither could rely on the other for balance.

The Panel noted that slide 19 of the presentation referred to Hunt and Clarke and stated that in an Allergan saline based LD_{50} assay Botox and Xeomin were found to have different potencies with the potency of three Xeomin 100U vials ranging from 69U/vial to 78U/vial. No comparable data for Botox was reported. It was stated that the saline-based assay reflected 'real world' clinical usage. Immediately below the Hunt and Clarke data was data from Dressler *et al* in which, using a Merz non saline-based LD_{50} assay, Botox and Xeomin were found to be equipotent. The mean potency of Botox was reported as 101.7U/vial whereas that for Xeomin was 103U/vial. Beneath the two tables of data from Hunt and Clarke and Dressler *et al* was the claim 'By using stabilizing agents for the bioassay, it was shown that 100 unit vials of Botox (Allergan, Irving, CA) containing complexing proteins, and 100 unit vials of Xeomin, a preparation free from complexing proteins, show equipotency in the mouse LD_{50} bioassay' referenced to Mander (2009).

The Panel noted that the summary slide (slide 34) did not refer to the comparative potencies of Botox and Xeomin. Slide 13 referred to the non-interchangeability of units of Xeomin, Dysport and Allergan (Vistabel) by reference to the products' SPCs.

The Panel noted that in Case AUTH/2183/11/08, Allergan had been ruled in breach of the Code; the Panel referred to its ruling in that case.

Case AUTH/2183/11/08

In the Panel's view the data presented in a product monograph and an objection handler which derived from Hunt *et al* implied that there was a difference in potencies between Xeomin and Botox in favour of Botox. This was inconsistent with the summaries of product characteristics (SPCs) which showed similar dosing regimens for the two products. The Panel accepted that there was some animal data that possibly showed a difference. However, the supplementary information to the Code was clear that animal data should not be extrapolated to the clinical situation unless there was data to show that it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the comparison could not be substantiated and did not reflect all of the evidence. Breaches of, *inter alia*, Clauses 7.2, 7.3 and 7.10 of the Code were ruled.

Case AUTH/2346/8/10

The Panel considered that the comparative data shown in the presentation was sufficiently different to the material considered in Case AUTH/2183/11/08 for it not to be caught by the undertaking given in that case. The previous material had not referred to Dressler *et al* or the Mander data. The Panel did not consider that the presentation was in breach of the undertaking given in Case AUTH/2183/11/08 and so

it ruled no breach of Clause 25. In that regard high standards had been maintained. No breach of Clause 9.1 was ruled.

The Panel considered that as there had been no breach of the undertaking there could be no breach of Clause 2. No breach of that clause was ruled.

APPEAL BY MERZ

Merz alleged that Allergan breached the undertaking given in Case AUTH/2183/11/08 by seeking to convince medical practitioners that Xeomin was less potent than Botox using the same data. This claim was inconsistent with the respective product SPCs and head-to-head clinical comparisons.

Merz alleged that the presentation at issue was clearly promotional as it was delivered as part of a commercial tendering process in order to convince the audience to purchase the product for the NHS. The invitation to present made this position clear. The fact that a commercial employee of Allergan was there clearly reinforced that the presentation was promotional and therefore subject to the Code.

The head-to-head comparisons of Xeomin vs Botox requested were addressed on slide 18 headed 'What Clinical Data Exists for Xeomin?'. Merz alleged that this title was derogatory since the audience would normally expect a review of a company's own product rather than its competitor's product, it was also misleading as it suggested that the slide contained the complete clinical dataset for Xeomin which it did not. This slide clearly discredited Xeomin. Whilst this slide did refer to the fact that Xeomin was demonstrated to be non-inferior to Botox in two studies, it did not mention the 1:1 dosing ratio used in Benecke *et al* and Roggenkämper *et al*. Dosing ratios were important as they had a direct impact on the relative cost of a medicine and were directly linked to product potency.

Merz alleged that slide 19 undermined the previous data and cast the potency of Xeomin in doubt. It presented the 'saline based', non-comparative assessment of Xeomin by Hunt and Clarke as the 'Allergan 100U Botox reference standard', approved by the regulator and 'real world' in design. This slide presented the assay as appropriate and approved by the regulator as a comparator assay for Xeomin, and carrying more weight than the 'Merz non-saline based' comparative assay by Dressler *et al*. The fact that the 'Merz non-saline based' assay performed by Dressler *et al* was the Xeomin 100 unit reference standard and the approved 'regulatory release' assay for Xeomin was deliberately omitted. Allergan therefore clearly intended to make the audience believe that its assay was the only 'reference standard' and credible evaluation tool; this misled the audience and discredited Xeomin. Further, the way the study was described as the 100U Botox reference standard, led the audience to believe that this was a comparative assay comparing Xeomin with Botox which it was not. There was only one comparative assay reported and that was by Dressler *et al*.

Merz alleged that the letter by Mander *et al* was not written in support of the publication by Hunt and Clarke but to refute it. Allergan failed to mention that this letter concluded that 'the differences observed by Hunt and Clarke are clearly artefacts created by the assay conditions used'. The reason for this was that the Allergan assay diluted Xeomin many times more than the maximum dilution specified in the SPC and therefore clearly did not reflect the 'real world' as suggested. There were clear reasons why the Allergan standard was not 'real world'. This standard diluted the toxin in saline up to 100ml, which was well beyond the dilutions specified in the respective Xeomin and Botox SPCs. Merz knew of no clinical situation where either 100 units of Botox or 100 units of Xeomin were diluted to a volume greater than 10ml. Xeomin 100 unit vials contained enough human serum albumin (HSA) to prevent the naked (150kD) toxin from being absorbed into the vial or syringe surface for dilutions up to 10ml. Dilutions substantially greater than this would overly dilute the HSA leading to absorption of the toxin into the vessel. This absorption was less for the complexed toxin. Thus it was clear that Botox could be expected to have an apparently higher potency than Xeomin if diluted to 100ml with saline but this was purely an artefact of the assay conditions used, as concluded by Mander *et al*. The use of stabilising agents in the Merz assay was appropriate for Xeomin and led to an outcome which was consistent with all the published clinical data and the appropriate product SPCs. Indeed, if information of the 1:1 dosing ratio used in the clinical evaluation of the products had been included in slide 18, it would have directly contradicted the message from the non-clinical evaluation of slide 19, that Xeomin was less potent than Botox.

Merz alleged that this position was directly supported by a very large clinical data set involving two regulatory, phase III clinical trials containing 763 patients that unequivocally showed that Xeomin was non-inferior, clinically no less effective, than Botox (Benecke *et al* and Roggenkämper *et al*). This data was accepted by the European regulators and was the basis upon which they gave Xeomin the identical dosing regimen to Botox as mentioned in the ruling in Case AUTH/2183/11/08.

Merz alleged that therefore it was clear that the animal data generated by Hunt and Clarke, which was an artefact of the assay conditions, was directly refuted by clinical data. The slide presented by Allergan was therefore incapable of substantiation, did not reflect all the data and would not lead to rational use of the medicine, the same ruling as in Case AUTH/2183/11/08. The fact that Allergan presented other data which it then attempted to discredit did not detract from this.

Allergan stated that it deliberately placed the clinical

evaluation of Botox and Xeomin in a section entitled 'Non-interchangeability of Botulinum Toxins', as it did not believe the products to be equivalent. This was not accurate as Allergan had clearly moved into clinical efficacy in the presentation of Xeomin clinical data in slide 18. Allergan also argued that clearly lack of equivalence and non-interchangeability were linked. Merz alleged that Allergan had sought to distort the purpose of a SPC product statement to its advantage providing a platform to cast doubt on the potency of Xeomin.

Merz alleged that for Allergan to have a clear position that the two products were not equivalent, there must have been a study designed to show equivalence that failed. This study had not been conducted and thus lack of equivalence, clinical or otherwise, could not be claimed or implied by Allergan. The saying 'lack of evidence was not evidence of lack' applied here and therefore Allergan's defence of lack of equivalence and lack of interchangeability being linked was equally incapable of substantiation.

Merz did not argue with the statement in the SPC about interchangeability of product units, quite the opposite. The non-interchangeability statement was one of caution to prescribers and pharmacists to ensure safe prescribing and administration of products that were not biochemically identical and to encourage brand prescribing. It did not, however, imply that two products could be of equal potency. This was made quite clear by the statement in the Bocouture SPC. Bocouture was exactly the same medicine as Xeomin but presented in a 50 unit vial. The Bocouture SPC contained the statement about lack of interchangeability of product units but also stated 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency'. The comparator product was the Allergan 900kDa toxin.

Merz alleged that the majority of the clinical data submitted to obtain the marketing authorization for Bocouture was the phase III studies used to obtain the marketing authorization for Xeomin (Roggenkämper *et al* and Mander *et al* [sic]). For both statements to appear on the SPC of a product the regulators had stated that the assays for the two products were different but also that clinical data suggested that the conventional botulinum toxin (Botox) was equipotent to Bocouture (which was identical to Xeomin). Clearly Allergan's statement that the products were not interchangeable and that they were not equivalent was intended to reinforce Allergan's message that Xeomin was less potent than Botox, however, both of these statements were incapable of substantiation.

Merz alleged that the presentation of data showing lower potency could only be to convey the message of lower potency using the same data as was ruled on in Case AUTH/2183/11/08. As observed by the Panel in Case AUTH/2335/7/10 with regard to the presentation of the two sets of data on one slide; 'The Panel considered that the audience would inevitably compare the figures from the two tables and conclude that Xeomin was less potent than Botox'.

Merz alleged that this represented a breach of undertaking as:

- The Allergan representative sought to convince the audience in a clearly promotional presentation that Xeomin was less potent that Botox by presenting animal data which conflicted with all relevant clinical evaluations.
- The additional data presented on the slide was dismissed, by implication, as not being 'real world' leaving only data that showed a difference from which the audience were expected to draw the conclusion that Xeomin was less potent than Botox.
- The animal data from which the audience's conclusion would be drawn were exactly the same data subject to the undertaking in Case AUTH/2183/11/08.
- The presentation of the data went against the Panel's view in Case AUTH/2183/11/08 and it remained inconsistent with the identical dosing regimens in the SPC.
- The presentation of the data could not be substantiated, did not reflect all the evidence would not encourage the rational use of the medicine. This was the same ruling in Case AUTH/2183/11/08.

Merz questioned the value of undertakings if they allowed a company to present data ruled in breach of the Code in a slightly different way but draw the same misleading conclusion. Merz alleged that Allergan intended the presentation to circumvent the undertaking given following Case AUTH/2183/11/08 whilst ensuring that the same message was communicated. This eroded the purpose of undertakings. The presentation of the data in this way to draw these conclusions was clearly in breach of the undertaking given in Case AUTH/2183/11/08 and therefore in breach of Clauses 2, 9.1 and 25.

COMMENTS FROM ALLERGAN

Allergan disagreed that it had breached the undertaking given in Case AUTH/2183/11/08. Allergan was well aware of that case and the undertaking it had given and had fully taken into account its undertaking; it was confident that the presentation did not constitute a breach of undertaking.

Allergan strongly refuted the allegation by Merz that it used the data at issue in the undertaking (Hunt and Clarke 2006 – now available as a full publication) to convince medical practitioners that Xeomin was less potent than Botox. As below, this data was used in a balanced manner, reflected the available evidence, to illustrate that unit doses of botulinum toxin products were not interchangeable.

Merz's appeal rested on the assertion that Allergan breached the undertaking in respect of Case AUTH /2183/11/08, the key concluding section of the Panel's ruling in that case was (* asterisked clarification by Allergan):

'The Panel considered that given the comparative potency information in the product monograph and objection handler (*derived from Hunt and Clarke (2006) – now available as a full publication) it was not unrealistic that representatives might have used this information when promoting Botox to health professionals. There was no instruction about how to use the information comparing the potency of Xeomin and Botox. The Panel considered on the balance of probabilities the Allergan representative had claimed there was a difference in potency for the products. This was inconsistent with the summaries of product characteristics (SPCs) which showed similar dosing regimens for the two products. The Panel accepted that there was some animal data that possibly showed a difference. However, the supplementary information to Clause 7.2 was clear that animal data should not be extrapolated to the clinical situation unless there was data to show that it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the product monograph and objection handler were misleading with regard to the information about potency. The comparison could not be substantiated and did not reflect all of the evidence. The material would not encourage the rational use of a medicine. Thus the Panel ruled breaches of Clauses 7.2, 7.3 and 7.10.'

Allergan submitted that it would be clear from the evidence below that it had taken into account the requirement for balance, reflection of all the available data and the care required when presenting and extrapolating animal data. Allergan had not breached the undertaking or attempted to circumvent the undertaking as alleged by Merz. Allergan submitted that it had complied with both the letter and spirit of the Code.

The Allergan presentation was given by a senior member of its scientific support team, not a 'commercial employee', in response to a scientific information request from an NHS foundation trust. Given this written request Allergan did not believe the presentation was promotional. Allergan had taken the Panel's view on board and would ensure that future presentations of this type were reviewed as promotional items. That said, the presentation was reviewed, approved and certified as a scientifically accurate and balanced presentation, provided on request and addressing the topics as stated in the invitation.

The first issue raised by Merz in its appeal was that slide 18 headed 'What Clinical Data Exists for Xeomin' was derogatory and discredited Xeomin. Allergan disagreed. Allergan was specifically asked to cover which head-to-head studies existed. This was a fair summary of the data and clearly stated that non-inferiority was established for efficacy variables in the two studies cited by Merz (Benecke *et al* and Roggenkämper *et al*). This information was provided for balance. If further detail on, for example, dose ratios selected in the trials, was requested by the audience, this would have been covered by the speaker. However, as indicated by Merz, Allergan's presentation focussed primarily on the data regarding Botox not Xeomin.

Merz then focussed on slide 19 which included the Hunt and Clarke data at issue. This slide was one of 16 contained in a section entitled non-interchangeability of botulinum toxins. Allergan (and Merz) had been specifically asked to address the topic of equivalence. The title of this section was important as Allergan did not believe the products were equivalent or that equivalence should be claimed.

As stated in the SPC for Botox:

> 'Botulinum toxin units <u>are not interchangeable from one product to another.</u>'
>
> 'Doses recommended for BOTOX are not interchangeable with other preparations of botulinum toxin.'

Similar statements were in the Xeomin SPC:

> 'Due to differences in the LD_{50} assay, these units are specific to Xeomin and are not interchangeable with other Botulinum toxin preparations.'
>
> 'Unit doses recommended for Xeomin are not interchangeable with those for other preparations of Botulinum toxin.'

Allergan submitted that Merz had previously been found in breach of the Code for trying to establish equivalence between Botox and Xeomin (Case AUTH/2119/4/08 and Case AUTH/2270/10/09). However, as established, most recently in Case AUTH/2270/10/09, and acknowledged by Merz, there was no data to support the equivalence of the two products and equivalence or equal potency could not be claimed from their non-inferiority studies The two non-inferiority studies (Benecke *et al*; Roggenkämper *et al*) demonstrated similar efficacy and safety profiles. They did not demonstrate equivalence.

Only slide 19 in the presentation discussed the Hunt and Clark data. Allergan submitted that these data were relevant in the context of this presentation, as they supported the fact that the botulinum toxin units were not interchangeable due to differences in LD_{50} assay techniques between different manufacturers. The data were balanced by the inclusion of Dressler *et al* which demonstrated similar number of potency units for Botox and Xeomin when tested using the Merz reference LD_{50} assay. Hunt and Clarke showed that in the Allergan LD_{50} assay, with Botox set as the reference standard, Xeomin units were not equivalent to Botox units.

The speaker used this data to support the fact that unit doses of the botulinum toxins were not interchangeable. This data was not used as Merz suggested to demonstrate a lack of potency, only to confirm, as stated in the SPCs, and established by case precedent, that botulinum toxin A units were not interchangeable. The data was further balanced by reference to correspondence from Mander *et al* which provided the counter view to that of Allergan with respect to the Hunt and Clarke data as discussed by Merz. However, Merz failed to mention that Hunt and Clarke stated in their response to Mander *et al* (Hunt and Clarke, Editorial Response Letter to Mander *et al*, 2009) that the assay used in their study was not selected to show differences but was used because it was the standard assay used to release Botox as approved and recognised by the international regulatory authorities. The assay was therefore suitable and appropriate for comparison.

The fact that different neurotoxins reacted differently in potency assays because the medicines differed substantiated that these medicines were not the same ie that units were not interchangeable.

Clearly Merz and Allergan disagreed as to the relevance of the diluents used in the assay. Allergan substantiated that because saline was used as a diluent, it was a clinically more relevant assay. Additives such as gelatine could alter and confound the results of potency assays and were not used in the clinical setting. This debate would continue but Allergan submitted that it had presented a balanced view of the evidence.

Allergan submitted that slides 18 and 19 were complementary. One summarised the clinical data available, including the European non-inferiority studies (Benecke *et al* and Roggenkämper *et al*) which established that Xeomin was not inferior to Botox, the European spasticity trials and the studies conducted in the US which were used to support the recent US registration of Xeomin (Grafe and Hanschmann, 2010). The other slide confirmed that units of the products were not interchangeable.

Allergan robustly defended the right to make clear, as stated in the SPCs, that unit doses of botulinum toxins were not interchangeable and that Botox and Xeomin were not equivalent.

Allergan submitted that the use of one balanced slide on the Hunt and Clarke data was relevant. The data supported the fact that the botulinum toxin units were not interchangeable due to differences in LD_{50} assay techniques between different manufacturers. The slide was within a section containing 16 slides which included clinical data. Therefore, these data were relevant to the clinical situation and their use did not go against the ruling in Case AUTH/2183/11/08.

In conclusion, Allergan noted that, as stated in the Panel's ruling, the comparative data at issue was sufficiently different to the material at issue in Case AUTH/2183/11/08. Balance was provided by Dressler *et al* and Mander *et al*, along with the summary slide of clinical data. Therefore, Allergan refuted the alleged breaches of Clauses 25, 9.1 and 2 of the Code.

FINAL COMMENTS BY MERZ

Merz submitted that Allergan's misrepresentation of previous Panel and Appeal Board cases needed to be addressed.

- In Case AUTH/2119/4/08 Merz was ruled in breach of Clause 3.2 for not including the statement about the lack of interchangeability of unit doses from the SPC. The complaint was not about any lack of demonstrated equivalency.
- In Case AUTH/2270/10/09 Merz was ruled in breach for using the statement 'at least as effective as' which Merz believed accurately described the outcome of a non-inferiority study. Whilst Merz accepted that there was no clinical data that demonstrated equivalence of Xeomin to Botox, this was not the claim at issue.

Allergan continued to suggest that this presentation was non-promotional. However the presence of commercial staff at a meeting where Allergan presented to an audience which was to decide on the purchase of botulinum toxin was clearly promotional, as accepted by the Panel.

With regard to Allergan's suggestion that the choice of diluents was a matter of debate, Merz submitted that the gelatine based assay had been accepted by regulatory authorities in Europe, Mexico, Argentina, Canada and the US for the assessment of Xeomin. It appropriateness for this use was thus not in doubt.

Merz noted that the Hunt and Clarke data was presented and it alleged that it did not comply with the requirements of the supplementary information to Clause 7.2 of the Code as the large clinical studies clearly showed that Xeomin was non-inferior to Botox. The Hunt and Clarke data therefore, however it was presented, should not be extrapolated to the clinical situation as the clinical data directly contradicted it. This was the basis for the ruling in Case AUTH 2183/11/08 and was still true. The invitation did not ask for potency data and therefore its inclusion and context (including the dismissal of the Merz assay) in the presentation could only have been to extrapolate it to the clinical situation to suggest that Xeomin was less potent than Botox. This was the basis of the ruling in Case AUTH/2183/11/08 and therefore the presentation now at issue represented a breach of undertaking.

APPEAL BOARD RULING

The Appeal Board noted that slide 19 of the presentation referred to Hunt and Clarke and stated that in an Allergan **saline-based** LD_{50} assay Botox and Xeomin were found to have different potencies. An adjacent table of data showed the potency of three Xeomin 100U vials, as tested in 2006, ranging from 69U/vial to 78U/vial. The same three lots were

tested again in 2007, with recorded potencies of 61-67U/vial (Hunt and Clarke). The 2007 potency data was linked to a statement 'Avg potency of 2 batches tested just before/after expiry'. The Appeal Board questioned the relevance of testing the potency just after expiry of the product. Text to the right of the data from Hunt and Clarke stated '- Allergan 100U BOTOX Reference Standard (regulatory release)' and '- Saline-based assay reflects "real world" clinical usage.'

Below the Hunt and Clarke data was data from Dressler *et al* in which, using a Merz non saline-based LD_{50} assay, Botox and Xeomin were found to be equipotent. The mean potency of Botox was reported as 101.7U/vial whereas that for Xeomin was 103U/vial. Beneath the two tables of data from Hunt and Clarke and Dressler *et al* was the claim 'By using stabilizing agents for the bioassay, it was shown that 100 unit vials of Botox (Allergan, Irving, CA) containing complexing proteins, and 100 unit vials of Xeomin, a preparation free from complexing proteins, show equipotency in the mouse LD_{50} bioassay' referenced to Mander *et al*.

The Appeal Board considered that presenting the Hunt and Clarke data at the top of the slide gave it more prominence than the Dressler *et al* data below. Further, the use of phrases 'Reference Standard (regulatory release)' and 'real world' implied that the Hunt and Clarke results were more robust than those of Dressler *et al*. The Xeomin assay, as used by Dressler *et al* was referred to as 'non saline-based'. The Appeal Board considered that by emphasising **'non saline-based'** implied that it was not as good. Both assays had been accepted by the regulators for the respective botulinum toxins.

The Appeal Board noted that the summary slide (slide 34) did not refer to the comparative potencies of Botox and Xeomin.

The Appeal Board noted that none of the slides referred to the statement in the Bocouture SPC that 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) [ie Botox] are of equal potency'. Both the Bocouture SPC and the data on file to support this SPC statement were available to Allergan when the presentation was delivered but were nonetheless not included.

Slide 19 was in a section headed 'Non interchangeability of Botulinium Toxins' which also included slide 13 headed, 'Regulatory agencies recognize non-interchangeability' that gave details of non interchangeability statements in the SPCs for Xeomin, Dysport and Vistabel. Slide 18, headed 'What Clinical Data Exist for Xeomin?', gave limited information about some of the clinical data for Xeomin.

The Appeal Board did not accept Allergan's submission that slide 19 was a balanced slide on the Hunt and Clarke data. Nor did it accept Allergan's submission that the presentation was substantially different to the materials at issue in Case AUTH/2193/11/08. The Appeal Board considered that the use of Hunt and Clarke data implied that Botox was more potent than Xeomin which was inconsistent with the product SPCs and the available clinical data. This was sufficiently similar to the point at issue in Case AUTH/2183/11/08 to be caught by the undertaking in that case. The Appeal Board ruled a breach of Clause 25. In that regard high standards had not been maintained. The Appeal Board ruled a breach of Clause 9.1. The appeal on both points was successful.

The Appeal Board noted that an undertaking was an important document. The Appeal Board considered that failing to comply with the undertaking and assurance in this instance had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board ruled a breach of Clause 2. The appeal on this point was successful.

The Appeal Board noted that Allergan had initially considered that the presentation was not promotional and had approved it in that context. That the presentation was non-promotional had been rejected by the Panel. The Appeal Board was concerned that Allergan's initial view regarding the status of the presentation showed a lack of understanding although at the appeal hearing the company made it clear that it now accepted that the presentation was promotional.

Complaint received **12 August 2010**

Case completed **6 December 2010**

CASE AUTH/2350/8/10

VIFOR PHARMA v PHARMACOSMOS

Promotion of Monofer

Vifor Pharma complained about the promotion of Monofer (iron isomaltoside 1000 solution for injection/infusion) by Pharmacosmos A/S Denmark. At issue were an announcement published on Pharmacosmos.com and an advertisement published in the June 2010 edition of Transfusion Alternatives in Transfusion Medicine (TATM).

The announcement was headed 'Pharmacosmos establishes UK subsidiary' (though a merger with Vitaline Pharmaceuticals in the UK) and referred to the company's aspiration to provide patients and health professionals with best-in-class treatment for iron deficiency anaemia. The announcement went on to refer to the launch of Monofer.

Vifor explained that the Monofer Public Assessment Report (PAR) stated that the efficacy of Monofer was assessed by combining data from two prospective, open-label and non-comparative clinical studies to establish the safety profile of the product; efficacy was a secondary endpoint.

