NUMBER 100 May 2018

CODE OF PRACTICE REVIEW

PMCPA | Prescription Medicines Code of Practice Authority

The Prescription Medicines Code of Practice Authority (PMCPA) was established by The Association of the British Pharmaceutical Industry (ABPI) to operate the ABPI Code of Practice for the Pharmaceutical Industry independently of the ABPI. The PMCPA is a division of the ABPI which is a company limited by guarantee registered in England & Wales no 09826787, registered office 7th Floor, Southside, 105 Victoria Street, London SW1E 6QT.

CONSULTANTS AND SOCIAL MEDIA

The guidance on digital communications issued by the Authority, and available on our website, advises companies to have policies and procedures in place to ensure that the personal use of email, Twitter and other social media platforms and the like by staff does not unwittingly lead to a breach of the Code. Companies should be aware that they may also be responsible for any social media engagement undertaken by their consultants or advisors particularly where such engagement relates to the project for which the consultant/advisor is employed. In the Authority's view, companies would be well advised to state in their written contracts or agreements with consultants/advisors that, unless specifically requested to do so, the consultant/advisor should not use any social media platform for any communication related to his/her services for the company.

PLEASE PRUNE PLASTICS!

The Authority appreciates the efforts made by companies regarding the presentation of materials submitted to it. Whilst it is very helpful to have documents neatly labelled and separated into bundles, it is often the case that individual papers / appendices within the bundles are enclosed in plastic folders and the like. At the completion of a case only the papers are kept and although where we can we reuse some of the plastic wallets most of them are discarded. Amid growing concerns about the environment and whilst not wishing to discourage the careful presentation of papers, the Authority asks companies to think twice before providing them in excessive amounts of plastic!

WEBSITE PLANS CONFIRMED

The proposal to update the PMCPA website has been agreed and an agency has been appointed to start work to move it to a more sustainable platform, update it and make it more user friendly. We are planning for a more intuitive search function and easier navigation for visitors as well as faster updating processes for administrators.

Consultations are taking place with users (to whom thanks).

Anyone with specific, detailed feedback on their own experience of using www.pmcpa.org.uk please contact Elly at ebutton@pmcpa.org.uk.

TIME FLIES…

Apologies that this quarterly Review is so late, the individual case reports are, however, published as soon as possible. The PMCPA has been very busy with a number of complex challenges. A new member of the Panel will start in September and more details will be revealed in the September Review.

PUBLIC REPRIMAND FOR PIERRE FABRE

Pierre Fabre has been publicly reprimanded by the Code of Practice Appeal Board for failing to provide complete and accurate information to the Panel (Case AUTH/2962/7/17).

In Case AUTH/2962/7/17 the Panel ruled breaches of the Code and on appeal the Appeal Board ruled a breach of Clause 2 in relation to briefing material for the Toviaz (fesoterodine) representatives.

The Appeal Board noted that the presentation provided by Pierre Fabre in response to the complaint was incomplete. Pierre Fabre was only able to provide the correct version of the slides which contained seven additional slides after being advised of the omission by the complainant in his/her appeal. In the Appeal Board's view, this omission was a serious matter. The Appeal Board queried the robustness of the company's original investigation and response on this point. The Appeal Board noted Pierre Fabre's submission that the responsible individual had since left the company. However, the Appeal Board noted and welcomed the fact that Pierre Fabre had taken significant and rapid action and had in place a comprehensive and timely action plan to make wholesale changes to address issues highlighted in this case. However, notwithstanding its comments the Appeal Board considered that it was essential that pharmaceutical companies provided complete and accurate information to the Panel.

Full details of Case AUTH/2962/7/17 can be found on page 45 of this issue of the Review.

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 full day seminars offer 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.

For dates of the Code of Practice Seminars in 2018 please see the PMCPA website.

Short training sessions on the Code or full 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 nalexander@pmcpa.org.uk).

HOW TO CONTACT THE AUTHORITY

Our address is:
Prescription Medicines Code of Practice Authority
7th Floor, Southside, 105 Victoria Street, London SW1E 6QT

www.pmcpa.org.uk

Telephone: 020 7747 8880

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or 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
Tannyth Cox: 020 7747 8883
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/2831/4/16

VOLUNTARY ADMISSION FROM CELGENE

Meetings organised by representatives

Celgene voluntarily admitted following a preliminary investigation a number of breaches of the Code with regard to two promotional meetings for Otezla (apremilast). Otezla was indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who had a contraindication to, or were intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA). Otezla was also indicated in the treatment of psoriatic arthritis.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Celgene.