Vifor submitted that with 202 patients in two key studies that were primarily safety studies, 'best-in-class' could not be substantiated. Other products had significantly more clinical study data than Monofer and so Vifor considered that 'best-in-class' was misleading. Vifor claimed that Monofer was expected to have a similar safety profile to that of Cosmofer [marketed by Vitaline] which was used as a reference for the licensing of Monofer. Based on these efficacy and safety outcomes, Vifor submitted that Monofer did not qualify as best-in-class.

The Panel noted that the announcement was dated July 8 ie. 7 days after Pharmacosmos and Vitaline had merged to form Pharmacosmos UK. The announcement referred to the new company's business in the UK and to treatment options for patients with iron deficiency anaemia in the UK. It was stated that a key task for Pharmacosmos UK would be the launch of Monofer. The Panel thus considered that although issued by Pharmacosmos in Denmark, the press release was on that company's website and referred to Vitaline being a preferred partner in the UK. It also referred the availability of Monofer in the UK. In that regard, the Panel considered that the press release was within the scope of the Code.

The Panel noted that the press release stated that Pharmacosmos and Vitaline shared an aspiration to provide 'best-in-class treatment for iron deficiency anaemia' and later referred to Monofer as a treatment for iron deficiency anaemia. The Panel thus considered that, by inference, many readers would assume that Monofer was a 'best-in-class treatment'. The Panel did not consider that such a claim represented the balance of the evidence and a breach of the Code was ruled.

Vifor alleged that the SPC which was cited in support of the claim 'A novel treatment of iron deficiency anaemia' did not substantiate it. Vifor stated that Monofer was an iron/dextran complex (iron isomaltoside 1000) as a colloidal suspension. Vifor submitted that dextran treatment had been around for years and this did not constitute a novel treatment.

The Panel noted that injectable iron complexes had been previously available to treat iron deficiency anaemia. In that regard Monofer was not a novel treatment although its formulation had resulted in some practical benefits regarding dosage and administration. The Panel considered that the description of Monofer as 'a novel treatment' did not reflect the data. A breach of the Code was ruled.

Vifor alleged that the 'Possibility of full iron repletion in one, rapid visit for more patients' was a hanging comparison and was not substantiated. Of the 583 doses administered in the P-CKD-01 study only 44 were given as total dose infusions (TDIs). Nevertheless, 2 of those 44 doses had not been one-visit repletions as they had been split into two administrations. So the claim 'the possibility of full iron repletion in one, rapid visit for more patients' was misleading.

The Panel considered that the claim at issue was a hanging comparison as alleged as it did not state that with which Monofer was being compared. A breach of the Code was ruled.

The Panel noted that the claim referred to the possibility of one-visit repletions; it did not state that all patients would only need one visit. The Panel further noted that in the P-CKD-01 study, 38 patients out of 182 who entered the study, received an undivided total dose infusion. The reference to the 'possibility' of 'one, rapid visit' was not misleading as alleged. No breach of the Code was ruled.

Vifor submitted that the NATA journal had a significant UK distribution and the advertisement that appeared in June 2010 had not been signed off under the ABPI Code and did not include UK abbreviated prescribing information. A breach of Clause 1.1 was alleged.

The Panel noted that the advertisement appeared in June 2010 which predated the merger of Vitaline and Pharmacosmos. The Panel noted that Pharmacosmos stated that it accepted that the advertisement needed to comply with the UK ABPI Code and all future international advertisements would include a UK abbreviated SPC. Neither the absence of prescribing information nor incorrect prescribing information could be a breach of the clause alleged by Vifor. Thus the Panel ruled no breach of the Code.

Vifor alleged that the cavalier approach to the Code and the delayed response, and the apparent lack of seriousness with which Pharmacosmos/Vitaline seemed to have handled this matter, brought discredit upon, and reduced confidence in, the pharmaceutical industry in breach of Clause 2.

The Panel considered that although breaches of the Code had been ruled, the matters overall were not such as to warrant a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure.

Vifor Pharma UK Limited complained about the promotion of Monofer (iron isomaltoside 1000 solution for injection/infusion) by Pharmacosmos A/S Denmark. Inter-company dialogue via Vitaline Pharmaceuticals in the UK had failed to resolve the matter. Pharmacosmos and Vitaline merged on 1 July 2010. At issue were an announcement published on Pharmacosmos.com and an advertisement published in the June 2010 edition of Transfusion Alternatives in Transfusion Medicine (TATM), the journal of the Network for Advancement of Transfusion Alternatives (NATA). Vifor supplied Ferinject (iron carboxymaltose).

A Announcement on Pharmacosmos.com

The announcement was headed 'Pharmacosmos establishes UK subsidiary' and referred to this as an important step forward for the company [which was otherwise based in Denmark]. The announcement also referred to the company's aspiration to provide patients and health professionals with best-in-class treatment for iron deficiency anaemia. The announcement went on to refer to the launch of Monofer.

1 Claim 'best-in-class'

COMPLAINT

Vifor alleged that this claim was unsubstantiated in breach of Clause 7.2.

Vifor explained that the Monofer Public Assessment Report (PAR) highlighted that the efficacy of Monofer was assessed by combining data from two clinical studies (P-CKD-01 and P-CHF-01). The main purpose of the studies was to establish the safety profile of the product; efficacy was a secondary endpoint. Both studies were prospective, open-label and non-comparative.

In P-CKD-01 182 patients entered the trial and had at least one dose of Monofer and hence constituted the safety analysis set (intention to treat (ITT)).

P-CHF-01 study included 20 CHF patients with anaemia who needed parenteral iron due to either absolute or functional iron deficiency anaemia.

In the P-CKD-01 trial, an increase in all sample estimates ((haemoglobin (Hb), haematocrit, (Hct), transferrin saturation (TSAT), serum iron (s-iron) and serum ferritin (s-ferritin)) over time compared with baseline was indicated by the p-values. S-ferritin was significantly increased at all visits ($p < 0.0001$). Hct was not significantly increased at visit 3 but significantly increased at visits 4-6 ($p \leq 0.0026$). Hb was not significantly changed at visits 3-4 but was significantly increased at visit 5-6 ($p < 0.0001$).

The largest difference in change from baseline in Hb was observed at visit 6 (8 weeks after baseline) with a value of 3.9g/L (0.245mmol/L). TSAT was significantly increased at all visits ($p \leq 0.0220$). S-iron was significantly increased at visits 3-5 ($p \leq 0.0378$), but not at visit 6. At a glance, the efficacy estimates (Hb, Hct, TSAT, s-iron and s-ferritin) in the P-CHF-01 trial seemed to be increased to a higher extent at all visits compared with the P-CKD-01 trial. However, many of the results were non-significant and the increase in Hb of 3.9g/dl was not clinically significant.

Vifor submitted that with 202 patients in two key studies that were primarily safety studies, 'best-in-class' could not be substantiated. As other products had significantly more clinical study data than Monofer, Vifor considered that 'best-in-class' was misleading. Monofer studies were open-label and non-comparative. Vifor claimed that as Monofer was a low molecular weight dextran with 3-5 glucose units, it was expected to have a similar safety profile as outlined in the summary of product characteristics (SPC) for Cosmofer [marketed by Vitaline] which was used as a reference for licensing Monofer (ref PAR). Based on these efficacy and safety outcomes, Vifor submitted that Monofer did not qualify as best-in-class.

RESPONSE

Pharmacosmos stated that Vifor's references to the PAR for Monofer were not in accordance with it.

Monofer was not 'a low molecular weight dextran with 3-5 glucose units', but an iron carbohydrate complex, where iron was complexed with chemically modified isomaltooligosaccharides.

Monofer had been approved with a distinctly better safety and product profile than iron dextran, eg, Cosmofer and so Vifor's submission that it would be expected to have a similar safety profile as outlined in the SPC for Cosmofer was not correct.

Pharmacosmos further noted that Vifor's comments about the chemistry, the designation for the active

pharmaceutical ingredient, the safety and product profile and the basis for regulatory approval of iron isomaltoside 1000, needed to be addressed:

Vifor had described the chemistry of iron isomaltoside, the active ingredient in Monofer, as follows:

> 'As Monofer was a low molecular weight dextran with 3-5 glucose units, it was expected to have a similar safety profile as outlined in the SPC for Cosmofer which was used as a reference for licensing for Monofer'.

The statement was not quoted correctly as, for example, the phrase 'is a low molecular weight dextran with 3-5 glucose units' was not in the PAR nor was it scientifically correct.

The chemistry of Monofer was clearly described in the PAR which defined Monofer:

> 'The active substance is iron (III) isomaltoside 1000 …

and

> Isomaltoside 1000 consists predominantly of 3-5 glucose units and originates from a chemical modification of isomalto-oligosaccharides present in Dextran 1 Ph. Eur. For approved indications, see the Summary of Products Characteristics.'

Accordingly, iron isomaltoside 1000 was an iron complex with chemically modified isomalto-oligosaccharides thus Monofer was distinctly different from iron dextran eg, Cosmofer and from 'low molecular weight dextran'.

Pharmacosmos further noted that Monofer had been approved as being distinctly different from iron dextran eg Cosmofer and with an improved safety and product profile.

Vifor's statement above connected the incorrect expression 'low molecular weight dextran with 3-5 glucose units' and a text from the PAR taken out of context, ie 'similar safety profile as outlined in the SPC of Cosmofer'.

However, it was clear that Monofer was expected to have an improved safety profile compared with Cosmofer as in the following quotation from the PAR:

> 'IV.5 Clinical Safety
> Monofer is expected to have a similar safety profile as outlined in the summary of product characteristics (SmPC) for Cosmofer. However, based on earlier clinical experiences with low molecular weight dextran fractions the incidence of dextran anaphylactoid reactions is expected to be lower. Based on the assumption that Monofer has a lower potential for anaphylactic reactions it was suggested that a test dose injected of the product should not be given before the IV application of a bolus dose or TDI [total dose infusion] of Monfer.'

Furthermore, the PAR stated as quoted below, the rationale for developing Monofer, iron isomaltoside 1000 with a distinctly different product profile compared with iron dextran eg Cosmofer/Dexferrum.

> 'However, the potential for anaphylactic reactions has been a concern for the clinical use of in particular high molecular weight iron dextran [Dexferrum – marketed by Vifor and partners in the US] and a test dose is necessary according to the SmPC of Cosmofer, which is a low molecular weight iron dextran.
>
> The acute and long term toxic properties of iron gluconate and iron sucrose necessitate the development of new iron compounds with a comparable efficacy but a superior short and long term safety profile allowing fast administration of high doses. If possible, full iron repletion during one single total dose IV infusion with a short infusion time should be provided. Additionally, a compound where it is not necessary to provide a test dose is warranted.
>
> Dextran 1, the carbohydrate fraction used in the production of isomaltoside 1000, is indicated for the prevention of anaphylactic reactions to clinical dextran infusions for plasma volume expansion. The rationale for developing Monofer was that, theoretically, the risk for anaphylactic/anaphylactoid or delayed allergic reactions may be reduced with Monofer compared to marketed iron dextrans'.

The authorities concluded on the clinical aspects:

> 'The data from trial P-CKD-01 and P-CHF-01 are considered sufficient to support the efficacy and safety of Monofer in the treatment of iron deficiency anemia. … A possible potential for Monofer to cause anaphylactoid reactions, as known for other parental products, cannot be ruled out. This is sufficiently reflected in the SmPC.'
>
> 'However, based on the Applicant's responses and the study data, there is sufficient support for the proposed omission of the test dose and the recommendation of a shorter infusion time of 30-60 minutes. The SmPC has been amended with adequate warnings and instructions on precautions to ensure safe use of the product.'

Consequently, Monofer was accepted by the decentralised procedure in 22 EU countries and had so far been granted marketing authorizations in 17 including the UK with a distinctly different product and safety profile than iron dextran, eg Cosmofer as documented in the PAR:

- approved with a chemically distinct new

designation isomaltoside 1000 of the carbohydrate moiety
- approved as iron isomaltoside 1000 and not as iron dextran
- approved with an accepted new immunological profile
- approved without use of any test dose contrary to iron dextran preparations
- approved for faster injection compared to iron dextran
- approved for rapid infusion in 30-60 minutes in high doses contrary to iron dextran which is approved for slow 4-6 hours infusion.

Monofer was accepted and approved based on the submitted data on iron isomaltoside active pharmaceutical ingredient and on Monfer solution for injection and referencing other iron carbohydrates, including Cosmofer.

In conclusion, Vifor's references to Monfer were not in accordance with the PAR. It seemed that Vifor had tried to invalidate the content and conclusions of the PAR.

With regard to the claim 'best-in-class', Pharmacosmos noted that the statement appeared under the following heading on Pharmacosmos.com:

> 'Pharmacosmos establishes UK subsidiary July 8, 2010'.

Vifor quoted the words 'best-in-class' from the Pharmacosmos public company web site. The quotation was, however, taken out of context as shown below:

> 'We are truly delighted to announce this important step forward for Pharmacosmos. Vitaline Pharmaceuticals has always been our preferred partner in the UK, because we feel a strong, shared aspiration for providing patients and healthcare professionals with best-in-class treatment for iron deficiency,' says the President and CEO of Pharmacosmos.

The wording 'best-in-class' was made in the context of expressing a corporate aim or ambition, rather than a direct or implied description of a product. Consequently, Pharmacosmos believed that there was no breach of the Code. The comment was not specifically aimed at health professionals nor was it used in association with the promotion of Monofer.

Vifor's comments on the Monofer clinical studies referenced in the PAR were irrelevant as its argument was based upon a misinterpretation of the communication.

Pharmacosmos had, however, decided not to refer to this expression and it had changed its web-site communication.

PANEL RULING

The Panel noted that the announcement on Pharmacosmos.com stated that Pharmacosmos and Vitaline had merged. The announcement was dated July 8 ie 7 days after Pharmacosmos and Vitaline had merged to form Pharmacosmos UK. The announcement referred to the new company's business in the UK and to treatment options for patients with iron deficiency anaemia in the UK. It was stated that a key task for Pharmacosmos UK would be the launch of Monofer. The Panel thus considered that although issued by Pharmacosmos in Denmark, the press release was on that company's website and referred to Vitaline being a preferred partner in the UK. It also referred the availability of Monofer in the UK. In that regard, and in accordance with Clause 24.2, the Panel considered that the press release was within the scope of the Code.

The Panel noted that the press release stated that Pharmacosmos and Vitaline shared an aspiration to provide 'best-in-class treatment for iron deficiency anaemia'. The press release later referred to Monofer as a treatment for iron deficiency anaemia. The Panel thus considered that, by inference, many readers would assume that Monofer was a 'best-in-class treatment'. The Panel did not consider that such a claim represented the balance of the evidence and a breach of Clause 7.2 was ruled.

The Panel noted that, although not agreed during inter-company dialogue, Pharmacosmos had decided not to use the phrase 'best-in-class treatment' and it had changed the announcement on its website accordingly.

2 Claim 'A novel treatment of iron deficiency anaemia'

COMPLAINT

Vifor alleged that the SPC which was cited in support of this claim did not substantiate it, in breach of Clause 7.2.

Vifor stated that as noted in the PAR, Monofer was a complex between a polynuclear ferric oxy-hydroxide and a low molecular weight dextran, hydrolized to 1000 Da fragments, called iron isomaltoside 1000 as a colloidal suspension. This being a new formulation, was not a novel treatment in iron deficiency anaemia. Based on the PAR this formulation was approved as a low molecular weight dextran based on the evidence from another dextran ie Cosmofer.

The PAR further stated that the use of iron carbohydrate complexes in the parenteral treatment of iron deficiency states was well established. The currently available parenteral iron preparations were generally considered equally efficacious but varied in molecular size, degradation kinetics, bioavailability, toxicology, and adverse events. Low

molecular weight and high molecular weight iron dextran were commercially available. The iron dextran compounds as well as Monofer were characterized by a strong colloidal complex of a ferric core surrounded by a carbohydrate moiety. Iron release from these compounds was gradual which implied a good toxicological profile, thus allowing it to be administered in high doses as a total dose infusion (TDI). As Monofer was a low molecular weight dextran with 3-5 glucose units, Monofer was expected to have a similar safety profile as outlined in the SPC for Cosmofer.

Vifor submitted that dextran treatment had been around for years and this did not constitute a novel treatment for iron deficiency. Once again with the available clinical evidence as highlighted above this was not a novel treatment for iron deficiency and the claim was thus in breach of Clause 7.2.

RESPONSE

Pharmacosmos stated that the word 'novel' was defined by the Merriam-Webster dictionary as:

> 'new and not resembling something formerly known or used'

Monofer was the first injectable iron that could be administered by rapid infusion in single doses up to 1000-2000mg in one hour and without a test dose (dose not to exceed 20mg/kg bodyweight).

Until now, other iron preparations had much more stringent single dose limitations or required much longer infusion times. Ferinject had a single dose limitation of 1000mg (not exceeding 15mg/kg bodyweight), and Venofer had a single dose limitation of 200mg. Furthermore, Cosmofer which might also be administered in high doses had a test dose requirement and a slow infusion time.

Further although patients could be treated with 1000mg Ferinject in one infusion, the patient had to weigh at least 67kg to receive this dose of Ferinject (because of the 15mg/kg bodyweight limit). According to European weight statistics, 30% of the European population above 18 years of age weighed 50-67kg. The 15mg/kg body weight limit meant that none of these patients could receive 1000mg Ferinject. Using Monofer at a dose of 20mg/kg bodyweight, all patients in excess of 50kg were able to receive doses in excess of 1000mg, if required. Monofer therefore allowed more patients to have their iron deficit corrected in one rapid visit which increased convenience for carers, patients, and hospital throughput.

Therefore, Monofer was a novel iron therapy that offered novel treatment options not previously available.

However, if according to the UK guidelines, the word 'novel' was not allowed to be used within the general criteria of the regulations, Pharmacosmos suggested to change the wording to:

> 'A new product for the treatment of iron deficiency anaemia'.

The arguments against the use of the phrase 'novel treatment' was in Pharmacosmos' opinion neither relevant nor correct.

This also applied to the final argument against the phrase 'novel treatment';

> 'Dextran treatment has been around for years and this did not constitute a novel treatment for iron deficiency'.

Pharmacosmos noted that Vifor's references to the Monofer PAR were incorrect. Namely:

- Monofer was not 'a low molecular weight dextran with 3-5 glucose units', but an iron carbohydrate complex, where iron was complexed with chemically modified isomaltooligosaccharides.
- Accordingly, it was not an iron complex 'with a low molecular weight dextran, hydrolysed to 1000 Da'.
- Monofer was not approved 'as a low molecular weight dextran based on the evidence from another dextran'.
- Monofer was not approved 'based on the evidence from another dextran, namely Cosmofer'. On the contrary, Monofer was approved based on Monofer data and referencing other iron carbohydrate compounds, including Cosmofer.
- Iron isomaltoside 1000 was a correct chemical designation for Monofer approved by EU authorities and the wording 'called iron isomaltoside 1000' was not valid and distorted the approved name iron isomaltoside 1000 by EU/UK Authorities.
- The word 'iron carboxymaltose' had been changed to 'Monofer' in the fourth sentence of the third paragraph of Vifor's complaint. Pharmacosmos noted that iron carboxymaltose was Ferinject.

Pharmacosmos further noted that Vifor had stated that based on the PAR [Monofer] was approved as a low molecular weight dextran based on the evidence from another dextran, namely Cosmofer. This statement was not quoted correctly as the phrase was approved as a low molecular weight dextran' was not in the PAR nor was it scientifically correct.

Pharmacosmos further noted that Vifor had stated that Monofer was a complex between a polynuclear ferric oxy-hydroxide and a low molecular weight dextran, hydrolysed to 1000 Da fragments, called iron isolmaltoside 1000 as a colloidal suspension. This description was incorrect; the carbohydrate

moiety in Monofer was not a complex with 'low molecular weight dextran, hydrolysed to 1000 Da fragments'.

The designation iron isomaltoside 1000 (or oligoisomaltoside 1000) was the correct chemical designation as approved by the EU authorities for iron (III) in complex with chemically modified a isomaltooligosaccharides as stated in the PAR.

By using the wording 'complex between a polynuclear ferric oxy-hydroxide and a low molecular weight dextran, hydrolysed to 1000 Da fragments', Vifor did not quote the PAR correctly, omitting the correct chemical designation for Monofer, ie iron isomaltoside 1000.

PANEL RULING

The Panel noted that injectable iron complexes had been previously available to treat iron deficiency anaemia. In that regard Monofer was not a novel treatment although its formulation had resulted in some practical benefits regarding dosage and administration. The Panel considered that the description of Monofer as 'a novel treatment' did not reflect the data. A breach of Clause 7.2 was ruled.

The Panel noted that, although not agreed during inter-company dialogue, Pharmacosmos had changed the announcement on its website and no longer described Monofer as a novel treatment.

3 Claim 'Possibility of full iron repletion in one, rapid visit for more patients'

COMPLAINT

Vifor alleged that this was a hanging comparison in breach of Clause 7.2 and also the claim was not substantiated.

Of the 583 doses administered in the P-CKD-01 study only 44 were given as total dose infusions (TDIs). Nevertheless, 2 of those 44 doses (average 975.3mg iron; range 462-1800mg iron) in the P-CKD-01 trial had not been one-visit repletions as they had been split into two administrations. So the claim 'the possibility of full iron repletion in one, rapid visit for more patients' was misleading in breach of Clause 7.2.

RESPONSE

Pharmacosmos submitted that Vifor's logic was not valid as it ignored the fact that 40 TDIs in the study were completed as one, rapid visit repletion (2 patient split in 2 TDIs). The term 'one, rapid visit repletion' was accordingly not misleading.

With regard to the phrase 'in more patients' Pharmacosmos submitted that it was a fact that Monofer offered a wider dose range than both Venofer and Ferinject. Furthermore, Monofer offered a reduced administration time, 1 hour compared with 5-7 hours with Cosmofer. Consequently, more patients could be offered the possibility of full iron repletion in one, rapid visit with Monofer.

Pharmacosmos had however, removed the wording 'more patients' from its website to comply with the Code with regard to the use of hanging comparisons.

PANEL RULING

The Panel considered that the claim at issue was a hanging comparison as alleged as it did not state that with which Monofer was being compared. A breach of Clause 7.2 was ruled.

The Panel noted that the claim referred to the possibility of one-visit repletions; it did not state that all patients would only need one visit. The Panel further noted that in the P-CKD-01 study, 38 patients out of 182 who entered the study, received an undivided total dose infusion. The mean infusion time was 58.8 minutes (range 20-90 minutes). The Panel thus did not consider that the reference to the 'possibility' of 'one, rapid visit' was misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that, although not agreed during inter-company dialogue, Pharmacosmos had changed the announcement on its website such that it no longer contained the claim at issue.

B Journal advertisement

COMPLAINT

Vifor submitted that the NATA journal had a significant UK distribution and the advertisement that appeared in June 2010 had not been signed off under the ABPI Code and did not include UK abbreviated prescribing information. This was a breach of Clause 1.1. Vifor also alleged that the advertisement included the following unsubstantiated claims, all of which were in breach of Clause 7.2:

- '4th generation solution'.
- With Monofer … iron treatment had come one step closer to perfection;
- 'The only total dose booster';
- 'provides more patients with the opportunity for rapid one-visit repletion';
- 'minimizes the risk of free iron'
- 'improves convenience for you and your patients'.

RESPONSE

Pharmacosmos did not understand this criticism as Vifor regularly described Ferinject as a 'next generation iron injections' or as a 'third generation iron injection'.

Pharmacosmos therefore suggested that it changed the wording to 'next generation iron injection'.

Pharmacosmos stated that it would stop using the claims 'With Monfer iron treatment has come one step closer to perfection' and 'The only total dose booster'.

The claim 'Provides more patients with the opportunity for rapid one-visit iron repletion' referred to the broader dose range compared with Ferinject and Venofer and the faster speed of infusion compared to Cosmofer. To comply with the Code, Pharmacosmos suggested that it would remove the words 'more patients' to avoid any hanging comparison.

Pharmacosmos stated that the claim 'minimizes the risk of free iron' referred to the SPC statement 'The Monofer formulation contains iron in a strongly bound complex that enables a controlled and slow release of bioavailable iron to iron-binding proteins with little risk of free iron'. If deemed necessary Pharmacosmos could update the claim to 'Strongly bound – with little risk of free iron' which was identical to the text in the SPC.

The claim 'improves convenience for you and your patients' referred to the fact that 'one dose iron repletion' improved convenience for health professionals and patients. Pharmacosmos stated that it would update the claim to: 'One-visit iron repletion improves convenience for both you and your patients' reference to Peebles and Fenwick (2008) and Peebles and Stanley (2004).

PANEL RULING

The Panel noted that the advertisement appeared in June 2010 which predated the merger of Vitaline and Pharmacosmos.