Celgene stated that the meetings at issue were organized by Celgene representatives with invitations emailed by a third party aesthetics company to its database. The first meeting took place in November 2015, and the second, due to take place in March 2016, at the same venue, was cancelled as soon as the matter came to Celgene's attention. The company had been informed by the aesthetics company that up to 50% of the recipients might not be health professionals as defined in the Code.

The March meeting was initiated by two key account managers (KAMs) from Celgene's immunology and inflammation business unit. The meeting 'An Evening on Psoriasis for the Private Dermatologist', had been developed as an educational meeting with three consultant dermatologists speaking on key clinical aspects of psoriasis including treatment options. The real world clinical experience of Otezla gained since launch formed a part of the meeting agenda.

Celgene stated that it had limited experience in communicating with dermatologists working outside the NHS. The KAMs seemed to have decided, therefore, to engage the third party aesthetics company to reach appropriate dermatologists with private practices who might wish to attend promotional meetings about Otezla. The third party company was involved in aesthetic dermatology and predominantly worked with dermatologists, aesthetic practitioners (non GMC registered dermatology specialists) and beauty salon therapists. In addition, it supplied certain non-prescription skincare products to registered aesthetic practitioners. Celgene understood that the third party had developed its database of customers predominantly through voluntary signing up at trade meetings and this gave it permission to contact those customers.

It seemed that the KAMs had an informal oral agreement with the aesthetics company such that it would invite its customers to attend the Celgene-sponsored meeting.

The meeting and associated materials had been certified. It seemed, however, that the invitation had been sent to the aesthetics company before it had been certified. In addition, the aesthetics company removed the adverse event reporting statement and black triangle from the prescribing information without reference to Celgene.

The invitation was emailed on 2 and 18 March 2016 to all of the aesthetics company's customers who appeared on its electronic database. Celgene was working to identify how many of these recipients were not health professionals; the aesthetics company had estimated that the proportion might be up to 50%.

Celgene stated that its investigation revealed that the same KAMs had similarly used the aesthetics company to invite dermatologists to attend the meeting in November 2015. Celgene assumed that some of the recipients of the emailed invitation would not have been health professionals. On that occasion the invitation and associated meeting materials were certified. That invitation was also modified by the aesthetics company before sending with the result that the prescribing information was removed. Again these changes were made without reference to Celgene. There was no written agreement in place to define the services to be provided by the aesthetics company.

Records showed that there were 13 attendees at the November 2015 meeting in addition to three speakers (consultant dermatologists), the two Celgene KAMs and representatives of the aesthetics company. The attendees included three dermatologists, one rheumatologist, four clinic directors, one GP, two dentists, one MSc student, and a theatre manager. Email exchanges suggested that the aesthetics company provided attendees with pens, product information and samples of their skincare products which were of no monetary value to the aesthetics company. No promotional aids or samples of Celgene products were distributed by the Celgene KAMs.

Celgene listed planned corrective and preventative actions and submitted that it was greatly concerned by this matter and remained committed to ensuring that all its employees operated within the Code at all times.

The response from Celgene is given below which includes details following further investigation.

The Panel noted that mid-2015, Celgene decided to engage with private practice in a particular area but that it had little experience in communicating with dermatologists working outside the NHS.

The Panel assumed that as a result of the decision to target private practice, the two meetings at issue were planned jointly by local field-based staff and the third party aesthetics company. An initial planning meeting between one of the KAMs and the aesthetics company took place in September 2015. An email to the aesthetics company stated 'I'm not sure this kind of thing has ever been done before …'. The email also referred to using the aesthetics company's contacts to 'secure a quality audience'. That email was copied to the other KAM and to his/her first- and second-line managers. It was thus clear from the outset that senior staff within Celgene knew that the KAM was proposing a 'unique collaborative venture' and intended to invite contacts of the aesthetics company. The Panel considered that the email should have prompted mangers to urgently and proactively investigate the proposed arrangements to ensure compliance with the Code. In the Panel's view, to know about the proposals but fail to guide more junior staff in an activity with which the company was unfamiliar, particularly when those staff appeared to be engaging a third party provider with whom Celgene had not worked before, was extremely poor.