The Panel noted that Pharmacosmos stated that it accepted that the advertisement needed to comply with the UK ABPI Code and all future international advertisements would include a UK abbreviated SPC.

It was possible that the journal might be exempt from the Code due to the supplementary information to Clause 1.1 regarding journals with an international distribution. This had not been submitted by Pharmacosmos and the Panel did not have sufficient information to make a decision that the journal was exempt from the Code.

With regard to the alleged breach of Clause 1.1 in relation to the absence of UK prescribing information, the Panel noted that Clause 4.1 required prescribing information and it noted that Clause 4.2 set out the details required.

Neither the absence of prescribing information nor incorrect prescribing information could be a breach of Clause 1.1. This aspect had been the subject of inter-company dialogue. There could be no breach of Clause 1.1 and the Panel ruled accordingly.

The Director noted that the allegations regarding the wording of the advertisement had not been the subject of inter-company dialogue as required by Paragraph 5.2 of the Constitution and Procedure. This aspect was not considered by the Panel.

C Alleged breach of Clause 2

COMPLAINT

Vifor was concerned about the cavalier approach to the Code and the delayed response and the apparent lack of seriousness with which Pharmacosmos/Vitaline seemed to have handled this matter.

In Vifor's view, this behaviour brought discredit upon, and reduced confidence in, the pharmaceutical industry in breach of Clause 2.

RESPONSE

Pharmacosmos did not comment on this point.

PANEL RULING

The Panel noted that its comments and rulings above. The Panel considered that although breaches of the Code had been ruled, the matters overall were not such as to warrant a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure. No breach of Clause 2 was ruled.

Complaint received **17 August 2010**

Case completed **1 November 2010**

LILLY v ROCHE

Promotion of Tarceva

Lilly complained about the promotion of Tarceva (erlotinib) by Roche. The items at issue were a leavepiece, an advertisement in Oncology Times and a sponsored feature in Oncology News. Tarceva was indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with stable disease after 4 cycles of standard platinum-based first-line chemotherapy. It was also indicated for treatment in locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Lilly supplied Alimta (pemetrexed).

Lilly stated that the items at issue all claimed that Tarceva was licensed for use as 'first-line maintenance' therapy in advanced NCSLC. Lilly had further complained to Roche that the front of the leavepiece stated that Tarceva was 'now licensed for first-line maintenance in patients with stable disease', without clarifying that the specific indication was for the treatment of advanced NSCLC.

The treatment algorithm for patients with advanced lung cancer was complex. Lilly explained that first-line and maintenance treatment of locally advanced or metastatic NSCLC were two distinct and specific indications; first-line being the indication of induction treatment, usually with platinum-based combination chemotherapy, followed by maintenance treatment which was the initiation of treatment in patients whose disease had not progressed immediately following first-line therapy. The majority of the patients were treated with first-line treatment options and observed until disease progression became evident, at which stage licensed second-line treatment options could be considered. Until recently, no medicine was specifically licensed for the maintenance setting. The first product licences for maintenance treatment were granted for Alimta in 2009 and Tarceva in 2010. Alimta was indicated as monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease had not progressed immediately following platinum-based chemotherapy. First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.

Currently, licensed medicines were available for first-line, second-line or maintenance. Patients whose disease had progressed after first-line or maintenance therapy were eligible for second-line treatment. Roche had argued that 'first-line maintenance' was used to distinguish from second-line maintenance. However, a licence for second-line maintenance *per se* did not exist.

Given the multiple treatment variations, possible treatment algorithms and the inherent potential for confusion, the Tarceva and Alimta indications, as defined by the European regulators, were very specifically worded. Lilly alleged that the claim 'first-line maintenance' was ambiguous, misleading and not consistent with the Tarceva SPC.

In the absence of a clear statement on the front of the leavepiece of the intended therapeutic use, Lilly believed that physicians might believe that Tarceva could be used in unlicensed NCSLC settings (eg stage IIIA patients) or indeed in any other cancer. Lilly alleged that such omission amounted to misleading promotion outside the licensed indication in breach of the Code.

The Director noted that the leavepiece had been withdrawn by Roche during inter-company dialogue. Inter-company dialogue had been partially successful. The new leavepiece however, still included the claims cited by Lilly above and so these were referred to the Panel.

The detailed response from Roche is given below.

The Panel noted that the Alimta SPC referred to its use as first-line treatment, maintenance treatment following first-line chemotherapy and second-line treatment in NSCLC. Tarceva was indicated for maintenance treatment following first-line chemotherapy and for treatment following the failure of at least one prior chemotherapy regimen. The Panel noted that the Tarceva leavepiece included the claims 'Now licensed for first-line maintenance in patients with stable disease' and 'Tarceva now approved as first-line maintenance'. There were other references to 'first-line maintenance'. 'First-line maintenance' was not used in the Tarceva SPC. This appeared to be a term used by Roche to describe Tarceva's use in stable disease following platinum doublet chemotherapy. In the Panel's view, the use of the term 'first-line maintenance' therapy was ambiguous; it implied that there might be a product for second-line maintenance or that Tarceva should be used for maintenance therapy before any other therapies also licensed for maintenance. Neither was so. The Panel noted Roche's submission that 'first-line maintenance' was cited in the medical literature. Nonetheless the promotion of a medicine must not be inconsistent with the particulars listed in its SPC. The Tarceva SPC did not refer to 'first-line maintenance'. In that regard the Panel considered that the use of 'first-line maintenance' was misleading and inconsistent with the Tarceva SPC.

The product had not been licensed or approved as 'first-line maintenance' as stated. Reference to the product licence in this regard appeared to validate Roche's description. Breaches of the Code were ruled. This ruling was appealed by Roche.

The Panel considered that the absence of the licensed therapeutic use on the front page of the new leavepiece was not in itself misleading. The front of the leavepiece did not mention any type or stage of cancer. In this regard it was not inconsistent with the SPC and no breach of the Code was ruled.

The Panel noted that the advertisement was headed 'A lifeline after first-line chemotherapy in advanced NSCLC' followed by a photograph of the palm of a hand beneath which was the claim 'Now licensed for first-line maintenance in patients with stable disease*'. The explanation for the asterisk appeared in smaller typesize immediately beneath the claim 'Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of platinum based first-line chemotherapy'. The Panel noted that it was a principle under the Code that claims should be capable of standing alone without relying on footnotes to provide further explanation.

The Panel considered that the claim in the advertisement 'Now licensed for first-line maintenance in patients with stable disease' was in breach of the Code for similar reasons to the leavepiece. This ruling was appealed by Roche.

The Panel noted that each page of the four page article 'First-line maintenance (1LM) treatment: a new strategy to treat advanced NSCLC' was headed, in a small font size, 'Sponsored Feature'. The author was a consultant medical oncologist. At the foot of the first page was a statement that the article was commissioned by Roche Products Ltd, that medical writing support was provided by Darwin Healthcare Communications, paid for by Roche and that the views expressed were those of the author. At the foot of pages 2-4 of the article was the highlighted statement 'This article is supported by Roche Products Ltd'.

The Panel noted that Roche had not commented on whether or not the sponsored feature was promotional material. The approval certificate stated that the signatories considered it was not promotional and was in accordance with, *inter alia*, the Code.

The Panel noted that whether a company was responsible for sponsored material depended on a number of factors including whether the material was initiated by a third party, although that in itself did not automatically absolve the company from responsibility under the Code for its content. It had previously been decided in relation to material aimed at health professionals that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable it if 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 content, 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 the ZINC job summary indicated that Roche had been asked to sponsor a topical article in the Oncology News and that it approached the author and asked him to write an article about first-line maintenance. It was stated that the author retained full editorial control. The objective was to inform readers of the rational and clinical data behind first-line maintenance treatment in NSCLC. In the 'Notes' section it was stated that there were plans to get reprints of the article for the HSSs to provide to customers.

The Panel thus considered that there was no arms length arrangements between Roche and the other parties. Roche was inextricably linked to the content of the article. Although the author had retained editorial control, he had been chosen by Roche and the company had defined the scope of the article. The article referred to erlotinib and bevacizumab (Roche's product Avastin). In the Panel's view, Roche's failure to recognise that the article constituted promotional material showed a lack of understanding of the requirements of the Code.

The Panel referred to its comments above in relation to the leavepiece and noted that the article stated that erlotinib could be used for 'first-line maintenance' treatment when such an indication was not referred to in the SPC. A breach of the Code was ruled. This ruling was appealed by Roche.
The Appeal Board noted that the Code required that a medicine must be promoted in accordance with the terms of its marketing authorization and that promotion must not be inconsistent with the particulars listed in the medicine's SPC. The Appeal Board further noted that the Code did not require claims to use identical wording to that found in the SPC. In the Appeal Board's view one of the effects of the Code was to protect patient safety and to stop a patient receiving a medicine when it was inappropriate for them to do so.

The Appeal Board noted that Tarveva materials were targeted at physicians experienced in the use of anti-cancer therapies. In the Appeal Board's view, experienced oncologists would not be misled as to Tarceva's position in the management of NSCLC. The Appeal Board did not consider that, to an oncologist, 'first-line maintenance' might imply 'first-line treatment' or that 'first-line' in this context implied the preferred choice. The materials at issue all referred to the use of Tarceva after first-line chemotherapy.

The Appeal Board did not consider that claims in the leavepiece regarding 'first-line maintenance' were either misleading or inconsistent with the particulars listed in the Tarceva SPC as alleged. In the Appeal Board's view, having read the leavepiece, experienced oncologists would be in no doubt which patients should receive Tarceva. The Appeal Board ruled no breach of the Code. The Appeal Board considered its comments and rulings similarly applied to the advertisement and the sponsored feature. The appeal on all points was thus successful.

Eli Lilly and Company Limited complained about the promotion of Tarceva (erlotinib) by Roche Products Limited. The items at issue were a leavepiece (ref TARC00522), an advertisement in Oncology Times (ref TARC00568a) and a sponsored feature in Oncology News (ref TARC00592). Inter-company dialogue had failed to resolve the matter.

Tarceva was indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with stable disease after 4 cycles of standard platinum-based first-line chemotherapy. It was also indicated for treatment in locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

Lilly supplied Alimta (pemetrexed).

COMPLAINT

Lilly stated that the items at issue all claimed that Tarceva was licensed for use as 'first-line maintenance' therapy in advanced NCSLC.

Lilly's initial email to Roche related to the use of 'first-line maintenance' in all three promotional items for erlotinib. Lilly also pointed out to Roche that when the flaps of the leavepiece were unfolded, the first part of the claim 'Tarceva as first-line' separated from the second part, 'maintenance therapy'.

Lilly further complained to Roche about the absence of the intended therapeutic use of Tarceva on the front of the leavepiece. This item stated that Tarceva was 'now licensed for first-line maintenance in patients with stable disease', without clarifying that the specific indication was for the treatment of advanced NSCLC.

The summary of product characteristics (SPC) for Tarceva stated that: 'Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with stable disease after 4 cycles of standard platinum-based first-line chemotherapy'.

The treatment algorithm for patients with advanced lung cancer was complex. Lilly explained that first-line and maintenance treatment of locally advanced or metastatic NSCLC were two very distinct and specific indications; first-line being the indication of induction treatment, usually with licensed platinum-based combination chemotherapy, followed by maintenance treatment which was the initiation of treatment in patients whose disease had not progressed immediately following first-line therapy. The majority of the patients in routine clinical practice were treated with first-line treatment options and observed until disease progression became evident, at which stage licensed second-line treatment options could be considered. Until recently, no medicine was specifically licensed for the maintenance setting. The first product licences for maintenance treatment were granted for Alimta in 2009 and Tarceva in 2010. Alimta was indicated as monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease had not progressed immediately following platinum-based chemotherapy. First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.

Currently, licensed medicines were available for first-line, second-line or maintenance indications. Patients whose disease had progressed after first-line or maintenance therapy were eligible for second-line treatment. Roche had argued that 'first-line maintenance' was used to distinguish from second-line maintenance. However, a licence for second-line maintenance *per se* did not exist.

Given the multiple treatment variations, possible treatment algorithms and the inherent potential for confusion, the wording of the Tarceva and Alimta indications, as defined by the European regulators, were very specific. Lilly alleged that the claim for 'first-line maintenance' was not consistent with the Tarceva SPC, created ambiguity in the mind of the prescriber and misled.

Roche had agreed in inter-company correspondence that in the leavepiece the separation of the first part of the claim 'Tarceva as first-line' from the second part, 'maintenance therapy,' might confuse and mislead physicians. In that regard Roche had therefore withdrawn and amended the leavepiece accordingly. Roche had however, not amended its use of 'first-line maintenance' to describe the licensed indication for Tarceva. Lilly nevertheless believed that the use of 'first-line maintenance' when referring to the indication for Tarceva, was misleading and inconsistent with the particulars listed in its SPC, as it implied that Tarceva was licensed for use in first-line initial treatment, rather than for maintenance treatment in patients who had already received first-line treatment with another chemotherapy. Lilly believed that given the prominence of the 'first-line maintenance' claims readers would be misled as to the licensed indication. Lilly therefore alleged that 'first-line maintenance' was in breach of Clauses 3.2 and 7.2.

Additionally, in response to Lilly's concern regarding the lack of information about the intended therapeutic use on the front of the leavepiece, Roche

had also stated that it would not make any changes. In the absence of a clear statement of the intended therapeutic use, Lilly believed that physicians might believe that Tarceva could be used in unlicensed NCSLC settings (eg stage IIIA patients) or indeed in any other cancer. Lilly therefore considered that such omissions amounted to promotion which was misleading and outside the licensed indication in breach of Clauses 3.2 and 7.2.

Whilst Lilly agreed that differences of opinion could exist in a clinical and academic setting to define what constituted first-line and maintenance indications, these arguments were not valid in a promotional setting. Promotional claims needed to be consistent with the SPC. The SPC did not refer to 'first-line maintenance' while defining the indication for Tarceva. Lilly alleged that the promotional use of 'first-line maintenance' over-shadowed other explanations and over-interpreted the SPC definition.

Lilly had suggested that alternative terminology such as 'maintenance after first-line treatment' instead of 'first-line maintenance' might be acceptable, but Roche wished to continue to use the latter.

RESPONSE

Roche explained that the standard treatment for inoperable NSCLC was systemic therapy, most commonly with cytotoxic medicines (chemotherapy). Chemotherapy was usually given in courses of several cycles followed by a period off treatment for patients who had benefited. The terms 'first-line maintenance', 'second-line' treatment etc were generally used to describe successive courses with second-line treatment only given after disease progression. For example, in the UK, as elsewhere the standard first-line chemotherapy was 4 cycles of chemotherapy with a two medicine regime including a platinum-containing medicine ('platinum doublet chemotherapy').

Recently there had been interest in providing ongoing treatment to patients who had benefited from first-line chemotherapy. Alimta and Tarceva were indicated for such use.

The Tarceva SPC stated that 'Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy'. Roche had used 'first-line maintenance' to describe this indication which it believed was consistent with the SPC and precisely and concisely defined the use of Tarceva in its licensed indication – to maintain the benefits achieved after successful first-line chemotherapy.

However Lilly appeared to believe that 'first-line maintenance' was misleading and implied that Tarceva could be used as a substitute for first-line chemotherapy. This was clearly not so, as without a first-line treatment that stabilized disease, there could be no benefit to maintain.

In Roche's initial response to Lilly, Roche agreed that the chemotherapy given before maintenance 'first-line', (sometimes referred to as 'induction') and 'maintenance' were distinct indications. However, Roche did not agree that 'first-line maintenance' implied use as an initial first-line therapy. Roche believed that 'first-line treatment' and 'first-line maintenance' clearly and unambiguously described different licensed indications and were not misleading or confusing. Indeed, Roche believed that 'first-line maintenance' was less ambiguous then the unqualified term 'maintenance'. It allayed confusion about the appropriate positioning of Tarceva (which was specifically approved as a maintenance treatment after first-line but not after second-line or subsequent chemotherapies) whilst remaining consistent with the marketing authorization and SPC.

Furthermore, Roche noted that the SPC stated 'Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy' where the maintenance setting was prior to progression of disease and the institution of second-line treatment (this had also been acknowledged by Lilly in its complaint), thus rendering it as treatment in the first-line setting. As such, Roche believed that 'first-line maintenance' was wholly consistent with the marketing authorization and SPC, and therefore not in breach of Clause 3.2 and 7.2.

Roche noted that 'first-line maintenance' was commonly used in clinical practice not only in NSCLC (Patel *et al* 2009) but also in other tumour settings such as breast cancer, haematological malignancies, and had been cited quite often in the medical literature including that produced by Lilly for pemetrexed which was also licensed in the maintenance setting for the treatment of NSCLC.

The Tarceva SPC clearly stated that 'Tarceva treatment should be supervised by a physician experienced in the use of anti-cancer therapies'. Roche was confident that physicians experienced in the management of NSCLC would not confuse first-line maintenance with first-line treatment.

Subsequent to this initial dialogue, Lilly suggested alternative wording 'maintenance therapy after first-line treatment' which it considered was 'less ambiguous' than 'first-line maintenance'. Roche deemed both of these terms acceptable in defining the appropriate positioning of Tarceva as first-line maintenance therapy in NSCLC. However, Roche believed that the preferred terminology of 'first-line maintenance' was more specific since it described maintenance treatment given before first progression whereas 'maintenance therapy after first-line treatment' was less specific and could cover the institution of maintenance therapy following any

line of treatment including after second and subsequent lines of chemotherapy where it was unlicensed.

Roche noted Lilly's concern about the separation of the first part of the claim 'Tarceva as first-line' from the latter part 'maintenance therapy' when the leavepiece was unfolded. In response to this Roche had submitted that this could, unintentionally introduce ambiguity and had agreed to withdraw and amend the leavepiece to ensure that this separation did not occur. Withdrawal had taken place and the amended leavepiece was provided.

Lilly had also complained during inter-company dialogue that the claim on the front of the leavepiece 'Now licensed for first-line maintenance in patients with stable disease' did not clearly describe the intended therapeutic use of Tarceva. Although this issue was only raised in the final letter to Roche, and as such had not been adequately discussed through inter-company dialogue, Roche was happy to have this resolved as part of this complaint.

Roche believed that when reviewed in its entirety, the positioning of Tarceva in advanced NSCLC as first-line maintenance therapy following first-line chemotherapy in patients with stable disease was made quite explicit in several places in the leavepiece including; the first tag line before the leavepiece was unfolded, the design of the SATURN trial and the exact wording of the licensed indication, the title of the overall survival Kaplan Meier curve, and the clear diagrammatic depiction of the place of Tarceva in the treatment pathway for patients with advanced NSCLC which thus left little room for misinterpretation. In addition, it was clearly stated on the front of the leavepiece where the prescribing information could be found detailing the licensed indication for Tarceva in accordance with the SPC and marketing authorization. As such, Roche denied a breach of Clauses 3.2 and 7.2.

Roche noted that it had not intended to promote Tarceva as upfront 'first-line' therapy in advanced NSCLC and therefore great care had been taken in the generation of claims and materials relating to the licensed indications for Tarceva.

1 Leavepiece

PANEL RULING

The Director noted that the leavepiece (ref TARC00522) had been withdrawn by Roche during inter-company dialogue as Roche had agreed with Lilly's concern that it could unintentionally introduce ambiguity. Inter-company dialogue had been partially successful, as acknowledged by Lilly, and so that aspect of the complaint was not referred to the Panel. The new leavepiece (TARC00601) however, still included some of the claims at issue in the original leavepiece. Inter-company dialogue had not been successful in relation to all the claims and as they were still being used the outstanding matters in relation to the new leavepiece were referred to the Panel.

The Panel noted that the Alimta SPC referred to its use as first-line treatment, maintenance treatment following first-line chemotherapy and second-line treatment in NSCLC. Tarceva was indicated for maintenance treatment following first-line chemotherapy and for treatment following the failure of at least one prior chemotherapy regimen. The Panel noted that the Tarceva leavepiece included the claims 'Now licensed for first-line maintenance in patients with stable disease' and 'Tarceva now approved as first-line maintenance'. There were other references to 'first-line maintenance'. 'First-line maintenance' was not used in the Tarceva SPC. This appeared to be a term used by Roche to describe Tarceva's use in stable disease following platinum doublet chemotherapy. In the Panel's view, the use of the term 'first-line maintenance' therapy was ambiguous; it implied that there might be a product for second-line maintenance or that Tarceva should be used for maintenance therapy before any other therapies also licensed for maintenance. Neither was so. The Panel noted Roche's submission that 'first-line maintenance' was cited in the medical literature. Nonetheless the promotion of a medicine must not be inconsistent with the particulars listed in its SPC. The Tarceva SPC did not refer to 'first-line maintenance'. In that regard the Panel considered that the use of 'first-line maintenance' was misleading and inconsistent with the Tarceva SPC. The product had not been licensed or approved as 'first-line maintenance' as stated. Reference to the product licence in this regard appeared to validate Roche's description. Breaches of Clauses 3.2 and 7.2 were ruled.

The Panel considered that the absence of the licensed therapeutic use on the front page of the new leavepiece was not in itself misleading. The front of the leavepiece did not mention any type or stage of cancer. In this regard it was not inconsistent with the SPC and no breach of Clauses 3.2 and 7.2 was ruled.

2 Advertisement

PANEL RULING

The Panel noted that the advertisement was headed 'A lifeline after first-line chemotherapy in advanced NSCLC' followed by a photograph of the palm of a hand beneath which was the claim 'Now licensed for first-line maintenance in patients with stable disease*'. The explanation for the asterisk appeared in smaller typesize immediately beneath the claim 'Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of platinum based first-line chemotherapy'. The Panel noted that it was a principle under the Code that claims should be capable of standing alone without relying on footnotes to provide further explanation.

The Panel considered that the claim in the advertisement 'Now licensed for first-line maintenance in patients with stable disease' was in breach of Clauses 3.2 and 7.2 for similar reasons to the leavepiece.

3 Sponsored feature

PANEL RULING

The Panel noted that each page of the four page article 'First-line maintenance (1LM) treatment: a new strategy to treat advanced NSCLC' was headed, in a small font size, 'Sponsored Feature'. The author was a consultant medical oncologist. At the foot of the first page was a statement that the article was commissioned by Roche Products Ltd, that medical writing support was provided by Darwin Healthcare Communications, paid for by Roche and that the views expressed were those of the author. At the foot of pages 2-4 of the article was the highlighted statement 'This article is supported by Roche Products Ltd'.

The Panel noted that Roche had not commented on whether or not the sponsored feature was promotional material. The approval certificate stated that the signatories considered it was not promotional and was in accordance with, *inter alia*, the Code.

The Panel noted that whether a company was responsible for sponsored material depended on a number of factors including whether the material was initiated by a third party, although that in itself did not automatically absolve the company from responsibility under the Code for its content. It had previously been decided in relation to material aimed at health professionals that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable it if 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 content, 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 the ZINC job summary stated in the 'Background/Objective' section that Roche had been asked to sponsor a topical article in the Oncology News and that it approached the author and asked him to write an article about first-line maintenance. It was stated that the author retained full editorial control. The objective was to inform readers of the rational and clinical data behind first-line maintenance treatment in NSCLC. In the 'Notes' section it was stated that there were plans to get reprints of the article for the HSSs to provide to customers.

The Panel thus considered that there was no arms length arrangements between Roche and the other parties. Roche was inextricably linked to the content of the article. Although the author had retained editorial control, he had been chosen by Roche and the company had defined the scope of the article. The article referred to erlotinib and bevacizumab (Roche's product Avastin). In the Panel's view, Roche's failure to recognise that the article constituted promotional material showed a lack of understanding of the requirements of the Code.

The Panel referred to its comments above in relation to the leavepiece and noted that the article stated that erlotinib could be used for 'first-line maintenance' treatment when such an indication was not referred to in the SPC. A breach of Clauses 3.2 and 7.2 was ruled.

APPEAL FROM ROCHE

Roche re-iterated that standard treatment for inoperable NSCLC was systemic therapy, most commonly with cytotoxic medicines (chemotherapy). Chemotherapy was usually given in courses of several cycles followed by a period off treatment for patients who had benefitted. The terms 'first-line treatment', 'second-line treatment' etc were generally used to describe successive courses with second line treatment only given after disease progression. For example, in the UK, as elsewhere the standard first-line chemotherapy for treating NSCLC was 4 cycles of chemotherapy with a two medicine regimen including a platinum-containing medicine ('platinum doublet chemotherapy').

Roche submitted that the division of systemic treatment in first-line, second-line etc, with each new line introduced after disease progression was a well established concept within oncology, it was not terminology coined by Roche and could be found in many SPCs eg pemetrexed, bevacizumab, capecitabine, navelbine and irinotecan. It was well understood by those at whom Tarceva promotional materials were directed ie physicians experienced in the use of anti-cancer therapies. Recently there had been interest in providing immediate ongoing treatment to patients who had benefitted from first-line chemotherapy in order to sustain its benefit, namely 'maintenance therapy', and two medicines were licensed in this situation – Alimta (pemetrexed; Lilly) and Tarceva (erlotinib; Roche). As maintenance therapy was instituted before disease progression (which conventionally defined the need for second-line therapy) immediately following first line chemotherapy it could be considered as a treatment in the first-line setting. Maintenance therapy, by its very nature, could not exist in isolation and was part of a package with the induction chemotherapy that produced the benefit which it was used to maintain.

To clarify NSCLC medicine treatment Roche provided a treatment algorithm which showed the progression from first line to second line.

1 Leavepiece

Roche noted that the Panel had decided that the use of 'first-line maintenance' was ambiguous and that it implied that there might be a product for second-line maintenance or that Tarceva should be used for maintenance therapy before any other therapies licensed for maintenance, in turn it ruled that the use of the term 'first-line maintenance' was in breach of Clauses 3.2 and 7.2 of the Code.

Roche highlighted that, in contrast, Lilly had alleged that 'first-line maintenance' implied that Tarceva was licensed for use in first-line initial treatment.

Roche disagreed on both accounts; it believed that 'first-line maintenance' unambiguously described the appropriate positioning of Tarceva within the treatment pathway for NSCLC ie to maintain the benefit of the first-line chemotherapy to which it was inextricably linked. In this context, it must be remembered that those involved in this area already understood the term first-line chemotherapy. Not to qualify the term 'maintenance' was genuinely ambiguous and gave no indication as to where within the treatment pathway it should be used. The unqualified term would imply that it could be used as maintenance after any line of chemotherapy, which was inconsistent with its marketing authorization

Roche disagreed with the Panel's view that the use of 'first-line maintenance' was problematic because it implied that there might be a product for second-line maintenance. Not only was there no rationale for considering that the licence for one product would influence clinicians' beliefs about where another product was licensed, but Roche understood this complaint was about whether clinicians were clear about Tarceva's licence, not those of other products. Roche submitted that the potential to confuse and mislead health professionals to prescribe Tarceva as 'second-line maintenance' treatment (where it was clearly not licensed) was eliminated by the use of the term 'first-line maintenance' whilst remaining wholly consistent with Tarceva's licensed indication.

Roche also disagreed with the Panel's view in that the use of 'first-line maintenance' implied that Tarceva should be used for maintenance therapy before any other therapies licensed for maintenance. Roche assumed that the Panel formed this view because it considered that 'first-line' was synonymous with 'first-choice' and implied a claim of superiority or priority over other products. As already explained, 'first-line' was used to define systemic treatment administered for NSCLC prior to first disease progression and was well understood by both the regulatory authorities who had endorsed its use in the Tarceva marketing authorization and by clinicians working in the area. It would be perverse to believe that the latter might interpret 'first-line' in the way that Panel appeared to have done.

In relation to Lilly's assertion that 'first-line maintenance' implied that Tarceva was licensed for use in first-line initial treatment, Roche had already asserted that 'first-line' and 'first-line maintenance' were distinct indications and that 'first-line maintenance' was less ambiguous than the unqualified use of 'maintenance'. Furthermore, 'first-line maintenance' inherently implied that 'first-line' treatment had already been instituted for which the benefit achieved could be maintained by the institution of 'first-line maintenance' treatment ie without a first-line treatment that successfully stabilised disease, there could be no benefit to maintain. This was made quite explicit within the leavepiece where several references had been made for the use of Tarceva as 'first-line maintenance treatment in patients with stable disease' which further emphasized Tarceva's place as 'first-line maintenance' therapy in patients who had achieved stable disease following their 'first-line' treatment in concordance with Tarceva's SPC and marketing authorization.

Roche agreed with the Panel that the promotion of a medicine should not be inconsistent with the particulars listed in its SPC and maintained that 'first-line maintenance' was not inconsistent with Tarceva's licensed indication and particulars of its SPC. As explained above, Roche submitted that as maintenance therapy was instituted before disease progression immediately following first-line chemotherapy, it was a treatment therapy in the first-line setting and thus the use of the term 'first-line maintenance' remained consistent with the particulars of the Tarceva SPC. Roche had noted that whilst the claims 'first-line maintenance in patients with stable disease' or 'Tarceva now approved as first-line maintenance' were not verbatim representations of the particulars listed in the SPC ('Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy') they were not inconsistent with the licensed indication as required by the Code. Roche also highlighted that the Code did not require verbatim duplication of the particulars of SPCs to be part of all claims within promotional material for a medicine, but more importantly that all claims should not be inconsistent with the licensed indication and SPC.

The Panel had also noted that Tarceva had not been licensed for 'first-line maintenance' implying that 'first-line maintenance' and 'maintenance' treatment were distinct indications. Roche disagreed with this viewpoint and regarded 'first-line maintenance' as maintenance treatment delivered after successful first-line induction chemotherapy.

Furthermore, Roche submitted that 'first-line maintenance' was widely used and understood by those cancer specialists who might prescribe Tarceva. To support this Roche provided extensive references to illustrate that 'maintenance' and 'first-line maintenance' were used interchangeably to describe the same treatment setting and noted that

one of the references was authored by representatives of Lilly which further validated Roche's assertion that 'first-line maintenance' and 'maintenance' were regarded as the same indication. Roche understood that 'first-line treatment' and 'first-line maintenance treatment' were distinct indications and noted that the wording used within all claims for Tarceva in the maintenance setting ensured full use of 'first-line maintenance' without separation to ensure that health professionals were neither misled nor confused as to the positioning of Tarceva for treating NSCLC.

Since Tarceva had been launched in the maintenance setting Roche had not received any queries regarding the term 'first-line maintenance' and did not believe that confusion existed for clinicians who could prescribe.

For the reasons cited above, Roche submitted that the use of 'first-line maintenance' in the promotional material was wholly consistent with the marketing authorization and SPC, and therefore not in breach of Clauses 3.2 and 7.2.

2 Advertisement

Roche noted that the Panel had considered that the claim 'Now licensed for first-line maintenance in patients with stable disease' was a breach of Clauses 3.2 and 7.2. Roche appealed this ruling for the reasons highlighted above and maintained that 'first-line maintenance' was consistent with Tarceva's licensed indication and particulars of its SPC.

3 Sponsored feature

Roche noted that the Panel had considered that the claim that Tarceva could be used for 'first-line maintenance' was a breach of Clauses 3.2 and 7.2. Roche appealed this ruling for the reasons highlighted above and maintained that 'first-line maintenance' was consistent with Tarceva's licensed indication and particulars of its SPC.

RESPONSE FROM LILLY

Lilly considered that the claim 'first-line maintenance' was not consistent with the Tarceva SPC, was ambiguous, misleading and likely to confuse the reader.

Lilly noted that Roche had produced a flowchart for a possible treatment algorithm for advanced NSCLC. Lilly alleged that in relation to the pemetrexed and erlotinib maintenance licence, first-line induction therapy did not include or encompass maintenance as proposed by Roche in its flowchart. This was an important distinction in the maintenance licence for both medicines; maintenance was stated in the SPCs for both medicines as treatment after first-line therapy in patients who, in the case of pemetrexed achieved a clinical response (complete or partial response or stable disease), or in the case of erlotinib, achieved stable disease. Lilly also noted that both the pemetrexed and erlotinib licenses for maintenance therapy were restricted to patients who had not received those respective medicines as first-line treatment, and therefore it was important to maintain the distinction, as set out in the SPCs, between maintenance and first-line induction therapy, to avoid any confusion that the same medicine could be used from induction through to disease progression.

Lilly noted that Roche had submitted that 'maintenance', as it stood in the licence, required further qualification and inappropriately sought to qualify its precise meaning. The latter was a matter for Roche to take up with the relevant regulatory authorities. The final wording, and the meaning of statements incorporated in the erlotinib SPC were agreed between Roche and the European Medicines Agency, accordingly no further clarification was required. Lilly stated that 'second-line maintenance' had no meaning – if the patient's disease progressed they received some other line of treatment and not maintenance treatment. One of Roche's original arguments for use of the phrase 'first-line maintenance' - that it avoided possible confusion with use in second-line maintenance - was unjustifiable as no licence for second-line maintenance existed.

Further, as acknowledged by Roche, erlotinib was licensed solely for maintenance therapy in patients who had stable disease following first-line therapy with doublet chemotherapy. Therefore a claim of 'first-line maintenance' was inherently confusing even on the basis of Roche's own submission given that erlotinib was not licensed for maintenance treatment in patients who had achieved a complete or partial response following first-line treatment.

Lilly submitted that the Panel's observation that 'first-line maintenance' might imply that erlotinib should be used as a first choice maintenance treatment added further weight to the argument that confusion was likely to arise through use of the phrase.

Lilly noted that it had never suggested to Roche that the Code mandated verbatim use of SPC language. Roche seemed to imply that the only alternative to using 'first-line maintenance' was a verbatim use of SPC language. This was clearly not so, as indicated in inter-company correspondence. Lilly's position had consistently been that Roche should ensure that promotional claims for erlotinib were not inconsistent with the marketing authorization (as per Clause 3.2). Indeed, Lilly had previously suggested to Roche that it could employ the claim 'maintenance treatment after first-line chemotherapy'. Further, as maintenance therapy in advanced NSCLC was a newly approved indication, clarity and consistency of promotional claims with a medicine's SPC was even more important.

Lilly alleged that Roche's reliance on selective publications and clinical opinions was not objective or fair and further misled regarding the correct

interpretation of the licenced indication of erlotinib as stated in its SPC. Roche had used the claim in question to over interpret the SPC for commercial expediency.

APPEAL BOARD RULING

The Appeal Board noted that Clause 3.2 required that a medicine must be promoted in accordance with the terms of its marketing authorization and that promotion must not be inconsistent with the particulars listed in the medicine's SPC. The Appeal Board further noted that the clause did not require claims to use identical wording to that found in the SPC. In the Appeal Board's view one of the effects of Clause 3.2 was to protect patient safety and to stop a patient receiving a medicine when it was inappropriate for them to do so.

The Appeal Board noted that the target audience for the Tarceva promotional material was physicians experienced in the use of anti-cancer therapies. In the Appeal Board's view, experienced oncologists would not be misled as to Tarceva's position in the management of NSCLC. The Appeal Board did not consider that, to an oncologist, 'first-line maintenance' might imply 'first-line treatment' or that 'first-line' in this context implied the preferred choice. The materials at issue all referred to the use of Tarceva after first-line chemotherapy.

The Appeal Board did not consider that claims in the leavepiece regarding 'first-line maintenance' were either misleading or inconsistent with the particulars listed in the Tarceva SPC as alleged. In the Appeal Board's view, having read the leavepiece, experienced oncologists would be in no doubt which patients should receive Tarceva. The Appeal Board ruled no breach of Clauses 3.2 and 7.2. The appeal on this point was successful.

The Appeal Board noted its comments above in relation to the leavepiece and considered that they also applied to the advertisement. The Appeal Board ruled no breach of Clauses 3.2 and 7.2. The appeal on this point was successful.

The Appeal Board similarly considered that the sponsored feature was neither misleading nor inconsistent with the particulars listed in the Tarceva SPC as alleged. No breach of Clauses 3.2 and 7.2 were ruled. The appeal on this point was successful.

Complaint received **19 August 2010**

Case completed **10 November 2010**

CASE AUTH/2355/9/10

MEMBER OF THE PUBLIC v TAKEDA

Promotion of Mepact

The Authority received a complaint that visitors to Takeda's website were greeted by a news story that Mepact (mifamurtide) had not been approved by the National Institute for health and Clinical Excellence (NICE). The complainant alleged that the story, which did not sit behind a heath professional website, actively promoted Mepact in breach of the Code.

The detailed response from Takeda is given below.

Although the Panel considered that it was unclear whether the complaint was only about the statement on the home page of the website or if it also encompassed the press release to which it was linked, given that the two could not reasonably be separated both were considered together.

The Panel noted that the major portion of the home page of the Takeda UK website was comprised of a central section headed 'What's New'. Listed below the heading was a series of dates and below each was a brief description of a notable event or company achievement. Under 'August 2010' the following appeared:

> **'NICE says no to life saving treatment for childhood bone cancer.**
>
> **Takeda announces that in its draft appraisal [NICE] does not recommend the use of Mepact for the treatment of bone cancer (osteosarcoma) in children, adolescents and young adults'.**

By clicking onto the date the reader was taken to the full press release which was in the 'Media Centre' section of the website. Given the way in which it could be accessed however, the Panel queried whether the press release was in fact a public announcement.

The Panel considered that the announcement on the home page, which was the same as the title of the press release, 'NICE says no to life saving treatment for childhood bone cancer', was in effect a very strong claim for Mepact. The Panel queried whether such a claim was factual and presented in a balanced way. In addition the announcement on the home page raised unfounded hopes of successful treatment and would, on the balance of probabilities, encourage members of the public to read the whole of the press release. The press release began with some very positive bullet points for Mepact which referred, *inter alia*, to 'improve survival in childhood cancer', 'reduces the risk of death by almost one third' and 'save an additional eight lives each year'. It also stated that Takeda wanted to ensure that suitable young patients diagnosed with osteosarcoma were 'provided with a fighting chance …'. In the Panel's view the announcement on the home page and the press release itself would encourage members of the public to ask their health professional to prescribe Mepact, a prescription only medicine. A breach of the Code was ruled which was upheld on appeal by Takeda. The Panel further considered that as the short description of the press release on the homepage of the Takeda website and the press release itself both contained very strong claims that were contrary to the Code they were in effect advertisements for Mepact aimed at, *inter alia*, the public; a breach of the Code was ruled which was upheld on appeal by Takeda.

The Panel considered that to describe Mepact as a 'life saving treatment' meant that high standards had not been maintained. A breach of the Code was ruled which was upheld on appeal by Takeda.

The Panel also ruled a breach of Clause 2 of the Code because it considered that it was particularly important that information made available to the public about such a sensitive issue as survival in childhood cancer was fair and balanced and did not raise unfounded hopes of successful treatment.

Upon appeal by Takeda the Appeal Board noted that although it had upheld the Panel's other rulings it did not consider that the circumstances warranted a ruling of a breach of Clause 2 and no breach of Clause 2 was ruled.

The Authority received a complaint about the promotion of Mepact (mifamurtide) on Takeda UK Ltd's website.

COMPLAINT

The complainant noted that visitors to Takeda's website were greeted by a latest news story detailing Mepact's failure to win approval from the National Institute for health and Clinical Excellence (NICE). The story actively promoted Mepact and did not sit behind any health professional website. The complainant alleged a breach of the Code.

When writing to Takeda, the Authority asked it to respond in relation to Clauses 2, 9.1, 22.1 and 22.2 of the Code.

RESPONSE

Takeda refuted the allegation that the press release in question constituted promotion to the public. Like many pharmaceutical company websites, new material was highlighted on the home page. On the home page of the Takeda UK website, in a section entitled 'What's new?', there was a series of links to other areas of the website, including the media

section. One of these links was the factual statement 'NICE says no to life saving treatment for childhood bone cancer'. By clicking on this statement, the reader was directed to a press release in an area of the site clearly intended for the media, having the title 'Media Section'.

To address the specific allegation made by the complainant that the press release 'did not sit behind any health professional section', the supplementary information to Clause 22.2 permitted non-promotional information about prescription only medicines to be made available to the public in a number of ways, including via press announcements. Takeda believed that the press release in question fulfilled the requirements of Clause 22.2 and that it was non promotional.

The press release detailed a newsworthy topic ie the recent negative decision by NICE in relation to Mepact. The product was referred to in the introductory bullet points in order to put the subsequent information into context. The remainder and majority of the press release referred to osteosarcoma, for which the product was licensed, the process used by NICE to assess medicines and quotations from a number of stakeholders about the NICE opinion.

The few statements within the press release about Mepact were balanced and factual, and Takeda did not consider that they were promotional. Nor were they made to encourage members of the public to ask their health professional to prescribe a specific prescription only medicine.

Takeda also refuted any suggestion that the press release raised unfounded hopes of successful treatment, or that it was misleading with respect to the safety of the product. The press release did not state that Mepact was a 'cure', nor that it could be used in all osteosarcoma patients. The press release was clear that the product was for use in 'suitable young patients that are diagnosed with osteosarcoma' to provide them with a 'fighting chance'.

As press releases of this nature were permitted by the Code, Takeda strongly believed that it had maintained high standards in issuing this press release to the consumer media and placing it in the media area of its website, and was therefore not in breach of Clause 9.1. Takeda also refuted any allegation that it had brought discredit upon, or reduced confidence in the industry, contrary to the requirements of Clause 2.

PANEL RULING

The Panel considered that it was unclear whether the complaint was only about the statement on the home page of Takeda's website or if it also encompassed the press release. In the Panel's view, however, given the statement on the homepage was inextricably linked to the press release, the two could not reasonably be separated and in that regard both elements were considered together.

The Panel noted that the major portion of the home page of the Takeda UK website was comprised of a central section headed 'What's New'. Listed below the heading was a series of dates in reverse chronological order. Below each date was a brief description of a notable event or company achievement. Under 'August 2010' the following appeared:

> 'NICE says no to life saving treatment for childhood bone cancer.
>
> Takeda announces that in its draft appraisal [NICE] does not recommend the use of Mepact for the treatment of bone cancer (osteosarcoma) in children, adolescents and young adults'.

By clicking onto the date the reader was taken to the full press release which was in the 'Media Centre' section of the website. Given the way in which it could be accessed however, the Panel queried whether the press release was in fact a public announcement.

The Panel considered that the announcement on the home page, which was the same as the title of the press release, 'NICE says no to life saving treatment for childhood bone cancer', was in effect a very strong claim for Mepact. The Panel queried whether such a claim was factual and presented in a balanced way. In addition the announcement on the home page raised unfounded hopes of successful treatment and would, on the balance of probabilities, encourage members of the public to read the whole of the press release. The press release began with some very positive bullet points for Mepact which referred, *inter alia*, to 'improve survival in childhood cancer', 'reduces the risk of death by almost one third' and 'save an additional eight lives each year'. It also stated that Takeda wanted to ensure that suitable young patients diagnosed with osteosarcoma were 'provided with a fighting chance …'. In the Panel's view the announcement on the home page and the press release itself would encourage members of the public to ask their health professional to prescribe Mepact, a prescription only medicine. A breach of Clause 22.2 was ruled. The Panel further considered that as the short description of the press release on the homepage of the Takeda website and the press release itself both contained very strong claims that were contrary to Clause 22.2, they were in effect advertisements for Mepact aimed at, *inter alia*, the public; a breach of Clause 22.1 was ruled.

The Panel considered that to describe Mepact as a 'life saving treatment' meant that high standards had not been maintained. A breach of Clause 9.1 was ruled.

With regard to Clause 2, the Panel considered that it was particularly important that information made available to the public about such a sensitive issue as survival in childhood cancer was fair and balanced and did not raise unfounded hopes of successful treatment. Clause 2 was reserved as a sign of particular censure. The Panel considered

that the circumstances warranted such a ruling and a breach of Clause 2 was ruled.

APPEAL BY TAKEDA

Takeda submitted that the press release was issued to communicate the negative decision by NICE about the use of Mepact in the treatment of osteosarcoma. It was not a 'good news' story about the product. The intention also was to communicate Takeda's disappointment at this likely outcome. To put this into context, basic facts about the medicine's efficacy were included, all of which were factual and could be substantiated (Mepact summary of product characteristics (SPC), Meyers *et al* 2008, Picci 2007). As the main aim of Mepact treatment was to increase the overall survival of patients with osteosarcoma, it was impossible to refer to its efficacy without referring to the possibility of it saving lives.

Takeda addressed the points made in the Panel ruling.

'NICE says no to life saving treatment for childhood bone cancer'

In response to the Panel's query about whether the statement 'NICE says no to life saving treatment for childhood bone cancer' was factual and presented in a balanced way, Takeda noted that Section 5.1 of the Mepact SPC stated; 'MEPACT significantly increased the overall survival of patients with newly-diagnosed resectable high-grade osteosarcoma when used in conjunction with combination chemotherapy when compared to chemotherapy alone'.

Takeda noted that the Panel considered that the statement raised unfounded hopes of successful treatment. Mepact had been shown to significantly increase overall survival in osteosarcoma, therefore Takeda did not believe that stating that the product could save lives did raise unfounded hope. In addition, the announcement of a negative decision from NICE in relation to a medicine usually meant that it was unlikely to be available, therefore it reduced hope of access to treatment. The press release was aimed at journalists, but even if a patient found Takeda's website and went to this specific page, they were extremely unlikely to ask their physician for a medicine that they knew was unavailable on the NHS. Thus the press release could not be construed as encouraging members of the public to ask their health professional to prescribe a specific medicine. Takeda did not believe that the statement was contrary to the requirements of Clause 22.2.

'Given the way it could be accessed however, the Panel queried whether the press release was in fact a public announcement.'

Takeda submitted that this statement did not make clear what it was about 'the way it could be accessed' that changed this press release into a public announcement. This was an important issue, as factual press releases were specifically allowed under Clause 22.2, and this was the intent of this piece.

It could not be because it could be accessed without proof that the reader was a journalist, as this conflicted with previous case precedent where the Panel had ruled that it was acceptable to have press releases in a 'media section' of a company website (Cases AUTH/2160/8/08 and AUTH/2161/8/08). It was also not part of the original complaint, which asked why this press release was not behind a health practitioner barrier. As previously stated there was currently no such requirement for a press release.

Takeda submitted that if it was the fact that the press release could be accessed directly from the homepage, it was important to note that the fundamental function of a homepage was to be a central point from which everything on the website could be found. There were many other companies who had press releases on their websites and these were usually accessible via the homepage. Takeda provided examples of press releases of a similar nature to the one at issue, which were obtained from other corporate websites.

Takeda submitted that the term 'public announcement' implied that it was communicated to a large number of people, which was incorrect. Takeda was not such a well known company that people were likely to find its website by accident. Someone would have to specifically look for the Takeda UK website or for information on Mepact. 'Pageview' data taken from the website during the period immediately following the press release (from 13 August) showed that most visitors to the site did not access its media pages, and of those that did, only a very small number accessed this press release. If Takeda had attempted to make a 'public announcement' it would need a very different media outlet to reach patients.

Takeda noted that the small peak in usage of the Mepact press release coincided not with the actual announcement on 13 August, but with the date Takeda received the complaint ie the majority of people who viewed the page were the complainant and company personnel who needed to view it in order to respond to the complaint.

In summary Takeda did not believe that this item was a public announcement – it was intended to be a press release, and this was clear from its location on the website as well as its format, content and the reality of its actual use, which was by a very small number of people. It therefore did not constitute advertising to the public.

'The press release began with some very positive bullet points for Mepact'

Takeda submitted that all the statements included in the press release were factual and could be substantiated. They accurately reflected why Mepact had a licence, and the data that substantiated them was included in the SPC. As

noted above, these statements were included to put into context Takeda's disappointment, and the disappointment of a number of patient organisations, regarding the NICE announcement. The statements were not intended to raise unfounded hope of successful treatment or to encourage members of the public to ask their health professional to prescribe Mepact. As noted previously, the announcement of a negative decision from NICE in relation to a medicine meant that it was unlikely to be available, therefore it reduced hope of access to treatment.

For these reasons, Takeda did not believe that including the statements in the press release rendered it in breach of Clause 22.2.

'Takeda wanted to ensure that suitable young patients diagnosed with osteosarcoma were "provided with a fighting chance"'

Takeda submitted that the reference to a 'fighting chance' was in relation to the fact that Mepact significantly increased the overall survival of patients with newly-diagnosed resectable high-grade osteosarcoma when used in conjunction with combination chemotherapy when compared to chemotherapy alone. The SPC stated:

> 'Mepact significantly increased overall survival in patients with newly diagnosed resectable high grade osteosarcoma …'.
>
> 'In a randomised phase III study of 678 patients … the addition of Mepact to chemotherapy (either doxorubicin, cisplatin and methotrexate with or without ifosfamide resulted in a relative reduction of the risk of death of 28% (p = 0.0313, HR = 0.72 [95% confidence interval (CI): 0.53, 0.97])'.

This was based on the results of Meyers *et al*, the pivotal phase III study, in which the authors concluded 'The addition of MTP to chemotherapy resulted in improvement in 6-year overall survival from 70% to 78% (p = 0.03; relative risk = 0.71). This is an almost one third reduction in the risk of death'.