The Panel considered that the lack of guidance was further compounded by the fact that although the meetings approval form for the November meeting stated that the aesthetics company would 'help drive recruitment', none of the signatories thought to question what that meant or would entail. The company acknowledged that this was careless.

The collaboration between Celgene and the aesthetics company was informal and appeared to have been wholly arranged by junior staff. There was no written agreement detailing the arrangements and the responsibilities of the parties. The relationship between Celgene and the aesthetics company was described in various ways in the invitations.

The Panel noted that following approval of the invitation, which included the agenda, for the November meeting, the KAM responsible for the meeting attached a copy of the approved invitation to an email addressed to the aesthetics company but made no reference to the utmost importance of using that material as approved. Indeed the KAM stated 'I also had a play with a word document which you might want to use as an agenda?' It was that document which the aesthetics company emailed out. Thus the invitation sent out by the aesthetics company, for a promotional meeting, had not been certified and a breach of the Code was ruled. An indirect reference to Otezla and that, together with the fact that the meeting would promote Otezla, meant that prescribing information was required. Thus a breach of the Code was ruled. Another breach was ruled as there was no statement regarding the reporting of adverse events.

With regard to the invitation for the November meeting sent by Celgene, the Panel noted that although the electronic version was certified in its final form, the printed version, whilst identical to the electronic version, was not checked and signed in its final form until after it was posted. A breach of the Code was ruled.

The Panel noted that the meeting approval form for the November meeting stated that the aesthetics company would 'help drive the recruitment for the meeting'. In that regard the Panel noted its concerns above that Celgene had not appeared to do anything to find out what that meant. The company had not determined exactly who would be invited to the meeting by the aesthetics company which, it could be assumed, would also want some benefit out of the meeting. This was particularly important given that the products marketed by the aesthetics company were all cosmetics and so its customer base was different to and broader than health professionals or other relevant decision makers as defined in the Code.

The Panel noted Celgene's submission that the aesthetics company had emailed an invitation to the November meeting to its database of 3,000 customers of which only approximately 50% were health professionals. In that regard the Panel was concerned to note that the professional status of the customers on the aesthetics company database had never been discussed. The document provided to the aesthetics company did not refer to Otezla directly but it did refer to recent advances in treating psoriasis and question whether oral therapy was a new hope. The Panel noted that Otezla was not the only oral therapy for the treatment of psoriasis. The invitation referred to Celgene as described above. Although the document had been sent to those who were not health professionals, on balance the Panel did not consider that its content was such that Otezla had been promoted to the public and ruled no breach of the Code.

The Panel noted that the aesthetics company provided delegates with bags bearing the logo of one of its products. Each bag contained a number of sample packs of skin products marketed by the aesthetics company. Although none of the sample packs provided were available as a retail product, and each only had a nominal value to the company, they would nonetheless, have a perceived value to the recipients. Based on the retail cost of the products provided, the Panel calculated that the recipients had received just under £19 worth of skin care products together with a pen bearing the logo of one of the products and a large, silver, branded bag (approximate cost, £1.30) in which to put the samples, pen (23p) and promotional literature. The Panel considered that the provision of these items meant that attendees had been given gifts in connection with the promotion of Otezla and a breach of the Code was ruled.

The Panel considered that the KAMs responsible for the meeting should have stopped the distribution of the skin care samples, pens and bags. To not have done, having apparently told the aesthetics

company that samples could not be distributed but knowing that they had been sent to the meeting venue, was poor. Further, the Panel noted with concern Celgene's submission that the KAMs and their manager saw the bags but did not look into them or take one; they all assumed that the bags contained only promotional literature for the aesthetics company's products and pens – despite previous discussions. In the Panel's view the KAMs and their manager were likely to have seen delegates looking at the contents of the bag and queried why they did not identify the bags themselves as being in breach of the Code.

With regard to the March meeting, the Panel again noted Celgene's submission that the email invitation for the March 2016 meeting was certified before use. As with the November invitation, the printed version, whilst identical to the electronic version, was not checked and signed in its final form until after it was posted. The Panel ruled a breach of the Code in that regard.