In simple terms, a patient has more chance of survival if they received Mepact and chemotherapy than if they received chemotherapy alone. The phrase 'fighting chance' also acknowledged that no medicine was 100% effective, including Mepact. Takeda thus did not believe that including this statement in the press release was in breach of Clause 22.2.

Takeda agreed that statements in the press release were 'strong', but they were factual, and balanced in the context of the medicine's purpose and the intention of the item. Takeda did not believe that they were in effect an advertisement for Mepact aimed at the public and therefore disagreed with the ruling of a breach of Clause 22.1. The item was clearly in the media section of the website, and to assert that press releases could not contain positive, factual statements about a medicine would mean that no newsworthy information about a prescription only medicine could ever be communicated via a media item. This would be unfair to both the industry and patients, as they would effectively be prohibited from balancing negative media stories coming from other sources, leading to poor quality information being communicated to the public.

Describing Mepact as 'life saving treatment'

Takeda submitted that as Mepact had been shown to significantly increase the overall survival of patients with newly-diagnosed resectable high-grade osteosarcoma when used in conjunction with combination chemotherapy when compared to chemotherapy alone, it was difficult to describe what it did without stating that it could preserve life. There was no other reason to use the Mepact other than to try and achieve this aim. Mepact was not for symptomatic relief, and this licence was not based on surrogate markers. The Mepact licence was based entirely on saving lives, and this was reflected in the SPC as described above. As such, it was difficult for Takeda to describe the effect of Mepact in anything but these terms.

The number of patients' lives that could be saved was based on a simple, conservative calculation of the number of osteosarcoma patients in the UK, their current survival rate, and what the effect would be if the number of deaths was reduced by 29% (Picci).

Takeda submitted that it was appropriate to state the licensed effect of Mepact in a press release. Every press release for a study or new licence included this information. As noted above, Takeda had found several currently available press releases on other corporate websites that made positive factual statements about the relevant medicine. The press release was factual and in the media section of the website which was in line with previous rulings. Takeda thus did not believe that describing Mepact in this way failed to maintain high standards in breach of Clause 9.1.

Takeda did not consider that issuing a factual (and in context, mostly negative) press release about one of its medicines and adding it to the media section of its website brought the industry into disrepute. Takeda believed that the Panel's ruling of a breach of Clause 2 for the placement of the press release on the company website was inappropriate and inconsistent with previous rulings.

Takeda noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such circumstances. Examples of activities that were likely to be in breach of Clause 2 included prejudicing patient safety and/or public health, excessive hospitality, inducements to prescribe, inadequate action leading to a breach of undertaking, promotion prior to the grant of a marketing authorization, conduct of company employees/agents that fell short of competent care and multiple/cumulative breaches of a similar and

serious nature in the same therapeutic area within a short period of time. Takeda, therefore, did not believe that it had breached Clause 2. This was backed by case precedent, as in previous rulings on similar cases, even when the content of the press release was found to be in breach, no breach of Clause 2 was ruled (Cases AUTH/2147/7/08, AUTH/2160/8/08 and AUTH/2161/8/08).

Takeda took its responsibilities under the Code extremely seriously and pending the outcome of the case, it had removed the press release from its website. Takeda trusted that the details allayed concerns about the press release, its placement on Takeda's website, and demonstrated that the information contained therein was balanced within the context of the communication, factual and did not contravene the requirements of the Code.

COMMENTS FROM THE COMPLAINANT

The complainant considered that the appeal did not go far enough to explain why such an emotively worded press release was available to any site visitor as opposed to being made available solely for health professionals. In the complainant's view the Code (and spirit of the Code) rejected the notion that 'factual' claims could be worded in such a way that they replicated newspaper sub-headings – claims such as 'life saving' which, whilst arguable factually correct, were perceived differently by members of the public than they were by members of the pharmaceutical industry.

The complainant queried the company's claim that, as a relatively small company, it was not possible for people to stumble upon its corporate website. Whilst perhaps a realistic assessment of company size this was not a sound argument. If a 'strong statement' that could be considered to border on promotion reached one person it was the same as if it reached a thousand. The complainant considered that Takeda's argument that the website was not visited by a vast number of people was irrelevant. The company could not control who visited the website and therefore should assume that any number of people could see anything that it placed there.

APPEAL BOARD RULING

The Appeal Board noted that the press release entitled 'NICE says no to life saving treatment for childhood bone cancer' was written in response to the negative decision by NICE in relation to the use of Mepact in the treatment of osteosarcoma in children, adolescents and young adults. The Appeal Board noted Takeda's submission that the press release was issued to tell journalists about Takeda's disappointment about the decision by NICE. Takeda's representatives at the appeal noted that NICE was a public body and that its decision had effectively denied patients access to Mepact. The representatives further stated that Takeda had a corporate responsibility to ensure that patients had access to medicines.

The press release began with some very positive bullet points for Mepact which included '… the first treatment shown to improve survival in childhood bone cancer', '… reduces the risk of death by almost one third …' and '… potential to save an additional eight lives each year'. It also stated that Takeda wanted to ensure that suitable young patients diagnosed with osteosarcoma were 'provided with a fighting chance …'. The Appeal Board considered that the press release made strong claims for Mepact, the language was highly emotive and the press release lacked balance.

The Appeal Board considered that irrespective of whether members of the public read the press release, its emotive language and the fact that they could access it meant that it had the potential to encourage them to ask their health professional to prescribe Mepact, a prescription only medicine. The Appeal Board upheld the Panel's ruling of a breach of Clause 22.2. The Appeal Board further considered that as the short description of the press release on the homepage of the Takeda website and the press release itself both contained very strong claims that were contrary to Clause 22.2, they were in effect advertisements for Mepact aimed at, *inter alia*, the public. The Appeal Board upheld the Panel's ruling of a breach of Clause 22.1. The appeal on these points was unsuccessful.

The Appeal Board considered that the highly emotive and unbalanced language of the press release meant that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

Although it noted its rulings above, the Appeal Board did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and thus it ruled no breach of that clause. The appeal on this point was successful.

Complaint received **7 September 2010**

Case completed **4 February 2011**

CASE AUTH/2357/9/10

GENERAL PRACTITIONER v BOEHRINGER INGELHEIM

Promotion of Pradaxa

A general practitioner complained that an advertisement for Pradaxa (dabigatran), issued by Boehringer Ingelheim, included a claim for therapeutic equivalence with enoxaparin based on non-inferiority studies. To claim equivalence on the basis of such studies was misleading, exaggerated the facts, could not be substantiated and endangered patients safety. Non-inferiority was not the same as comparability. The complainant alleged that the claims in question implied a possible superiority of Pradaxa vs enoxaparin with regard to safety and efficacy. The complainant alleged that the general reference to safety in the claims was misleading as it implied that the safety profile of Pradaxa was equivalent/comparable to enoxaparin which was not so. The complainant also noted that the claims did not specify the dose of enoxaparin which suggested that Pradaxa was equivalent to any dose of enoxaparin which was not so, as shown in the RE-MOBILIZE study. The complainant further noted that the RE-MOBILIZE study, which failed to show non-inferiority vs enoxaparin, had not been cited by Boehringer Ingelheim and in this regard the complainant alleged that the company had cherry-picked the data. This misled clinicians as to the evidence base supporting the claims.

In addition to the advertisement, the complaint also referred to the activity of sales representatives.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that the advertisement at issue featured the claim 'Well balanced' beneath a depiction of a set of balanced scales. Beneath 'Well balanced' was the claim 'Once-daily, oral anticoagulation Efficacy and safety equivalent to enoxaparin in primary prevention of VTE [venous thromboembolism] after total knee or hip replacement surgery'. This claim was referenced to Eriksson *et al*, (2007a) (RE-NOVATE study) and Eriksson *et al*, (2007b) (RE-MODEL study). Both studies were non-inferiority studies to compare the efficacy and safety of Pradaxa with enoxaparin after total hip or total knee replacement respectively. The Panel noted that non-inferiority studies showed that even if one medicine was not as good as another, the difference between the two was not clinically important.

The Panel rejected the complainant's allegation that the claim in question implied a possible superiority of Pradaxa vs enoxaparin. Nonetheless the claim, together with the perfectly balanced scales, implied that Pradaxa had been shown to be unequivocally equivalent to enoxaparin and that was not so. In that regard the Panel considered that the claim was misleading and could not be substantiated. Breaches of the Code were ruled as accepted by Boehringer Ingelheim. The Panel further considered that the claim did not reflect the available evidence about the safety of Pradaxa. A further breach of the Code was ruled.

In the Panel's view the advertisement would be read in the context of the licenced doses of Pradaxa and enoxaparin after total knee or hip replacement surgery. The Panel did not accept that because the claim did not state the dose of enoxaparin that it implied that Pradaxa had been shown to be equivalent to any dose of enoxaparin. The Panel did not consider that the claim at issue was misleading in this regard and no breach of the Code was ruled. Upon appeal by the complainant, the Appeal Board considered that it was good practice to include the relevant dosage particulars in claims about medicines. Nonetheless, given the tightly defined dose of enoxaparin in the prevention of VTE after total hip or knee replacement surgery, the Appeal Board did not consider that it was misleading not to have stated the dose in the advertisement and it upheld the Panel's rulings of no breach of the Code.

The Panel further noted the allegation that by not referring to the RE-MOBILIZE study, Boehringer Ingelheim had 'cherry-picked' the data. The RE-MOBILIZE study had used a lower dose of enoxaparin ie 30mg/day, than that licensed in the UK for the prevention of VTE following total knee or hip replacement surgery ie 40mg/day. In that regard the Panel did not consider that the claim misled clinicians as to the evidence base to support the claim at issue as alleged. No breach of the Code was ruled. Upon appeal by the complainant the Appeal Board noted that the RE-MOBILIZE study had used enoxaparin 30mg twice daily ie a higher dose than that licensed in the UK. The Appeal Board considered that as the RE-MOBILIZE study had used a dose of enoxaparin not licensed in the UK, and therefore not relevant to UK prescribers, it was not misleading not to include the study in the evidence base to support the comparative claim at issue. The Appeal Board upheld the Panel's ruling of no breach of the Code.

With regard to the activities of sales representatives the Panel noted that the complainant had not made any specific allegations. The front page of the detail aid was visually similar to the advertisement. However, below the depiction of the scale pans was the claim 'Once-daily oral anticoagulation Efficacy and safety *comparable* to enoxaparin' (emphasis added). The claim was referenced to the RE-NOVATE and RE-MODEL studies. Throughout the detail aid Pradaxa and enoxaparin were variously described as being

'comparable' or 'similar'. The detail aid did not describe the two medicines as equivalent. The briefing notes for representatives referred to the comparability of Pradaxa to enoxaparin – not to their equivalence. The Panel did not consider that comparability implied equivalence – comparable only meant that the two products were able to be compared. The Panel did not consider that the material used by the representatives was misleading as alleged. No breach of the Code was ruled. Upon appeal by the complainant the Appeal Board did not consider, given the common understanding of comparable, that the detail aid was misleading as alleged. The Panel's ruling was upheld.

The Panel noted its rulings above and did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure. The Panel's ruling of no breach was upheld on appeal.

A general practitioner complained about the promotion of Paradaxa (dabigatran) by Boehringer Ingelheim Limited. The material at issue was an advertisement (ref DGB1729b) which was published in The Pharmaceutical Journal, 18 September 2010. The complainant also referred to the activity of sales representatives.

Pradaxa was indicated for primary prevention of venous thromboembolic events in adult patients who had undergone elective total hip replacement surgery or total knee replacement surgery.

COMPLAINT

The complainant noted that the advertisement at issue featured claims that Pradaxa was well balanced and that its efficacy and safety was equivalent to enoxaparin in the primary prevention of venous thromboembolism (VTE) after total knee or hip replacement surgery.

The complainant submitted that this claim of therapeutic equivalence, based on results derived from studies which employed a non-inferiority study design, appeared to be at odds with the clear and unambiguous ruling in Case AUTH/2270/10/09. Review of the two references cited as substantiation for these claims (Eriksson *et al*, 2007a (RE-NOVATE study) and Eriksson *et al*, 2007b (RE-MODEL study)), and the ruling in Case AUTH/2270/10/09 indicated that the only claim supported by these studies was that Pradaxa was non-inferior to enoxaparin. To suggest apparent equivalence to enoxaparin clearly exaggerated the facts, could not be substantiated and importantly endangered patient safety. There really was a difference between showing non-inferiority and showing comparability and Boehringer Ingelheim had conveniently ignored this salient fact. The claims in question implied a possible superiority of Pradaxa vs enoxaparin with regard to its efficacy and safety.

The complainant referred to some relevant background information on the RE-NOVATE, RE-MODEL and RE-MOBILIZE studies reported in a review regarding the evidence base for Pradaxa vs enoxaparin and that none of the studies supported a claim of equivalence or superiority (Weitz 2010). The complainant reproduced a table of data from Weitz.

The complainant was also concerned that the generalisations employed were misleading and potentially endangered patient safety. Firstly, the general reference to safety in the claims was misleading as it implied that the safety profile of Pradaxa was entirely equivalent/comparable to enoxaparin; this was not so given that the studies cited focused on bleeding outcomes and other specified thromboembolic outcomes as primary and secondary outcomes and that the hepatic and cardiac safety profiles, amongst other things, of these two medicines were not equivalent or comparable. Secondly, the clinical studies comparing Pradaxa with enoxaparin used differing doses of enoxaparin, as was the case in clinical practice. The claims did not specify the dosage of enoxaparin and so suggested that Pradaxa had been proven to be equivalent (or correctly, non-inferior) to any dose of enoxaparin; this was not so as shown by the not insignificant Phase 3 trial RE-MOBILIZE which used enoxaparin 30mg twice daily (instead of 40mg once daily) and importantly also failed to achieve non-inferiority vs enoxaparin. Thirdly, the latter clearly indicated that Boehringer Ingelheim had cherry-picked the data and referred only to those studies where non-inferiority vs enoxaparin had been achieved; this misled clinicians as to the evidence-base supporting these claims.

When writing to Boehringer Ingelheim the Authority asked it to respond in relation to Clauses 2, 7.2, 7.3, 7.4, 7.9 and 7.10, of the Code of Practice.

RESPONSE

Boehringer Ingelheim noted that the two principal clinical studies supporting the marketing authorization for the efficacy and safety of dabigatran in the EU employed a non-inferiority study design. Both studies, the RE-NOVATE study in total hip replacement and the RE-MODEL study in total knee replacement, demonstrated non-inferiority to enoxaparin in the prevention of major VTE and VTE-related mortality during treatment (the primary variable). There were no significant differences between dabigatran and enoxaparin on any safety parameters.

Each study compared the efficacy and safety of two doses of dabigatran, both of which had since received marketing approval, compared with enoxaparin. More detailed review of the results showed that at the higher approved dose of dabigatran (220mg) VTE was numerically lower than enoxaparin but major bleeding events were numerically higher although no differences achieved statistical significance. At the lower approved dose of dabigatran (150mg) VTE was numerically a little higher and bleeding events

numerically lower than enoxaparin again with no statistically significant differences. These results were reflected in the table of data from Weitz provided by the complainant. With regard to other adverse events the profiles of dabigatran and enoxaparin were very similar as reflected in the unwanted effects section of the Pradaxa summary of product characteristics (SPC).

Boehringer Ingelheim noted the allegation that the claims in question implied a possible superiority of Pradaxa vs enoxaparin with regard to its efficacy and safety and the complainant's reference to Case AUTH/2270/10/09 to support his position. Case AUTH/2270/10/09 referred to the claim 'at least as effective as…' which was ruled to imply superiority. Boehringer Ingelheim believed that this claim fundamentally differed from the claim 'equivalent to' which did not imply any degree of superiority (since it could only imply equivalence) and so strongly refuted the allegation of implied superiority.

Boehringer Ingelheim accepted that the data did not substantiate the claim of 'equivalent efficacy to enoxaparin'. Indeed this was accepted and fully reflected in earlier Pradaxa promotional materials where the corresponding claims referred to 'comparable' efficacy and safety profiles. Further investigation of the preparation and approval of the advertisement with regard to the change of wording was an oversight and not rejected during the approval process.

Boehringer Ingelheim agreed that the advertisement was in breach of Clauses 7.2, 7.3, 7.4 and 7.10, and had since rigorously reviewed its internal approval processes to ensure that this anomaly could not occur again.

Boehringer Ingelheim noted that the complainant also alleged that the company had 'cherry picked the data' as the RE-MOBILIZE study was not presented. The complainant surmised that the absence of information on the RE-MOBILIZE study might be because the study failed to demonstrate non-inferiority to a standard US regimen of enoxaparin. The RE-MOBILIZE study was not normally referred to in any UK, or indeed EU materials and was not referred to in the SPC as the study was designed for the US with a regimen for enoxaparin (30mg twice daily) which was fairly specific to that region and different from the standard EU regimen of 40mg once daily. The study did not demonstrate non-inferiority, possibly due to the higher dose regimen of enoxaparin. Omission of this study was not 'cherry picking', it was simply that the study covered a dosing regimen not commonly used in the UK, or Europe.

Boehringer Ingelheim noted the allegation that the 'general reference to safety … was misleading as it implied that the safety profile of Pradaxa was entirely equivalent/comparable to enoxaparin'. The materials in question referred to 'Well balanced combination of efficacy and safety', 'A safety profile comparable to enoxaparin after total hip or knee replacement' and 'VTE prevention comparable to enoxaparin after total hip or knee replacement'. Boehringer Ingelheim noted that it made no claim or implication of equivalence as alleged. Furthermore, Boehringer Ingelheim considered that these statements were appropriate and consistent with the data.

Any form of anticoagulation was subject to link between the level of anticoagulation which would affect efficacy and the associated risk of bleeding events (safety). In clinical studies, both licensed doses of Pradaxa had demonstrated non-inferiority to the current 'gold standard therapy' with a very similar incidence of bleeding events and a similar overall adverse event profile.

Boehringer Ingelheim submitted that data provided in the Pradaxa SPC illustrated these findings and fully substantiated claims of comparable efficacy and a comparable safety profile to enoxaparin. Importantly, the cardiac and hepatic safety profiles were specifically studied in the clinical trials and there was no evidence of important differences as alleged by the complainant.

Although not the subject of any specific aspect of the complaint, Boehringer Ingelheim provided copies of the detail aid and associated briefing material.

In response to a request for further information Boehringer Ingelheim stated that The Pharmaceutical Journal did not contain any other information about Pradaxa aside from the advertisement in question. Boehringer Ingelheim submitted that it was not clear which aspect of the sales representatives' activities was referred to by the complainant. In the absence of this additional information Boehringer Ingelheim did not believe it needed to comment further on Clauses 2, 7.2, 7.3, 7.4, 7.9 or 7.10.

PANEL RULING

The Panel noted that the advertisement at issue featured the claim 'Well balanced' beneath a depiction of a set of balance scales with the two pans, one red, one blue exactly balanced. Beneath 'Well balanced' was the claim 'Once-daily, oral anticoagulation Efficacy and safety equivalent to enoxaparin in primary prevention of VTE after total knee or hip replacement surgery'. This claim was referenced to Eriksson *et al*, (2007a) (RE-NOVATE study) and Eriksson *et al*, (2007b) (RE-MODEL study). Both studies were non-inferiority studies to compare the efficacy and safety of Pradaxa with enoxaparin after total hip or total knee replacement respectively. The Panel noted that non-inferiority studies showed that even if one medicine was not as good as another, the difference between the two was not clinically important.

The Panel rejected the complainant's allegation that the claim in question implied a possible superiority of Pradaxa vs enoxaparin. Nonetheless the claim, together with the perfectly balanced scales, implied

that Pradaxa had been shown to be unequivocally equivalent to enoxaparin and that was not so. In that regard the Panel considered that the claim was misleading and could not be substantiated. Breaches of Clauses 7.2, 7.3, 7.4 and 7.10 were ruled. The Panel noted that Boehringer Ingelheim had accepted that the claim was in breach of these clauses of the Code. The Panel further considered that the claim did not reflect the available evidence about the safety of Pradaxa. A breach of Clause 7.9 was ruled.

In the Panel's view the advertisement would be read in the context of the licenced doses of Pradaxa and enoxaparin after total knee or hip replacement surgery. The Panel did not accept that because the claim did not state the dose of enoxaparin that it implied that Pradaxa had been shown to be equivalent to any dose of enoxaparin. The Panel did not consider that the claim at issue was misleading because it did not state the dose of enoxaparin. No breach of Clause 7.2 was ruled on that narrow point.

The Panel further noted the allegation that by not referring to the RE-MOBILIZE study, Boehringer Ingelheim had 'cherry-picked' the data. The RE-MOBILIZE study had used a lower dose of enoxaparin ie 30mg/day, than that licensed in the UK for the prevention of VTE following total knee or hip replacement surgery ie 40mg/day. In that regard the Panel did not consider that the claim misled clinicians as to the evidence base to support the claim at issue as alleged. No breach of Clause 7.2 was ruled.

With regard to the activities of sales representatives the Panel noted that the complainant had not made any specific allegations. The front page of the detail aid was visually similar to the advertisement. However, below the depiction of the scale pans was the claim 'Once-daily oral anticoagulation Efficacy and safety *comparable* to enoxaparin' (emphasis added). The claim was referenced to the RE-NOVATE and RE-MODEL studies. Throughout the detail aid Pradaxa and enoxaparin were variously described as being 'comparable' or 'similar'. The detail aid did not describe the two medicines as equivalent. The briefing notes for representatives referred to the comparability of Pradaxa to enoxaparin – not to their equivalence. The Panel did not consider that comparability implied equivalence – comparable only meant that the two products were able to be compared. The Panel did not consider that the material used by the representatives was misleading as alleged. No breach of Clauses 7.2, 7.3, 7.9 and 7.10 was ruled.

The Panel noted its rulings above and did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure.

APPEAL FROM THE COMPLAINANT

The complainant welcomed the rulings of a breach of the Code but was disappointed that they had not been consistently applied to the representatives' materials which were ruled not to be in breach of the Code. The complainant was concerned that the Panel might have engaged in semantics without regard to the intelligence and common sense of health professionals to whom the claims in question of equivalence/comparability between dabigatran and enoxaparin were aimed.

On one hand the Panel suggested, in previous cases, that non-inferiority studies could not support any direct or implied claims of equivalence, similarity or superiority between two medicines. However, in this case it seemed that the Panel had decided that such studies allowed two medicines to be compared with each other thus allowing claims of comparability ie one medicine was comparable or similar to another. How was this different to assessing equivalence or otherwise?

The complainant questioned the purpose of comparing two medicines if it was not to invite health professionals to consider whether: the two were similar, equivalent, comparable or at least as good as each other; one was worse/inferior than the other; one was better or superior to the other or one was non-inferior to the other. Indeed, this was precisely how the data from non-inferiority studies and other comparative studies was used and considered by regulators, so why not health professionals?

The complainant submitted that the rulings of no breach suggested that sales materials and sales representatives could refer to the actual comparison between dabigatran and enoxaparin described in these non-inferiority studies as long as the materials or representatives somehow avoided inviting a discussion or consideration of the implication of the results to clinicians; this was patently nonsense and not what happened in practice. Did the Panel really suggest that the representatives who used promotional materials which referred to these claims were instructed to present a comparison of the two medicines but leave it to the health professionals to decide for themselves in which of the above four categories the comparison between dabigatran and enoxaparin belonged? This was not what the sales representative briefing instructed regarding the promotion of this claim.

COMMENTS FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim welcomed the opportunity to comment on the complainant's appeal and strongly endorsed the Panel's rulings of no breach on each of the following points.

1 Dose of Pradaxa not stated in the advertisement

Boehringer Ingelheim submitted that the indication for Pradaxa in the prevention of VTE after total hip and knee replacement surgery was clearly stated in the advertisement. The company thus agreed with the Panel's view that the advertisement would be read in the context of the licensed doses of Pradaxa and enoxaparin and so did not imply Pradaxa had

been proven to be equivalent to all doses of enoxaparin. Boehringer Ingelheim endorsed the Panel's ruling of no breach of Clause 7.2.

2 'Cherry-picking' data

The RE-MOBILIZE study used the standard regimen of enoxaparin (30mg bd) in the USA which was different from that used within the UK (Europe) (40mg od). In the EU this dosing regimen was not used, nor was it referred to in the SPC and so it was entirely acceptable to not refer to it in UK materials. Boehringer Ingelheim endorsed the Panel's ruling of no breach of Clause 7.2.

3 The interpretation of 'non-inferiority' studies

The original complaint referred specifically to a journal advertisement (ref DBG1729b) and also referred to the activity of sales representatives, although did not refer to any specific meeting with representatives nor to any sales materials. Moreover, the complainant did not detail any interactions he had had with the field force that had led to his concerns. This was an important point because the complainant stated that he was a general practitioner. Pradaxa was licensed for the primary prevention of venous thromboembolic events associated with hip and knee replacement surgery ie a specialised orthopaedic area and so Boehringer Ingelheim representatives did not promote Pradaxa to general practitioners. It was unclear how, if at all, this general practitioner could know about the promotion of Pradaxa by Boehringer Ingelheim representatives.

A formal complaint and its subsequent appeal should only be based on fact rather than supposition, otherwise credibility in the PMCPA complaints process could, and would be, questioned. The complainant appeared to have based his appeal on material which Boehringer Ingelheim provided to the PMCPA on request following the complaint. In this regard Boehringer Ingelheim questioned the validity of such an appeal.

The complainant appeared to question the interpretation of non-inferiority studies and the interpretation of their results. Boehringer Ingelheim endorsed the Panel's view that it was acceptable to use 'comparable' or 'similar to' in reference to studies where a medicine had been found to be non-inferior to another. However, there were a number of guidance documents on the subject of demonstrating non-inferiority and its interpretation.

Non-inferiority studies were designed to demonstrate that the difference between two medicines was not clinically relevant. The margin for this difference was set as the delta. In the ICH Guideline on 'Statistical Principles for Clinical Trials', Section 5.2.3 'Roles of Different Analysis Sets' it stated: 'The full analysis set and the per protocol set play different roles in superiority trials (which seek to show the investigational product to be superior), and in equivalence or non-inferiority trials (which seek to show the investigational product to be comparable, see section 3.3.2)'.

In 'Statistical Thinking for Non-statisticians in Drug Regulation' in Chapter 12 'Equivalence and non-inferiority', Section 12.1 'demonstrating similarity' page 174 it was stated: '… in a therapeutic setting we will use a non-inferiority design, where we are looking to establish that our new treatment is 'at least as good as' or 'no worse than' an existing treatment. We will, of course, need to define 'at least as good' or 'no worse than' in an operational sense for this to be unambiguous …'.

In The European Medicines Agency (EMEA) Guideline (EMEA/CPMP/EWP/2158/99) the following was stated '… there are many situations where a non-inferiority trial might be performed as opposed to, or in addition to, a superiority trial over placebo. These include:

- Applications based upon essential similarity in areas where bioequivalence studies are not possible, e.g. modified release products or topical preparations;
- Products with a potential safety advantage over the standard might require an efficacy comparison to the standard to allow a risk-benefit assessment to be made;
- Cases where a direct comparison against the active comparator is needed to help assess risk benefit;
- Cases where no important loss of efficacy compared to the active comparator would be acceptable;
- Disease areas where the use of a placebo arm is not possible and an active control trial is used to demonstrate the efficacy of the test product.'

Non-inferiority studies were inadequate to substantiate claims of 'equivalence' or 'superiority', however, in Boehringer Ingelheim's view, they could substantiate claims of 'similar to' and 'comparable to'. Boehringer Ingelheim considered that 'comparable to' and 'similar to' were synonymous. As acknowledged by the Appeal Board in its consideration of Case AUTH/2270/10/09 'non-inferiority studies showed that even if one product was worse than another it was only worse within clinically unimportant limits'. It must be the case that non-inferiority studies substantiated claims for similarity, as non-inferiority studies frequently provided the clinical data for approval of medicinal products on the basis that they were 'essentially similar' to an existing product.

It also appeared that the complainant might have misunderstood the ruling in Case AUTH/2270/10/09, which he referred to in his complaint. The previous case was about a claim that a product was 'at least as effective as' which, the Panel and Appeal Board considered implied superiority and could not be supported by data from non-inferiority studies alone.

In practice 'comparability' and 'similarity' or 'similar

to' (in relation to non-inferiority studies) were commonly used to describe the interpretation of these results in the academic, promotional and regulatory authority setting.

Boehringer Ingelheim believed that it had demonstrated without doubt that the Panel's rulings of no breach with regard to the points above were correct.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant stated that he was disappointed that Boehringer Ingelheim appeared to have missed the common sense points he had previously made. Instead the company appeared to question his personal qualification to complain about the promotion of Pradaxa. The complainant noted that he was a Fellow of the Royal College of Surgeons and, as a general practitioner, he had a specialist interest in orthopaedic surgery and worked in the accident and emergency department of his local hospital and as a general practitioner with a special interest in the consultant-led orthopaedics and minor trauma outpatient clinics. Regardless, of the latter, Boehringer Ingelheim appeared to be disconnected from reality if it supposed that general practitioners could only be promoted to by Boehringer Ingelheim's sales representatives. Boehringer Ingelheim's argument was not consistent or credible given that the advertisement for Pradaxa appeared in a non-specialist journal whose UK readership was not restricted to only specialists involved in orthopaedics.

Whilst it might suit Boehringer Ingelheim to skirt around the issue by reference to the EMA and ICH guidelines, what was conveniently obscured was the basic fact that these were relevant to product development and licensing of products but had no direct bearing on product promotion in the UK, the legitimacy of which was judged by reference to the Code.

Similarly, statistician's view, whilst interesting, did not address the fundamental failings of the misleading and unbalanced promotion of Pradaxa compared to enoxaparin by both the UK sales materials and the corporate website. The statistician was not a health professional and did not ultimately bear the responsibility of making an informed prescribing decision which, if based on false and misleading comparative claims, could compromise patient safety.

APPEAL BOARD RULING

The Appeal Board considered that, it was good practice to include the relevant dosage particulars in claims about medicines. The advertisement included a comparative claim about Pradaxa and enoxaparin without stating the dose of either. The complainant had alleged that this was misleading as it implied that Pradaxa was equivalent to all doses of enoxaparin. The Appeal Board noted, however, that for the primary prevention of VTE following total knee or hip replacement surgery, the only licensed dose of enoxaparin was 40mg daily (some special patient populations might require a lower dose). Given the tightly defined dose of enoxaparin in the general patient population, the Appeal Board did not consider that it was misleading not to have stated the dose in the advertisement. The implication was that the standard licensed dose was being compared, which it was. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2. The appeal on this point was thus unsuccessful.

The Appeal Board noted that the Panel had incorrectly stated that the RE-MOBILIZE study had used a lower dose of enoxaparin ie 30mg/day, than that licensed in the UK for the prevention of VTE following total knee or hip replacement surgery ie 40mg/day. The RE-MOBILIZE study had used enoxaparin 30mg **twice daily** ie a higher dose than that licensed in the UK. The Appeal Board nonetheless considered that as the RE-MOBILISE study had used a dose of enoxaparin not licensed in the UK, and therefore not relevant to UK prescribers, it was not misleading not to include the study in the evidence base to support the comparative claim at issue. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2 of the Code. The appeal on this point was thus unsuccessful.

The Appeal Board noted that the complainant had stated in his initial letter to the Authority that he was concerned, *inter alia*, about the promotion of Pradaxa by Boehringer Ingelheim's representatives. The Authority, when it informed the company about the complaint, asked for copies of the Pradaxa detail aid and briefing material. These were subsequently provided. The Appeal Board noted that the detail aid described enoxaparin and Pradaxa as being comparable. The Appeal Board did not consider that this implied equivalence. Given the common understanding of 'comparable' the Appeal Board did not consider that the detail aid was misleading as alleged. The Appeal Board upheld the Panel's rulings of no breach of Clauses 7.2, 7.3, 7.9 and 7.10. The appeal on this point was thus unsuccessful.

The Appeal Board noted its rulings above and upheld the Panel's ruling of no breach of Clause 2 of the Code. The appeal on this point was thus unsuccessful.

Complaint received **20 September 2010**

Case completed **8 December 2010**

CASE AUTH/2358/9/10

ANONYMOUS v GENUS

Role of nurse advisors

An anonymous and non-contactable complainant provided a copy of a journal advertisement for APO-go (apomorphine hydrochloride) issued by Genus. The complainant had highlighted the claim 'Pd [Parkinson's disease] specialist Nurse Advisors in APO-go (NAAs)' and alleged that this implied that the support offered by Genus was a team of Parkinson's disease specialist nurses which was not so. The majority of this team were undoubtedly APO-go nurse advisors but they were not Parkinson's disease nurse specialists and this terminology was wholly misleading.

The complainant noted from experience that team members frequently referred to their role as that of a Parkinson's disease nurse specialist. This was inappropriate, misleading and could confuse patients. That some of the team also changed patients' medicines – other than apomorphine – was a total scandal. Documentation from this team was scant and seldom appeared in patients' notes, communication was poor and overall the behaviour of this group created significant risk for patients.

The complainant requested that the Authority ensured that these nurses stopped referring to themselves as 'Parkinson's disease specialist nurse advisors'. The complainant also asked the Authority to review their business cards.

The detailed response from Genus is given below.

The Panel noted that the advertisement referred to 'Pd [Parkinson's disease] specialist Nurse Advisors in APO-GO (NAAs) – dedicated Pd trained nurse support'. The nurses fulfilling that role had various levels of expertise and experience with regard to Parkinson's disease from four who were NHS Parkinson's disease nurse specialists (PDNSs) to one who was a lead nurse in the blood service with a parent who had Parkinson's disease. Some already had, and others were working towards, the diploma in Parkinson's disease. Given that a PDNS was a recognised qualification and role in the NHS the Panel considered that it was misleading to refer to the APO-go nurse advisor team as Parkinson's disease specialist nurse advisors. Some readers might assume, not unreasonably, that all of the nurse advisors were PDNSs which was not so. The advertisement was misleading in that regard and the Panel ruled a breach of the Code. The Panel noted the submission from Genus that 'specialist' had only been used in the advertisement and that it would stop using that term when referring to the nurse team. In that regard the Panel noted that the business cards referred to 'Nurse Advisor in APO-go Therapy'.

The Panel noted that the business cards were headed with the product name, APO-go followed by 'Senior nurse advisor in APO-go therapy' or 'Nurse advisor in APO-go therapy' followed by the relevant name and contact details and the web address details. The reverse side included details of the APO-go helpline, an out-of-hours telephone number and the company name, address and contact details. The Panel did not consider that the business cards were misleading as to the status of the nurse advisors. No breach of the Code was ruled.

The Summary of Services booklet stated that the programme was non promotional and offered as a service to medicine. The Panel was unsure what was meant by the use of the term 'non promotional'. The service was linked to the use of APO-go such that the Panel considered that it was, in effect, offered as a package deal. The Panel noted that the Code did not prevent the offer of package deals. The Panel considered that there was no information before it to suggest that the package of care offered by Genus was a gift, benefit in kind or a pecuniary advantage given or offered to a health professional as an inducement to prescribe, supply, administer, recommend, buy or sell APO-go. No breach of the Code was ruled.

Given that the service offered by Genus bore the name of APO-go and was inextricably linked with the product, it could not be considered to be a medical or educational good or service and thus no breach was ruled in that regard.

The Panel noted that the Summary of Services booklet detailed the nurse support programme. The double page centre spread referred, *inter alia*, to the Parkinson disease guidelines issued by NICE. Extracts from those guidelines were quoted in the booklet and referred to PDNSs and the essential skills of a PDNS. The booklet stated that the initiation of apomorphine should be restricted to expert units with the availability of a home monitoring system by a suitably trained heath professional such as a PDNS. Under the heading 'Nurse Advisor in APO-go' it was stated that in order to assist the NHS to implement the NICE guidelines, Genus had established a network of nurse advisors to assist in various aspects of APO-go therapy. The stated skill set of a PDNS was referred to. In the Panel's view it was not unreasonable that some readers might assume that all of the nurse advisors provided by Genus were PDNSs which was not so. Under the same heading, a bulletin from the Royal College of Nurses entitled 'Specialist Nurses "targeted" to cut costs' was referred to which strengthened the impression that

the nurse advisors in APO-go were specialist nurses ie PDNSs. The Panel considered that the booklet was not sufficiently clear with regard to the qualifications and status of the APO-go nurse advisors and a breach of the Code was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of the Code was ruled. The Panel, however, did not consider that the matter was such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

An anonymous and non-contactable complainant provided a copy of a journal advertisement (ref APG.API.V11) for APO-go (apomorphine hydrochloride) issued by Genus Pharmaceuticals Ltd. The complainant had highlighted the claim 'Pd [Parkinson's disease] specialist Nurse Advisors in APO-go (NAAs)'.

COMPLAINT

The complainant stated that the advertisement implied that the support offered by Genus was a team of Parkinson's disease specialist nurses and this was not the case. The majority of this team were undoubtedly APO-go nurse advisors but they were not Parkinson's disease nurse specialists and this terminology was wholly misleading.

The complainant noted from experience that this impression was further reinforced by their behaviour 'in the field' where this team frequently referred to their role as that of a Parkinson's disease nurse specialist. This was inappropriate, misleading and could confuse patients. That some of the team also changed patients' medicines – other than apomorphine – was a total scandal. Documentation from this team was scant and seldom appeared in patients' notes, communication was poor and overall the behaviour of this group created significant risk for patients.

The complainant requested that the Authority ensured that these nurses stopped referring to themselves as 'Parkinson's disease specialist nurse advisors'. The complainant also asked the Authority to review their business cards.

When writing to Genus, the Authority asked it to respond in relation to Clauses 2, 7.2, 9.1, 18.1 and 18.4 of the Code.

RESPONSE

Genus explained that APO-go was administered subcutaneously either as an intermittent injection, using a pen device, which was useful for patients on oral therapies, who needed to boost their medicine when they experienced 'wearing-off' or 'off' periods (as they were referred to by health professionals) or by continuous infusion administered via the APO-go pump device. The latter method of administration was suitable for more complex (and usually later stage) Parkinson's patients. Both regimes required the patients to receive a 'challenge' which identified that they were suitable to receive APO-go, determined their response in terms of efficacy and allowed dose titration. The challenge in the majority of cases required the patient to go into hospital, either as a day-case or longer for more complex cases, which in itself caused issues in terms of availability of beds and medical staff qualified to administer the challenge. There could often be a delay of several months before patients received an effective treatment, during which time their condition might deteriorate significantly.

The package of care that Genus offered, once it had been decided to treat appropriate patients with APO-go, was for the sole purpose of improving the quality of healthcare provided to patients with complex Parkinson's disease and who were going to receive APO-go. Through the advertisement, Genus offered a number of support services within the package of care to help health professionals deliver the highest quality of care to patients with complex Parkinson's disease, but only after it had been decided to use APO-go in the management of their disease.

Genus submitted that this aligned perfectly with the government's drive to improve patient choice and patient experience and become a part of the decision making process about their treatment. The package of care and in particular the nurse advisors team also helped to deliver quality of care when patients had been discharged which again fitted perfectly with the 30 day post discharge responsibility that now fell to secondary care trusts. Patients were fully involved in the decision to use the nurse advisors in APO-go at the outset of their treatment. The nurse advisor input would not proceed without the patient's agreement. As such the patients were part of the decision making process, which aligned very closely with the White Paper 'Equity and Excellence, Liberating the NHS'.

The registered nurses employed to work with health professionals and patients had strong backgrounds in neurology. Four were NHS Parkinson's disease nurse specialists, three worked in neurology alongside patients with Parkinson's disease and were involved in APO-go therapy management, two were multiple sclerosis nurse advisors, and one a lead nurse in the blood service with a parent who had Parkinson's disease. All had, or were working towards, the diploma in Parkinson's disease. All provided Parkinson's disease teaching, education and mentorship for NHS staff and some taught on the junior doctor training schemes with national coverage.

The nurses had all undergone a comprehensive and intensive training programme when they joined the company on all aspects of APO-go and the management of patients with Parkinson's disease. In addition to the experience and training each nurse worked within the constraints of an honorary contract which had to be approved by the trust

personnel department and the appropriate consultants. It could not be approved by any other person including specialist Parkinson's disease nurse specialists. A copy of the honorary contract was provided.

In support of the excellent work done over the last two years, Genus provided several testimonials to demonstrate the high degree of value that health professionals placed on the package of care but in particular on the support nurse advisors delivered to patients and the NHS. Genus also provided an example of their business cards and name badges as there was a suggestion within the complaint that these were also misleading.

In conclusion, Genus considered that the nurse advisor team was highly experienced and effective in supporting patients who were receiving APO-go treatment. Their sole aim was to improve the quality of care that APO-go patients received and to assist the NHS and health professionals to deliver, in a timely fashion, the best possible quality of care for patients. Given their level of experience, qualifications and training it was fair to describe them as Parkinson's disease specialist nurse advisors in APO-go as the emphasis was on being specialists in APO-go not Parkinson's disease in general. However, in order to avoid any ambiguity, Genus had withdrawn any reference to 'specialist' when referring to the nurse team. In fact the only reference made to 'specialist' was in the advertisement. This had now been withdrawn. There was never any intent to mislead or deceive.

With regard to the allegation that some of the nurses changed patients' medicines – other than apomorphine, Genus submitted that the team provided medical support relating to the use of APO-go therapy under the auspices of an honorary contract, issued/signed by trust personnel ie consultant and personnel department (a Parkinson's disease nurse specialist signature was not acceptable). Medicines were changed upon instruction only. A nurse advisor would never work independently without the instruction of the lead consultant. However APO-go therapy might be discontinued if this was deemed best for the patient. The emphasis was on optimal/best practice therapy for each individual patient, which might no longer include treatment with APO-go. The patient was always consulted and contributed to the process, the nurse acted as the patient's advocate, and the patient was Genus' primary concern.

On every occasion and in every circumstance, the nurse advisors adhered to the Nursing and Midwifery Council code of conduct and fulfilled their duty of care to the patient.

Genus therefore concluded that the provision of its nurse advisors could not bring discredit to or reduce confidence in, the industry (Clause 2). Conversely, Genus had invested a great deal of time in developing a package of care that greatly enhanced the provision of service and quality of care the NHS delivered to its Parkinson's disease patients and was an excellent example of the industry and the NHS working in partnership to deliver the highest level of service possible to its patients. This was in line with the aims and ambitions set out in the White Paper 'Equity and Excellence, Liberating the NHS' and very much about quality outcomes and the patient experience.

As demonstrated above, the nurse advisor team was very experienced, well qualified and received a high degree of training on a continuous basis about the therapy area and APO-go. The matter in question depended on the definition of 'specialist'. One such definition would be a medical practitioner who devoted attention to a particular class of diseases or patients. Using this definition Genus considered that the term Parkinson's disease specialist nurse advisor in APO-go was justified, taking account of their role, experience, training and qualifications as outlined above. However as mentioned above, the term 'specialist' had only appeared in the advertisement and did not appear on business cards or name badges. Genus therefore denied a breach of Clause 7.2.

The aim of the advertisement had been to inform health professionals of the new 'APO-go homecare delivery' service that had been added to the package of care support from Genus. The aim was to improve the convenience for patients with complex Parkinson's disease, many of whom found walking to the local pharmacy quite difficult and inconvenient. The service, which included regular telephone calls to check patients' medicine supply, helped monitor adherence and avoid stock piling (a significant cost to the NHS) and arranged the efficient and effective disposal of sharps boxes. Genus believed the advertisement was informative and accurate and of a high quality and standard; it denied a breach of Clause 9.1.

The package of care was designed to assist and support patients who had been identified as suitable for treatment with APO-go due to the efficacy of their oral medicine failing. This positioning was supported and recommended by the National Institute for health and Clinical Excellence (NICE), as per its guidelines of 2006. This decision was made purely on the basis of the patient's condition and the advancing nature of the disease. There was no benefit in kind to any health professional directly and therefore there was no inducement to prescribe APO-go. The benefits were totally focused on the patients with regards to the nurse advisor's support, 24/7 helpline, educational support and assistance with the dedicated infusion pump and all necessary peripherals. As a 'package of care' Genus did not believe this was a 'good and service' as usually interpreted within the Code. Genus therefore strongly believed that there had been no breach of Clause 18.1.

Genus believed that the nurse advisors were an integral part of the package of care offered by Genus to support patients who had been identified

as being suitable to receive APO-go therapy. As such Genus did not believe they should be classed as a 'service or goods' as defined within Clause 18.4. With reference to the educational element of the package of care offered to patients, this was a support that was offered to patients who were already receiving APO-go for their Parkinson's disease, and was specific to the disease area and the role of APO-go in their treatment. Genus thus denied a breach of Clause 18.4.

In response to a request for further information Genus outlined the process by which the nurse advisors would get involved in changing a patient's medication:

- The patient, responsible clinician and trust agreed to use the services of the nurse advisor as demonstrated by a signed patient consent form, programme agreement and honorary contract.
- Only when the patient had been identified and/or started on APO-go therapy was the service of the nurse advisor initiated with a referral form (and often telephone call in addition). At no point was the nurse advisor involved in the recruitment of patients by any means whatsoever.
- The nurse advisor would work with the doctor and/or specialist nurse in an educational capacity to learn about and identify the nature of the parkinsonian symptoms specific to the patient in relation to APO-go therapy. Inevitably, the patient was reviewed as a 'whole' and this included, but was not limited to, other possible medicines, social activities, diet and sleep etc.
- If a change in medicine was indicated and the doctor or Parkinson's disease nurse specialist were unable to make the changes personally eg when the patient was at home with no access to primary care Parkinson's disease services, the following steps would be taken:

    - The nurse advisor would visit the patient – as agreed in consultation with relevant health professionals.
    - Conduct a clinical assessment using accepted Parkinson's disease documentation, such as the Unified Parkinson's Disease Rating Scale Part III.
    - Speak to the doctor and/or nurse and complete nursing notes about the patient's condition.
    - The doctor/Parkinson's disease nurse specialist would instruct the nurse advisor to make the relevant changes, taking into account the patient's condition.
    - This was recorded in the nursing/patient notes and shared with all NHS health professionals.
    - The nurse advisor would conduct the follow up visits as agreed by the relevant health professional to ensure the changes had not caused any untoward effect and the anticipated benefit was realised. Each visit was recorded and the record sent back to the responsible health professional immediately.
    - The only change that the nurse advisor would initiate without prior consultation was if an emergency arose, eg if the patient experienced severely low blood pressure, whereupon the APO-go infusion was stopped, patient's safety stabilised, emergency services called if necessary, and the responsible NHS health professional contacted immediately.
    - At all times the patient was consulted and included in the care plan and could ask the nurse advisor to leave at any time.

PANEL RULING

The Panel noted that the complainant had commented in general about the role of the APO-go nurse advisor team but had requested that 'for the moment' the Authority ensure that the nurses stop referring to themselves as 'Parkinson disease specialist nurse advisors'. The Panel noted that the advertisement at issue referred to 'Pd [Parkinson's disease] specialist Nurse Advisors in APO-GO (NAAs) – dedicated Pd trained nurse support'. The nurses fulfilling that role had various levels of expertise and experience with regard to Parkinson's disease from four who were NHS Parkinson's disease nurse specialists (PDNSs) to one who was a lead nurse in the blood service with a parent who had Parkinson's disease. Some already had, and others were working towards, the diploma in Parkinson's disease. Given that a PDNS was a recognised qualification and role in the NHS the Panel considered that it was misleading to refer to the APO-go nurse advisor team as Parkinson's disease specialist nurse advisors. Some readers might assume, not unreasonably, that all of the nurse advisors were PDNSs which was not so. The advertisement was misleading in that regard and the Panel ruled a breach of Clause 7.2. The Panel noted the submission from Genus that 'specialist' had only been used in the advertisement and that it would stop using that term when referring to the nurse team. In that regard the Panel noted that the business cards referred to 'Nurse Advisor in APO-go Therapy'.

The Panel noted that the business cards were headed with the product name, APO-go followed by 'Senior nurse advisor in APO-go therapy' or 'Nurse advisor in APO-go therapy' followed by the relevant name and contact details and the web address details. The reverse side included details of the APO-go helpline, an out-of-hours telephone number and the company name, address and contact details. The Panel did not consider that the business cards were misleading as to the status of the nurse advisors. No breach of Clause 7.2 was ruled.

The Summary of Services booklet stated that the programme was non promotional and offered as a service to medicine. The Panel was unsure what was meant by the use of the term 'non promotional'. The service was linked to the use of APO-go such that the Panel considered that it was, in effect, offered as a package deal. The Panel noted

that Clause 18.1 did not prevent the offer of package deals whereby the purchaser of particular medicines received with them other associated benefits provided that the transaction as a whole was fair and reasonable and the associated benefits were relevant to the medicines involved. The Panel considered that there was no information before it to suggest that the package of care offered by Genus was a gift, benefit in kind or a pecuniary advantage given or offered to a health professional as an inducement to prescribe, supply, administer, recommend, buy or sell APO-go. No breach of Clause 18.1 was ruled.