The Panel noted Celgene's submission that one of the KAMs, who had worked with a design agency to develop the invitation to the meeting, had been sent an electronic copy of the final document which he/she sent to his/her peers one of which was the other KAM who then forwarded it to the aesthetics company. That document had not been certified. The aesthetics company then, without consulting Celgene, cut and pasted the invitation into the body of an email and in doing so removed the information on adverse event reporting. The Panel thus ruled a breach of the Code. The invitation sent by the aesthetics company had not been certified and a breach was ruled. The Panel ruled no breach of the Code as prescribing information had been included.

The Panel noted that although the meeting had been cancelled, the aesthetics company had, as before, emailed the invitation to 3,000 of its customers of which, according to Celgene, only approximately 50% were health professionals. The Panel noted that one recipient was one of Celgene's own staff who was not a health professional but who in a previous role, had signed up to receive mailings from the aesthetics company. The Panel considered that a member of the public had thus received promotional material about Otezla, a prescription only medicine and a breach of the Code was ruled.

The Panel was concerned about the activities of the KAMs and their manager as outlined above. In the Panel's view almost every aspect of the arrangements for the meetings at issue either showed a flagrant disregard for the requirements of the Code or a profound lack of knowledge. The Panel ruled a breach of the Code as the KAMs and their manager had failed to maintain a high standard of ethical conduct in the discharge of their duties and had not complied with the requirements of the Code.

The Panel noted its comments and rulings above and ruled a breach of the Code as the company had failed to maintain high standards.

The Panel considered that overall the conduct of many employees had fallen short of competent care leading to multiple breaches of the Code. The Panel considered that the company's conduct was such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was extremely concerned that this case highlighted multiple and serious compliance failings at all levels including the actions of first and second-line field staff, the failure to properly manage those staff, use of uncertified materials, non-adherence to company standard operating procedures (SOPs), lack of action by those approving meetings and the extremely informal arrangements for the engagement of third parties. In the Panel's view there appeared to be a laissez-faire or reckless attitude to compliance by many within Celgene and so it decided, in accordance with Paragraph 8.2 of the Constitution and Procedure, to report Celgene to the Appeal Board for it to decide whether further sanctions were required.

Celgene submitted that it took compliance very seriously and was committed to the highest standards of compliance and ethical conduct. Celgene accepted that there were failings in its management of the meetings and associated materials, and that the company's procedures and execution should be improved. Nevertheless, Celgene submitted that what had occurred did not represent the compliance culture at Celgene. The language used by the Panel to describe Celgene's employees' intentions was not supported by any of the evidence before it.

Upon discovery, Celgene immediately conducted a thorough investigation and found no evidence to suggest deliberate non compliance with the Code or a reckless attitude towards it. On the contrary, all of those involved were genuinely dismayed when they discovered the consequences of their actions.

Celgene had urgently addressed the certification failures and submitted that its systems were now robust. The other shortcomings that had resulted in multiple breaches in this case had been addressed within a comprehensive corrective and preventative action (CAPA) plan.

In summary, although there were lapses, Celgene submitted that the facts did not show recklessness or a pervasive 'laissez-faire' attitude toward compliance. To the contrary, as soon as this matter came to Celgene's attention, it immediately investigated and concluded that a voluntary admission to the PMCPA would be consistent with the expectation placed on ABPI member companies, in keeping with the spirit of the Code.

The Appeal Board noted that this case had arisen from a voluntary admission and it was grateful for the company's apology; the company had started to implement a CAPA plan. The Appeal Board further noted Celgene's submission that in early 2015 dermatology had taken the company into a new therapeutic area and this had been

accompanied by a rapid increase in the number of employees and commercial activity. The Appeal Board nonetheless noted that very basic mistakes had been made by a number of staff including senior managers. The Appeal Board noted that Celgene should have immediately recognised that there would be a number of Code and compliance issues to address. What should have been obvious and potential problems appeared to have been ignored and mistakes had been made at all levels within the company; in that regard the Appeal Board was concerned about Celgene's supervision of its staff and oversight of the meetings at issue.

Despite Celgene's quick reaction once it was aware of the matters at issue and its voluntary admission, the Appeal Board decided, given its serious concerns noted above, to require in accordance with Paragraph 11.3 of the Constitution and Procedure, an audit of Celgene's procedures in relation to the Code.

Celgene was audited in October 2016 and on receipt of the audit report in November the Appeal Board noted Celgene's acknowledgement that leadership oversight had been deficient and that staff had been given too much autonomy. The Appeal Board was concerned about the poor quality of training. The culture of trust and empowerment was not supported by appropriate checks and balances. It appeared that the importance and significance of the compliance challenges were down played. The company appeared not to have a positive, pro-active culture of compliance.