Clause 18.4 related to the provision of medical and educational goods and services. The supplementary information to that clause stated that the goods or service must not bear the name of any medicine. Given that the service offered by Genus bore the name of APO-go and was inextricably linked with the product, it could not be considered to be a medical or educational good or service. It was not covered by Clause 18.4 and thus no breach of Clause 18.4 was ruled.

The Panel noted that the Summary of Services booklet detailed the nurse support programme. The double page centre spread headed 'Background' referred, *inter alia*, to the Parkinson disease guidelines issued by NICE. Extracts from those guidelines were quoted in the booklet and referred to PDNSs and the essential skills of a PDNS. The booklet stated that the initiation of apomorphine should be restricted to expert units with the availability of a home monitoring system by a suitably trained heath professional such as a PDNS. Under the heading 'Nurse Advisor in APO-go' it was stated that in order to assist the NHS to implement the NICE guidelines, Genus had established a network of nurse advisors to assist in various aspects of APO-go therapy. The stated skill set of a PDNS was referred to. In the Panel's view it was not unreasonable that some readers might assume that all of the nurse advisors provided by Genus were PDNSs which was not so. Under the same heading, a bulletin from the Royal College of Nurses entitled 'Specialist Nurses "targeted" to cut costs' was referred to which strengthened the impression that the nurse advisors in APO-go were specialist nurses ie PDNSs. The Panel considered that the booklet was not sufficiently clear with regard to the qualifications and status of the APO-go nurse advisors. The Panel ruled a breach of Clause 7.2.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel, however, did not consider that the matter was such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

Complaint received **22 September 2010**

Case completed **26 January 2011**

CASE AUTH/2361/10/10

ANONYMOUS EX-EMPLOYEE v CEPHALON

Inappropriate hospitality and in-house feedback document

An anonymous ex-employee complained that, in 2009, Cephalon provided inappropriate hospitality to delegates it had sponsored to attend a European congress in Lisbon. The complainant referred to a congress feedback document which, *inter alia*, stated 'we then went to a few bars and to a club until 3am – a few good photos to prove it!!!'. The complainant also submitted that the document implied that sublingual Effentora (fentanyl) had been promoted before the marketing authorization for such use had been granted. The complainant further noted that the document referred to the differentiation between Effentora and ProStrakan's Abstral (fentanyl) and alleged that implied comparisons had been made that were incapable of substantiation and potentially misleading. The complainant considered that the document, which had not been approved as briefing material, gave a very poor impression; the representatives involved did not appear fully conversant with the Code and had failed to maintain high standards. Breaches of the Code were alleged, including a breach of Clause 2.

The detailed response from Cephalon is given below.

The Panel noted that the complaint had been prompted by an internal feedback document detailing the aspects of a congress in Lisbon to which Cephalon had sponsored thirteen health professionals. The document made much of the hospitality provided to customers with phrases such as 'Dinner was fantastic', 'great night again', 'took them clubbing' and 'we then went to a few bars and to a club until 3am – a few good photos to prove it!!!'. The document concluded with 'All the customers were really looked after and spoke positively about Effentora – lets make sure they start Rxing now!'. The Panel noted that the feedback document had been distributed within Cephalon including to sales teams. The Panel considered that recipients would read the document and assume that it represented accepted practice with regard to hospitality. The Panel considered that the feedback document was, in effect, briefing material which advocated a course of action which would be likely to lead to a breach of the Code. A breach of the Code was ruled.

The Panel considered that the impression given by the feedback document of a general party atmosphere, recorded on camera, was wholly unacceptable. In that regard the Panel considered that high standards had not been maintained. The Panel further considered that the references to the hospitality provided were such as to bring discredit upon the industry. Breaches of the Code were ruled including a breach of Clause 2.

Receipts from various restaurants and bars were provided. Restaurant costs ranged from £43 to £57/head. One bill was inflated as only 15 people attended but the 20 covers booked had to be paid for. Early morning bar bills included the purchase of spirits and cocktails. On one evening the group had watched fire-eaters and the feedback document implied that the evening finished at 3am.

Overall, the Panel considered that, on a cumulative basis, the hospitality provided went beyond subsistence. It appeared that the hospitality was not secondary to the main purpose of being in Lisbon ie to attend a congress. That one of the Cephalon employees photographed the group added to the overall impression of a social event and general party mood. The Panel noted that the Code stated that the impression created by the arrangements for any meeting must always be kept in mind. The Panel considered that the hospitality had been excessive and in that regard high standards had not been maintained. The Panel further considered that the arrangements were such as to bring discredit upon the industry. Breaches of the Code were ruled including a breach of Clause 2.

The Panel considered that Cephalon's representatives had not maintained a high standard of ethical conduct and in that regard it ruled a breach of the Code.

The Panel noted its rulings above and considered that Cephalon had not complied with all applicable codes. A breach of the Code was ruled.

With regard to compliance, the Panel noted that Cephalon had submitted that it had provided significant training to all staff in the past 2 years. There was no evidence to show that staff had not been trained on the Code. No breach of the Code was ruled.

The Code required companies to be responsible for the actions of their representatives if these were within the scope of their employment even if they were acting contrary to the instructions which they had been given. In that regard Cephalon had clearly taken responsibility for its representatives. No breach of the Code was ruled.

The Panel noted that the feedback document stated that at the Cephalon-sponsored symposium it was announced that sublingual use of Effentora had been approved in Europe. Cephalon had submitted that there was no evidence of this and that the licence for sublingual administration was not granted until three months later. Sublingual placement was referred to in the symposium but the Panel did not consider that this was necessarily unacceptable; the

legitimate exchange of medical and scientific information during the development of a medicine was not prohibited providing any such information or activity did not constitute promotion. Regardless of what was said in the symposium the Panel considered that the complaint was about the conduct of Cephalon's representatives because at the outset the complainant stated that he was surprised at some of the things that other hospital specialists got away with and how the managers encouraged it. The Panel considered that there was no evidence to show that the representatives had promoted Effentora in a manner inconsistent with the particulars listed in its summary of product characteristics. No breach of the Code was ruled.

The Panel noted that the feedback document stated that one of the delegates asked for clear differentiation between Effentora and Abstral and that this was 'a good opportunity to sell'. The complainant alleged that this implied that comparisons were made that were potentially misleading and which could not be substantiated. The Panel noted that there was no information as to what the representatives had said to the delegate in response to his request. On that basis the Panel ruled no breach of the Code.

An anonymous complainant writing as an 'Ex-Cephalon hospital specialist', complained about the hospitality offered by Cephalon (UK) Limited to delegates it had sponsored to attend a European pain congress in Lisbon in September 2009.

COMPLAINT

The complainant submitted that until recently he was a hospital specialist at Cephalon. He was sometimes surprised at some of the things that other hospital specialists got away with, and how the managers encouraged it.

The complainant provided a copy of a congress note from his time at Cephalon and submitted that some of the behaviour referred to in the document did not do him, other good representatives at the company or the industry any favours.

The complainant understood that the document was not approved as representative briefing material, which it should have been since it referred to a product and its indication; it bore no reference number or date. The complainant alleged a breach of Clauses 15.9 and 15.10.

The complainant further submitted that the meeting took place before the sublingual use of Effentora (fentanyl) had been approved and so this would have been promotion outside the licence, in breach of Clause 3.2.

The complainant noted that the document included a comment about differentiation between Effentora and ProStrakan's Abstral (fentanyl), 'so a good opportunity to sell'. The complainant stated that hospital specialists were only trained to refer enquirers to the relevant summary of product characteristics (SPC) if asked about Abstral. Implied comparisons were made that were incapable of substantiation and potentially misleading in breach of Clauses 7.1 and 7.2.

The complainant was surprised to read 'We then took them out to the hotel until 2am and then [a named Cephalon employee] took them clubbing until 4am!'. This was surely inappropriate hospitality in breach of Clause 19.1, the representatives involved obviously failed to maintain high standards (Clause 15.2) and did not appear fully conversant with the requirements of the Code (Clause 16.1). The impression created brought discredit upon the industry in breach of Clause 2. The company had failed to comply with all applicable codes, laws and regulations, in breach of Clause 1.7.

Not only was such inappropriate hospitality extended once, but a second time according to the document: 'We then went to a few bars and to a club until 3am – a few good photos to prove it!!!'. Here again was inappropriate hospitality in breach of Clause 19.1, the representatives concerned failed to maintain high standards (Clause 15.2) and did not appear fully conversant with the requirements of the Code (Clause 16.1) and the impression created brought discredit upon the industry in breach of Clause 2. The company had failed to comply with all applicable codes, laws and regulations in breach of Clause 1.7.

When writing to Cephalon, the Authority asked it to respond in relation to Clause 9.1 in addition to the clauses cited by the complainant.

RESPONSE

Cephalon noted that the complaint concerned arrangements for a meeting in Lisbon in September 2009. Despite having ample opportunity to raise concerns through company procedure, the complainant had waited 13 months to complain to the Authority. This made any subsequent investigation more difficult and meant that any necessary corrective actions that might have been identified could not be implemented. In this regard, the complainant had failed in his duty to both the company and the Code by not raising his concerns earlier.

Cephalon submitted that the feedback document provided by the complainant was a memorandum drafted and sent by an executive hospital specialist who attended the meeting. The company had been able to verify certain facts, in particular relating to expenses incurred at the meeting, but much of its understanding of the events relied on the memories of those who attended.

Arrangements for the meeting

Cephalon stated that it sponsored thirteen health professionals to attend the meeting and they were accompanied by a senior product manager (SPM), an

executive hospital specialist (EHS) and a hospital specialist (HS). However, the SPM returned to the UK for another meeting on the morning of Thursday, 10 September and so was only present for the evening of Wednesday, 9 September.

The delegates were sponsored on the basis of their experience in treating breakthrough cancer pain. The sponsorship consisted of economy flights (£188.28/head), registration to the congress (£7,000 for all attendees, registration costs varied depending on membership status), three nights' accommodation in a four star hotel in central Lisbon (£172/night) and subsistence.

Unfortunately, although the standard operating procedure (SOP) in place at the time required certification for such meetings and there were job bags for the international meetings arranged six months before and after this meeting, no job bag could be found for the meeting arrangements. Cephalon accepted that this omission was in breach of Clause 14.2 of the Code.

The delegates arrived on separate flights on Wednesday, 9 September and a number met for dinner in the hotel that evening. Although the company did not have a list of attendees at that meal, the recollection of the employees who were interviewed separately suggested that there were between seven and nine health professionals plus the three Cephalon employees (although both the EHS and SPM stated that they had arrived during the meal). Before dinner, HS and some of the delegates had a pre-dinner drink in the hotel bar. HS's expenses show that €44.20 [£39 approximately] was spent, which was in keeping with a single drink for each attendee. At the dinner, the recollection was that three bottles of wine and some bottles of water were ordered with the meal and that following the meal, some of the party returned to the bar for drinks and coffee. The expenses of HS showed costs in line with this (€153 [£134 approximately] for the wine/water and €85.50 [£75 approximately] for the post dinner drinks). The total cost of the meal and drinks was between €49 and €58 [£43 – £51 approximately] per person depending on whether the total was ten or twelve attendees. The approximate exchange rate in September 2009 was €1.14 = £1.

On Thursday, 10 September, as part of the Congress, a Cephalon sponsored symposium took place from 6.30 – 8.30pm and was followed by a dinner at a restaurant for all of the attendees. This was arranged and paid for by Cephalon's EU headquarters at a cost per head of €65 [£57 approximately]. The feedback stated that 'We took [the delegates] out to [a named] hotel until 2am and then [a named Cephalon employee] took them clubbing until 4am'. EHS submitted an expenses for four drinks at the hotel where some of the health professionals were staying, costing €24 [£21 approximately] at 12.37am and HS submitted a receipt for three drinks costing €20.50 [£18 approximately] at 1.11am, consistent with them returning to the hotel for a drink, but there was no evidence in either employee's expenses to corroborate the second part of the statement regarding 'clubbing'.

On the Friday, there was a dinner held for the Cephalon UK sponsored group. This had been arranged and booked in advance by Cephalon UK. The meal cost €42 [£37 approximately] per person excluding drinks and the table was booked for twenty people, however only fifteen attended. The party walked from the hotel to the restaurant. The meal consisted of a tapas style menu and fourteen alcoholic drinks and two soft drinks were ordered. The service during the meal was very slow and at the end there was a discussion between the restaurant and EHS/HS because although only fifteen had eaten, the restaurant demanded full payment for twenty. This further delayed departure. The bill was paid at 1.13am and the party left shortly afterwards.

Both EHS and HS stated that the party left the restaurant at around 1.15am and was unable to find taxis back to the hotel. According to EHS, they decided to walk, but got lost. Further, HS had stated that the party then split up and a small group went into a bar to ask for a taxi (EHS submitted a receipt for a tea and an iced tea) and a larger group, including HS, continued to a bar. The two groups then met up again later. Based on receipts, it appeared that HS went to two different bars, the second after the two groups had joined again. HS submitted receipts from the two bars. The quantity of drinks purchased was in keeping with a single drink per person. From there, they both stated that the group went back to the hotel. Although two bars were visited, this did not appear to constitute 'clubbing' in the accepted interpretation of the word.

In retrospect, EHS accepted that her description of the hospitality as written in the congress note was not completely correct and that she had embellished the facts. HS's statement about the Friday night was consistent with both the version of EHS and was supported by the expense reports.

With regard to the photographs referred to in the congress note, most were of Lisbon and some of EHS and HS. There were seven pictures of the health professionals and a further nine of some fire eaters who they saw on the Friday night. The pictures that included four health professionals appeared to be taken inside a bar. They did not suggest that excess alcohol had been consumed and appeared to show the group sat together having a drink.

Based on the receipts and expenses submitted by HS and EHS, the level of hospitality provided to the health professionals on Wednesday, Thursday and during the meal on Friday appeared to be reasonable and acceptable. On leaving the restaurant on Friday night, EHS had a receipt for a bar where a cup of tea and an iced tea were ordered. This did not seem inappropriate or excessive. HS submitted two receipts from separate bars. At each location, six alcoholic drinks and two waters were ordered which was in keeping with one drink per attendee.

Cephalon accepted that this exceeded the level of hospitality that should be provided, contrary to its SOP and in breach of Clause 19.1, and that HS failed to maintain high standards in breach of Clauses 15.2 and 9.1 of the Code.

Cephalon stated that it undertook regular training on the Code and ensured that all staff were conversant with its requirements. The company did not accept the alleged breaches of Clause 1.7 or 16.1.

While the level of hospitality following the dinner on the Friday night was greater than that which should have been provided, EHS had claimed that the feedback document was embellished and exaggerated the hospitality provided. This was supported by the expenses claims that were processed for EHS and HS. No complaints had been received from health professionals or other companies; rather a written testimonial from a health professional who attended the meeting congratulated the company on the professionalism of the arrangements and EHS and HS. Cephalon therefore did not believe that this represented a breach of Clause 2.

Review process for the feedback document

Cephalon was deeply concerned about how the 'feedback' document was drafted, reviewed and the fact that it was distributed within the organisation given its content.

The company did not believe that all internal communication to representatives constituted 'briefing material' and although this document referred to Effentora and the indication, it represented a sharing of information about a meeting rather than briefing materials. As such, the company did not consider that it required certification and therefore did not accept the alleged breaches of Clause 15.9 and 15.10 of the Code.

Investigation had shown that the draft feedback was sent by EHS to HS for comments and was minimally changed. It was then sent to SPM, who 'approved' it and instructed that it should be sent to the sales team, the regional sales managers, the national sales manager, the medical director, the general manager. It was a serious error of judgement and inexcusable that SPM did not realise that the feedback document contained claims of activities that were in breach of Cephalon policy and the Code. Any of the recipients should have identified the serious nature of the activities listed and taken the appropriate actions. However, only one regional sales manager, the medical director and the national sales manager had any reaction. The primary concern appeared to have been the issue of whether Effentora had received the sublingual licence; only the medical director queried the reported hospitality.

One regional sales manager stated during the course of the investigation that he did not read the document. However, once it became apparent that the document had not been fully approved he asked the medical director if the document should be withdrawn but received no reply. The regional sales manager also emailed SPM to ask whether the sublingual licence for Effentora had been granted. This prompted a corrective email to the sales team stating that Effentora was not licensed for sublingual use and that it must not be promoted. Any question that the team received on this matter had to be sent to medical information. The regional sales manager did not question the hospitality and related activities described in the document.

The national sales manager stated that he twice discussed his concerns about the content of the feedback document with the medical director who reassured him that he was taking action.

The medical director, who had subsequently left Cephalon, initially emailed one of the regional sales managers to ask if the feedback document had been sent out to anyone else, and stated that it would need head office approval before circulation. The medical director also stated that the feedback document was a 'great initiative', but did not raise any concern about the content. Nearly six hours later he emailed the national sales manager, the general manager and SPM to express his concerns over some of the comments made and state that the company should be 'careful since this document would clearly be seen as implying inappropriate activities if it were to reach the PMCPA'. The medical director did not suggest that any action should be taken, or an investigation initiated; he merely stated that 'obviously we're doing things to improve understanding of the Code and compliance. Any further suggestions?' The general manager could not recall the email, or taking any action having received it, and there was certainly no written reaction from him or the other recipients. It appeared, from discussions with the individuals involved and the review of email communication, as well as the general manager's own recollection of the matter, that the medical director took no further action in response to this matter. He had, however, emailed the feedback document to his personal email address immediately after his email in which he had expressed his concerns.

Although the general manager was also copied on the email distributing the feedback, he could not remember reading it. Certainly there was no email from him about the subject following the distribution. He also could not remember the level of hospitality ever being raised as an issue by the medical director or any of his team. When he saw the complaint, he was shocked by the claims and if he had known about this previously, he was certain that he would have immediately initiated an investigation and further actions as appropriate. However, as general manager, he accepted full responsibility for the actions of his team.

Cephalon UK had made significant progress in driving compliance as a core value and had provided significant training to all staff in the past two years. New SOPs had been implemented, including a new

meetings and hospitality SOP. Although this programme had been affected by the turnover in staff, particularly in the medical team, every member of staff recognised the importance of compliance and strove to achieve this.

Mention of the sublingual licence for Effentora at the Cephalon symposium

The Cephalon symposium at the Lisbon meeting was held on Thursday, 10 September from 6.30 – 8.30pm and Cephalon provided copies of the presentation entitled 'New Drug Delivery Technology Applied to Fentanyl: The Pharmacodynamics and Pharmacokinetics of Effentora' delivered by a senior company scientist. Data was presented comparing buccal vs sublingual placement of the tablets. This showed that the sublingual route was at least as good as the buccal route and this data formed the evidence for the application for sublingual use. Aside from the feedback document, Cephalon was not aware of any evidence that it was stated during the symposium that Effentora was now licensed for sublingual use in EU. Indeed, the licence for sublingual administration was not granted until December 2009.

As soon as the feedback document was circulated, as described above, it was identified that the licence for sublingual administration of Effentora had not been granted. Consequently the field force was reminded that any discussion about sublingual administration would be off-label and that any enquiry on this should be sent to medical information. Cephalon did not believe that there was any evidence of promotion of sublingual Effentora and therefore no breach of Clause 3.2.

Cephalon submitted that the allegation that the statement in the feedback 'there is a comment about differentiation between Effentora and Abstral "so a good opportunity to sell"' implied that misleading claims were then made was spurious and unsubstantiated and as such there could be no breach of Clauses 7.1 or 7.2.

Summary

The events in Lisbon in September 2009 demonstrated an error of judgement of HS, who was no longer with the company. In failing to maintain the high standard expected of him, he let himself and the company down and his actions were in breach of Clauses 9.1 and 15.2.

A review of expenses for all attendees at international meetings in the past year showed that all were in line with Cephalon's policy of hospitality which suggested that there was a high level of compliance in this area within the company generally.

EHS who wrote the feedback document had subsequently stated that the claims about 'going clubbing' were exaggerated and false. In addition, the failure by SPM to properly review the feedback note before it was circulated was inexcusable. Both staff members were currently undergoing disciplinary action.
The failure to take corrective action when the 'feedback' was sent to a variety of managers was also unacceptable and was the subject of internal review and possible disciplinary action. This represented a failure to maintain high standards and a breach of Clause 9.1.

Cephalon also submitted that the failure to certify the arrangements for the meeting was in breach of Clause 14.2.

Cephalon denied breaches of Clauses 1.7, 3.2, 7.1, 7.2, 15.9, 15.10 or 16.1 as alleged by the complainant.

The facts of this case showed failings with regard to the level of hospitality provided to health professionals. However, Cephalon believed that the description in the feedback document of the actual hospitality provided was exaggerated, and it did not believe that the actual hospitality provided brought the industry into disrepute. There had been no complaints about Cephalon's activities at this meeting from other companies, or from health professionals. In fact, the company received a note of thanks from a physician in the sponsored group. Accordingly, Cephalon did not believe that this warranted a breach of Clause 2.

PANEL RULING

The Panel noted that the complainant was anonymous and uncontactable and that, as set out in the introduction to the Constitution and Procedure, complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and like all complaints were judged on the evidence provided by the parties.

The Panel noted that the complaint had been prompted by an internal feedback document detailing the aspects of the EFIC pain congress in Lisbon to which Cephalon had sponsored thirteen health professionals. The document made much of the hospitality provided to customers with phrases such as 'Dinner was fantastic', 'great night again', 'took them clubbing' and 'we then went to a few bars and to a club until 3am – a few good photos to prove it!!!'. The document concluded with 'All the customers were really looked after and spoke positively about Effentora – lets make sure they start Rxing now!'. The Panel noted that the feedback document had been distributed within Cephalon including to sales teams. The Panel considered that recipients would read the document and assume that it represented accepted practice with regard to hospitality. The Panel considered that the feedback document was, in effect, briefing material which advocated a course of action which would be likely to lead to a breach of the Code. A breach of Clause 15.9 was ruled.

The Panel considered that the impression given by

the feedback document of a general party atmosphere, recorded on camera, was wholly unacceptable. In that regard the Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel further considered that the references to the hospitality provided were such as to bring discredit upon the industry. A breach of Clause 2 was ruled.

The receipts from the various restaurants visited showed that on Wednesday evening a total bill of €588.70 (£516.40 approximately) was spent on food and drink (€306 on food and €282.70 on beverages) in the hotel where the delegates were staying. The approximate amount spent per head was thus £43 – £51 depending on whether 10 or 12 people had been present. On Thursday evening delegates attended a Cephalon-sponsored symposium and then had dinner in a restaurant at a cost of approximately £57/head. After the dinner two of the representatives returned to the hotel where some of the delegates were staying and expense receipts showed early morning bar bills which included the purchase of spirits and cocktails. On Friday evening the restaurant bill for 15 attendees was approximately £831 ie £55.40 per head. The restaurant had, however, demanded payment for the 20 covers booked and the bill appeared to show that the meal (excluding drinks) was to cost approximately £36.80 per head. On leaving the restaurant the group had walked back to the hotel, got lost, visited two bars (the receipts submitted were modest, approximately £30) watched fire-eaters and the feedback document implied that the evening finished at 3am.

Overall, the Panel considered that, on a cumulative basis, the hospitality provided went beyond subsistence. It appeared that the hospitality was not secondary to the main purpose of being in Lisbon ie to attend a European congress. That one of the Cephalon employees photographed the group added to the overall impression of a social event and general party mood. The Panel noted that the Code stated that the impression created by the arrangements for any meeting must always be kept in mind. The Panel considered that the hospitality had been excessive and a breach of Clause 19.1 was ruled. In that regard, high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel further considered that the arrangements were such as to bring discredit upon the industry. A breach of Clause 2 was ruled.

The Panel considered that Cephalon's representatives had not maintained a high standard of ethical conduct and in that regard it ruled a breach of Clause 15.2.

With regard to compliance, the Panel noted that Cephalon had submitted that it had provided significant training to all staff in the past 2 years. There was no evidence to show that staff had not been trained on the Code. No breach of Clause 16.1 was ruled.

The Panel noted its rulings above and considered that Cephalon had not complied with all applicable codes. A breach of Clause 1.7 was ruled.

The Panel noted that the complainant had alleged a breach of Clause 15.10. That clause, however, set out a principle of the Code ie that companies were responsible for the actions of their representatives if these were within the scope of their employment even if they were acting contrary to the instructions which they had been given. In that regard Cephalon had clearly taken responsibility for its representatives. No breach of Clause 15.10 was ruled.

The Panel noted that the feedback document stated that at the Cephalon-sponsored symposium it was announced that sublingual use of Effentora had been approved in Europe. Cephalon had submitted that there was no evidence of this and that the licence for sublingual administration was not granted until three months later on 10 December. Sublingual placement was referred to in the symposium but the Panel did not consider that this was necessarily unacceptable. The supplementary information to Clause 3 of the Code stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited providing any such information or activity did not constitute promotion which was prohibited under Clause 3 and any other clause. Regardless of what was said in the symposium the Panel considered that the complaint was about the conduct of Cephalon's representatives because at the outset the complainant stated that he was surprised at some of the things that other hospital specialists got away with and how the managers encouraged it. The Panel considered, however, that there was no evidence to show that the representatives had promoted Effentora in a manner inconsistent with the particulars listed in its summary of product characteristics. No breach of Clause 3.2 was ruled.

The Panel noted that the feedback document stated that one of the delegates asked for clear differentiation between Effentora and Abstral and that this was 'a good opportunity to sell'. The complainant alleged that this implied that comparisons were made that were potentially misleading and which could not be substantiated. The Panel noted that there was no information as to what the representatives had said to the delegate in response to his request. On that basis the Panel ruled no breach of Clauses 7.1 and 7.2.

Complaint received **5 October 2010**

Case completed **1 December 2010**

ANONYMOUS v BAYER SCHERING PHARMA

Conduct of representatives

An anonymous complainant, writing as 'a very disappointed nurse', alleged that, at a meeting on sexual health, two named Bayer Schering Pharma representatives, were, *inter alia*, poorly informed about contraception and generally unprofessional, in breach of the Code.

The complainant stated that both representatives gave wrong information from a study which estimated the relative cost-effectiveness of various reversible long-term hormonal contraceptives in the UK which was highly misleading. It was also alleged that the representatives had provided an out-of-date question and answer booklet about Yasmin. The complainant alleged that the representatives' overall knowledge about contraception was very poor; they were unable to answer the complainant's questions.

The detailed response from Bayer Schering Pharma is given below.

The Panel noted that the complainant was anonymous and non contactable. Complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and, like all complaints, judged on the evidence provided by the parties. The complainant had submitted no material to support his/her position.

The Panel noted that Bayer Schering Pharma stated that the meeting, as identified by the complainant, had not taken place. A meeting had taken place in a different area on the day after that mentioned by the complainant. This was attended by the representatives in question. Bayer Schering Pharma had responded in relation to that meeting.

The Panel noted that complaints about promotional meetings were within the scope of the Code. The complainant had identified the representatives by name. The parties' submissions differed on all other points including the date and location of the meeting. The meeting identified by Bayer Schering Pharm may indeed have been that about which the complainant was concerned however it was impossible to clarify the situation. The Panel noted that the complainant bore the burden of proof and considered that he/she had not established their case on the balance of probabilities. No breach was ruled.

An anonymous complainant, writing as 'a very disappointed nurse', alleged that, at a meeting on sexual health, two named Bayer Schering Pharma representatives, were, *inter alia*, poorly informed about contraception and generally unprofessional, in breach of the Code.

COMPLAINT

The complainant stated that the representatives sponsored a sexual health stand meeting. Details of the area and date were provided. The complainant stated that both representatives gave wrong information from a study looking at the relative cost-effectiveness of Depo-Provera, Implanon and Mirena in reversible long-term hormonal contraception in the UK which was highly misleading. (This study appeared to be Varney and Guest 2004).

The complainant alleged that the representatives' overall knowledge about contraception was very poor and they were highly unprofessional, laughing and joking about private matters within the complainant's ear shot and that of other health professionals which was very inappropriate.

The complainant stated that an out-of-date question and answer booklet about Yasmin was provided. The representative was unable to pronounce ethinylestradiol and drospirenone and they were unable to answer the complainant's questions.

The complainant found both representatives very disappointing as previous dealings with Bayer Schering had always been very positive.

When writing to Bayer Schering Pharma the Authority asked it to respond in relation to Clauses 7.2, 9.1, 15.1 and 15.2 of the Code.

RESPONSE

Bayer Schering Pharma submitted that no meeting took place in the area on the date specified by the complainant. However, the two representatives did go to a meeting in a different area on the day after that mentioned by the complainant which was attended by 125 health professionals; a mixture of nurses and doctors, from the generalist and specialist settings.

As the complainant had not given any details of the alleged misleading information, Bayer Schering Pharma stated it was unable to respond specifically to his/her concern. The company did not cite Varney and Guest in any of its promotional materials, nor was it supplied to representatives. Neither representative had ever talked about this paper to customers and it was not on the list of materials provided at the meeting.

Bayer Schering Pharma was confident of the representatives' general knowledge of the therapy area as well as their specific product knowledge and noted that the complainant had not provided an example of a question that could not be answered.

Both could pronounce the names of products. Details of the representatives' training and its validation were provided. Both had passed the ABPI's Medical Representatives Examination. Bayer Schering Pharma stated that the professionalism of either representative had never previously been questioned. Both denied laughing and joking about private matters within earshot of health professionals or having such a conversation. None of the 96 respondents providing feedback expressed any of the concerns raised by the complainant.

There was currently no Yasmin question and answer document in active promotional use. Neither representative had any Yasmin-related question and answer document. It was not on the list of materials supplied for the meeting.

In summary, Bayer Schering Pharma did not believe there were grounds to uphold any of the allegations. It denied that it had provided misleading information contrary to Clause 7.2, there was ample evidence for the adequate training and good conduct of its representatives as required by Clauses 15.1 and 15.2 and the high standards required by Clause 9.1 had been maintained.

PANEL RULING

The Panel noted that the complainant was anonymous and non contactable and that, as set out in the introduction to the Constitution and Procedure, complainants had the burden of proving their complaint on the balance of probabilities.

Anonymous complaints were accepted and, like all complaints, judged on the evidence provided by the parties. The complainant had submitted no material to support his/her position. The Panel also noted the difficulty of dealing with complaints based on one party's word against the other.

The Panel noted that Bayer Schering Pharma stated that no such meeting as identified by the complainant had taken place. A meeting had taken place in a different area on the day after that mentioned by the complainant, attended by the representatives in question. Bayer Schering Pharma had responded in relation to that meeting and denied any breach of the Code.

The Panel noted that complaints about promotional meetings were within the scope of the Code. The complainant had identified the representatives by name. The parties' submissions differed on all other points including the date and location of the meeting. The meeting identified by Bayer Schering Pharma might indeed have been that about which the complainant was concerned however it was impossible to clarify the situation. The Panel noted that the complainant bore the burden of proof and considered that he/she had not established their case on the balance of probabilities. No breach of Clauses 7.2, 9.1 and 15.2 was ruled.

Complaint received **18 October 2010**

Case completed **5 November 2010**

ANONYMOUS v SANOFI-AVENTIS

Advance notification document: Pipeline Update

An anonymous, non contactable complainant alleged that a document 'Oncology Product Pipeline Update' was provided to Sanofi-Aventis representatives so that they could promote and discuss with customers upcoming new products which did not have licences. The front of the document stated that it was 'Advanced Notification' and intended for national horizon scanning organisations, NHS managers and other professionals with a responsibility for the planning and commissioning of cancer services.

The detailed response from Sanofi-Aventis is given below.

The Panel noted that the document referred to five medicines and for each included details of; anticipated marketing indication, licence status in EU/UK, administration, replacement for/addition to other treatment options, estimated cost per patient course, service implications, eligible patients, evidence base and NICE status. No actual acquisition costs were given as these were yet to be determined. The document stated that the annual cost of each medicine was expected to be in line with other products including recently launched innovative cancer therapies.

The document was to be used by the oncology healthcare specialists. Sanofi-Aventis submitted that this team did not discuss or promote licensed medicines.

The email accompanying the document when it was distributed to the oncology sales representatives stated that the document was 'for information internally only'. The Panel noted that the document had been distributed in error to the representatives and they had had to return it.

The Panel considered that on the information before it the representatives had not been instructed to promote unlicensed medicines. The Panel considered that it was not unacceptable to send the document to the representatives but queried why, in some instances more than one copy had been sent when the information was for internal use only. Multiple copies might imply that copies had been provided to give to others and given the prohibition on the promotion of unlicensed medicines, the Panel considered that it would have been helpful if the covering note had clearly stated that the representatives must not discuss the document with anyone upon whom they called. However, on the evidence before it the Panel did not consider that representatives had promoted unlicensed indications or unlicensed products. No breach including of Clause 2 was ruled.

During its consideration of this case the Panel noted that although there was no complaint about the intended use of the document, it was nonetheless extremely concerned about its content and considered that Sanofi-Aventis would be well advised to ensure that it met all of the elements of the relevant supplementary information to the Code.

An anonymous, non contactable complainant complained about a document 'Oncology Product Pipeline Update' provided to Sanofi-Aventis representatives.

The front of the document stated that it was 'Advanced Notification' and intended for national horizon scanning organisations, NHS managers and other professionals with a responsibility for the planning and commissioning of cancer services.

COMPLAINT

The complainant stated that the document was given to sales representatives in oncology to promote and discuss with customers upcoming new products which did not have licences.

When writing to Sanofi-Aventis the Authority asked it to respond in relation to Clauses 2, 3.1, 3.2 and 9.1 of the Code.

RESPONSE

Sanofi-Aventis stated that the document was prepared for exclusive use by the team of oncology healthcare specialists who had a specific role in working with the cancer networks providing advance information to those in the NHS responsible for making policy decisions on budgets, providing them with an opportunity to prepare for medicines which might significantly affect their level of expenditure during the next few years. The purpose of the document was clearly described as an item to provide advanced notification of new products. Sanofi-Aventis submitted that it met the requirements of Clauses 3.1 and 3.2.

Unfortunately, following an administrative error, the oncology sales representatives were each sent between one and three copies of the document on 23 September 2010. No formal briefing document was included but an enclosed note stated that the document was for internal use only. Although the oncology sales representatives received this item, albeit in error, they were not directed to use it, were not trained in its use, and were specifically told that it was provided only for their own information. On this basis, Sanofi-Aventis did not consider that there was any intention or direction to the sales team to

use the item for promotion; the opposite being implied from the cover note. As such, Sanofi-Aventis did not consider there to be any direction to use the material in a way that would result in a breach of Clauses 3.1 or 3.2.

Sanofi-Aventis became aware of the distribution error at a regional sales meeting on 14 October and immediately initiated a withdrawal procedure, as well as launching an internal investigation to determine how the error occurred. This process was initiated before the complaint was received. Withdrawal had been completed, with written confirmation of the return of the document from all oncology sales representatives.

Sanofi-Aventis acknowledged that there was an error in distributing the document to sales representatives, but considered that the company took very swift action to correct this error as soon as it became apparent, in keeping with the requirement to maintain high standards at all times. There was no breach of Clauses 2 and 9.1.

In response to a request for further information Sanofi-Aventis provided job descriptions for an oncology healthcare specialist and an oncology specialist representative. The oncology healthcare specialist team was formed in September 2010. A new job description that included the standard accountability for compliance with the Code which was standard for customer-facing teams was provided. There was no written briefing instruction for using the document at issue but the team was informed verbally how to use it in line with the statement in the front of the booklet. Oncology healthcare specialists did not currently discuss or promote licensed medicines.

PANEL RULING

The Panel noted that the complainant was anonymous and that, as set out in the introduction to the Constitution and Procedure, complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and like all complaints were judged on the evidence provided by the parties.

The Panel noted that the document referred to five medicines and for each included details of; anticipated marketing indication, licence status in EU/UK, administration, replacement for/addition to other treatment options, estimated cost per patient course, service implications, eligible patients, evidence base and the National Institute for Health and Clinical Excellence (NICE) status. No actual acquisition costs were given as these were yet to be determined. The document stated that the annual cost of each medicine was expected to be in line with other products including recently launched innovative cancer therapies.

The document was to be used by the oncology healthcare specialists. Sanofi-Aventis submitted that this team did not discuss or promote licensed medicines. The email accompanying the document when it was distributed to the oncology sales representatives stated that the document was 'for information internally only'. The Panel noted that the document had been distributed in error to the representatives and they had had to return it.

The Panel considered that on the information before it the representatives had not been instructed to promote unlicensed medicines. The Panel considered that it was not unacceptable to send the document to the representatives but queried why, in some instances more than one copy had been sent when the information was for internal use only. Multiple copies might imply that copies had been provided to give to others and given the prohibition on the promotion of unlicensed medicines, the Panel considered that it would have been helpful if the covering note had clearly stated that the representatives must not discuss the document with anyone upon whom they called. However, on the evidence before it the Panel did not consider that representatives had promoted unlicensed indications or unlicensed products. No breach of Clauses 3.1 and 3.2 were ruled. It thus followed that there was no breach of Clauses 2 and 9.1 and the Panel ruled accordingly.

During its consideration of this case the Panel was extremely concerned about the use of the document. It noted Sanofi-Aventis's submission that the document was intended to be used for advanced notification of new products which **might** significantly affect expenditure. The Panel noted the supplementary information to Clause 3.1, Advance Notification of New Products or Product Changes, stated that health authorities and health boards and their equivalents, trust hospitals and primary care trusts and groups needed to establish their likely budgets two to three years in advance in order to meet Treasury requirements and there was a need for them to receive advance information about the introduction of new medicines, or changes to existing medicines, which might significantly affect their level of expenditure during future years. It was noted that when this information was required, the medicines concerned would not be the subject of marketing authorizations (though applications would often have been made) and it would thus be contrary to the Code for them to be promoted. The supplementary information gave guidance on the basis on which such advance information could be provided including the requirement to include the likely cost and budgetary implications which **must** make significant differences to the likely expenditure of heath authorities etc.

In general the products detailed in the document were expected to have marketing authorizations in 2011 or 2012. In that regard, the Panel queried whether the information had been supplied early enough for some of the products such that budget holders etc could be reasonably expected to act upon it.

Information could only be supplied if the product

had a significant budgetary implication. For all of the medicines detailed it was stated that there would be, or there were likely to be, budgetary and resource implications. The budgetary implications, however, had not been quantified in the document in question.

The Panel was also concerned about the job description for the oncology healthcare specialists. It queried whether it was consistent with the supplementary information to Clause 3.1 of the Code and the need for such a role to be non promotional. In this regard the Panel noted that one of the key accountabilities was to ensure that the uptake of national guidance/guidelines was maximised for Sanofi-Aventis products and the need to contribute to regional sales goals.

There was no complaint about the intended use of the document. The Panel, however, considered that Sanofi-Aventis would be well advised to ensure that the document met all the elements of the relevant supplementary information to Clause 3.1. The Panel requested that its serious concerns be drawn to Sanofi-Aventis' attention.

Complaint received **19 October 2010**

Case completed **5 November 2010**

CASE AUTH/2374/12/10

ANONYMOUS v PFIZER

Failure to sit ABPI Medical Representatives Examination

The Authority received an anonymous complaint that Pfizer did not require some of its regional account directors to sit and pass the ABPI Medical Representatives Examination. The regional account directors saw NHS customers and discussed brand strategic position. The complainant alleged that this was potentially in breach of the Code.

The detailed response from Pfizer is given below.

The Panel noted that the job description for a regional account director provided by the complainant differed from that provided by Pfizer. Neither document was dated. The role purpose in the document provided by the complainant was to maximise the performance of accounts through the development and execution of the strategic health economy plan incorporating specialist network plans. The role purpose in the document provided by Pfizer referred to directing, leading and motivating local account managers to implement customer implementation strategy/plans and brand strategy/POAs through functional excellence in account management with the support of sales [department] in local health economies; by managing regional accounts (strategic health authorities and larger primary care trusts) directly and by influencing opinion-formers on regional NHS topics. The Pfizer document included as key accountabilities, *inter alia*, participation as a member of a cross functional team to achieve business objectives and the delivery of sales targets within the plan through the local account manager and corresponding sales managers for the specific local health economies within the plan. The regional account directors were required, *inter alia*, to have strong negotiation/selling skills and to be able to influence external customers.

The Panel noted that the Code required the Medical Representatives Examination to be taken by representatives whose duties comprised or included one or both of 'calling upon doctors and/or dentists and/or other prescribers' and 'the promotion of medicines on the basis, *inter alia*, of their particular therapeutic properties'. The Code defined a representative as someone who called on members of the health professions and administrative staff in relation to the promotion of medicines. In the Panel's view such people would often have job titles other than 'representative'. Promotion was any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription, supply, sale or administration of its medicines.

The Panel considered that the role of a regional account director met the broad definition of a representative. The Panel noted Pfizer's submission that the regional account directors did not promote medicines on the basis of their therapeutic properties nor did they discuss efficacy or safety. It thus appeared that other aspects of a medicine, such as cost could be discussed. Although the regional account directors called upon prescribers in their role as business managers, the Code did not make such a distinction. In the Panel's view if a company representative called upon a prescriber in association with the promotion of medicines then that representative would need to pass the Medical Representatives' Examination. Two of the regional account directors had been in post for 2 years and had not taken the examination as required. Thus the Panel ruled a breach of the Code.

The Authority received an anonymous complaint that Pfizer Limited did not require some of its customer facing employees to sit and pass the ABPI Medical Representatives Examination.

COMPLAINT

The complainant queried why Pfizer's regional account directors were exempt from doing the ABPI Medical Representatives Examination. The regional account directors saw NHS customers and discussed brand strategic position. The complainant alleged that this was potentially in breach of the Code.

The Authority asked Pfizer to respond in relation to Clause 16.4 of the Code.

RESPONSE

Pfizer explained that its regional account directors met customers who were not doctors, dentists or other prescribers and did not promote medicines on the basis, *inter alia*, of their particular therapeutic properties. The only customers they saw were senior business managers in the NHS. Some of these customers might have a prescribing background, however a regional account director would meet a customer in his/her capacity as a business manager, typically a primary care trust or strategic health authority chief executive or directors of finance, public health, commissioning or strategy.

The regional account director would never promote a brand to a customer, even if that customer was also a prescriber. If the customer asked about Pfizer's medicines, the regional account director would politely decline to discuss the clinical efficacy or safety profile of a product and would offer to bring in an appropriate colleague who could have a brand discussion. Pfizer had trained and guided regional account directors to behave in a responsible, ethical and professional manner which

complied with the Code and ensured high standards at all times.

Given the above, Pfizer had not made the ABPI Medical Representatives Examination a requirement of the regional account director role. Pfizer provided details of the examination status of the nine regional account directors. The seven that had passed the examination had been required to do so in a prior role which promoted medicines. The team of regional account directors was predominantly comprised of colleagues had started their careers as representatives and progressed to a senior management position. To add business and customer management experience from other industries, two regional account directors had been recruited from outside the pharmaceutical industry.

Pfizer submitted that the regional account director role profile demonstrated that a key part of the role was the internal development of a regional business strategy in response to customer needs and the local environment. The nine regional account directors managed a team of sixty-four local account managers who were responsible for leading the business strategy at a local level in their local health economies. The local account managers predominantly called on payers but they might call upon prescribers and enter into a brand promotional conversation. Therefore, all local account managers had passed the ABPI Medical Representatives Examination.

Pfizer considered that as the regional account directors did not call upon doctors, dentists and/or other prescribers and did not promote medicines on the basis, *inter alia*, of their particular therapeutic properties, they were not required to pass the ABPI examination and, in that regard, it denied a breach of Clause 16.4 of the Code.

In response to a request for clarification about whether the regional account directors called upon doctors, dentist or prescribers, Pfizer stated that regional account directors met customers in their capacity as strategic health authority chief executives, finance directors, directors of public health, directors of commissioning or strategy directors. Some might have a clinical background or prescribing background but were consulted in their role as business managers and not as clinicians or prescribers.

PANEL RULING

The Panel noted that the job description for a regional account director provided by the complainant differed from that provided by Pfizer. Pfizer had not addressed this in its response. Neither document was dated. The role purpose in the document provided by the complainant was to maximise the performance of accounts through the development and execution of the strategic health economy plan incorporating specialist network plans. The role purpose in the document provided by Pfizer referred to directing, leading and motivating local account managers to implement customer implementation strategy/plans and brand strategy/POAs through functional excellence in account management with the support of sales [department] in local health economies; by managing regional accounts (strategic health authorities and larger primary care trusts) directly and by influencing opinion-formers on regional NHS topics. The Pfizer document included as key accountabilities, *inter alia*, participation as a member of a cross functional team to achieve business objectives and the delivery of sales targets within the plan through the local account manager and corresponding sales managers for the specific local health economies within the plan. The regional account directors were required, *inter alia*, to have strong negotiation/selling skills and to be able to influence external customers.

The Panel noted that Clause 16.3 required representatives to pass the relevant examination. Clause 16.4 required that the Medical Representatives Examination must be taken by representatives whose duties comprised or included one or both of 'calling upon doctors and/or dentists and/or other prescribers' and 'the promotion of medicines on the basis, *inter alia*, of their particular therapeutic properties'. Clause 16.4 was a statement of principle and failure to comply with it would be a breach of Clause 16.3.

Clause 1.6 defined a representative as someone who called on members of the health professions and administrative staff in relation to the promotion of medicines. In the Panel's view such people would often have job titles other than 'representative'. The term promotion was defined in Clause 1.2 as any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription, supply, sale or administration of its medicines.

The Panel considered that the role of a regional account director met the broad definition of a representative in Clause 1.6. The Panel noted Pfizer's submission that the regional account directors did not promote medicines on the basis of their therapeutic properties nor did they discuss efficacy or safety. It thus appeared that other aspects of a medicine, such as cost could be discussed. Although the regional account directors called upon prescribers in their role as business managers, Clause 16.4 did not make such a distinction. In the Panel's view if a company representative called upon a prescriber in association with the promotion of medicines then that representative would need to pass the Medical Representatives' Examination. Two of the regional account directors had been in post for 2 years and had not taken the examination as required by Clause 16.3. Thus the Panel ruled a breach of Clause 16.3.

Complaint received **3 December 2010**

Case completed **3 February 2011**

CODE OF PRACTICE REVIEW – February 2011

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

2335/7/10	**Merz/Director v Allegan**	**Breach of undertaking**	**Breaches of Clauses 2, 9.1 and 25**	**Appeal by complainant**	**Page 3**
2346/8/10	**Merz/Director v Allergan**	**Breach of undertaking**	**Breaches of Clauses 2, 9.1 and 25**	**Appeal by complainant**	**Page 15**
2350/8/10	**Vifor Pharma v Pharmacosmos**	**Promotion of Monofer**	**Three Breaches of Clause 7.2**	**No appeal**	**Page 24**
2351/8/10	Lilly v Roche	Promotion of Tarceva	No breach	Appeal by respondent	Page 31
2355/9/10	**Member of the Public v Takeda**	**Promotion of Mepact**	**Breaches of Clauses 9.1, 22.1, 22.2**	**Appeal by respondent**	**Page 40**
2357/9/10	**General Practitioner v Boehringer Ingelheim**	**Promotion of Pradaxa**	**Breaches Clauses 7.2, 7.3, 7.4, 7.9 and 7.10**	**Appeal by complainant**	**Page 45**
2358/9/10	**Anonymous v Genus**	**Role of nurse advisors**	**Two Breaches Clause 7.2 Breach Clause 9.1**	**No appeal**	**Page 51**
2361/10/10	**Anonymous Ex-Employee v Cephalon**	**Inappropriate hospitality and in-house feedback document**	**Two Breaches Clause 2 Two Breaches Clause 9.1 Breaches Clause 1.7, 15.2,15.9 and 19.1**	**No appeal**	**Page 56**
2364/10/10	Anonymous v Bayer Schering Pharma	Conduct of representatives	No breach	No appeal	Page 62
2365/10/10	Anonymous v Sanofi-Aventis	Advance notification documents: Pipeline update	No Breach	No appeal	Page 64
2374/12/10	**Anonymous v Pfizer**	**Failure to sit ABPI Medical Representatives Examination**	**Breach Clause 16.3**	**No appeal**	**Page 67**

PMCPA | Prescription Medicines Code of Practice Authority

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself. Compliance with the Code is obligatory for ABPI member companies and, in addition, over sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about prescription only medicines made available to the public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the sponsorship of attendance at meetings organised by third parties
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio or video-recordings in any format, broadcast media, non-print media, the Internet, interactive data systems and the like.

It also covers:

- the provision of information on prescription only medicines to the public either directly or indirectly, including by means of internet
- relationships with patient organisations
- the use of consultants
- non-interventional studies of marketed medicines
- the provision of items for patients
- the provision of medical and educational goods and services
- grants and donations to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the four members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. One member of the Panel acts as case preparation manager for a particular case and that member is neither present nor participates when the Panel considers it.

Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry. Independent members, including the Chairman, are always in a majority when matters are considered by the Appeal Board.

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 under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY

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by email to: complaints@pmcpa.org.uk.