On receipt of further information in December 2016, and on noting key dates in 2017 for compliance objectives etc, the Appeal Board decided that the company should be re-audited in May 2017. On receipt of the report for the re-audit the Appeal Board would decide whether further sanctions were necessary.

Celgene was re-audited in May 2017 and on receipt of the re-audit report in June the Appeal Board noted that although some progress had been made the report highlighted a number of issues and concerns to be addressed.

On receipt of further information in July 2017 regarding, *inter alia*, Celgene's compliance plan and despite requesting further updated responses, the Appeal Board decided that the company should be re-audited in January 2018. On receipt of the report for the re-audit the Appeal Board would decide whether further sanctions were necessary.
Celgene was re-audited in February 2018 and on receipt of the report the Appeal Board considered that Celgene had made progress. The Appeal Board was very concerned about some of the issues being found however it noted that Celgene UK was proactively dealing with issues as they arose.
The Appeal Board noted that Celgene had a comprehensive compliance action plan for 2018 to address recommendations from the re-audit which stated that progress had already been made. The global company appeared not to be checking with Celgene UK regarding meetings and activities despite the SOPs requirement that it should.
The Appeal Board considered that, on the basis that issues continued to be addressed, the compliance plan followed, and all staff continued to take a proactive, positive and personal role in compliance, no further action was required.

Celgene Limited voluntarily admitted a number of breaches of the Code with regard to two promotional meetings for Otezla (apremilast). Otezla was an oral prescription only medicine indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who had a contraindication to, or were intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA). Otezla was also indicated in the treatment of psoriatic arthritis.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Celgene.

VOLUNTARY ADMISSION

Celgene stated that it might have breached Clauses 4.1, 4.10, 15.2 and 26.1 of the 2015 and 2016 Codes. Celgene emphasized that it was still at an early stage of its investigation: it had yet to interview all of the employees who might be concerned in the matter as some were absent.

Celgene explained that invitations for two Otezla promotional meetings organized by Celgene representatives were emailed by a third party aesthetics company, to its database of customers. The first meeting took place in November 2015 and the second had been due to take place in March 2016, at the same venue, but was cancelled as soon as the matter came to Celgene's attention. The company had been informed by the third party aesthetics company that up to 50% of the recipients might not be health professionals as defined in the Code.

March 2016
A member of the Celgene field medical team reported that an invitation to the March meeting had been sent to his/her personal email address. Otezla was a prescription only medicine and so realizing that he/she should not have received this invitation in his/her personal capacity as he/she was not a health professional, the employee immediately notified the Celgene compliance team, which opened an investigation.

The meeting at issue was initiated by two key account managers (KAMs) from Celgene's immunology and inflammation business unit. The meeting 'An Evening on Psoriasis for the Private Dermatologist', had been developed as an educational meeting on key aspects of psoriasis. Three consultant dermatologists were contracted by Celgene to speak on key clinical aspects of psoriasis including treatment options. The real world clinical experience of Otezla gained since launch formed a part of the meeting agenda.

Celgene stated that it had limited experience in communicating with dermatologists working outside the NHS. The KAMs seemed to have decided, therefore, to engage the third party aesthetics company to reach appropriate dermatologists with private practices who might wish to attend promotional meetings about Otezla. The third party company was involved in aesthetic dermatology practices such as dermal fillers, Botox and dermal peels and predominantly worked with dermatologists, aesthetic practitioners (non GMC registered dermatology specialists), and beauty salon therapists. In addition, it supplied certain non-prescription skincare products to registered aesthetic practitioners. Celgene understood that the third party had developed its database of customers predominantly through voluntary signing up at trade meetings and this gave it permission to contact those customers.

It seemed that the KAMs had an informal oral agreement with the aesthetics company such that it would invite its customers to attend the Celgene-sponsored meeting. No written agreement was drawn up and Celgene's investigation had not revealed any transfer of funds between the two parties.

The meeting and associated materials had been certified, as required by Celgene's internal standard operating procedure (SOP). It seemed, however, that the invitation had been sent to the aesthetics company before it had been certified. In addition, the aesthetics company removed the adverse event reporting statement and black triangle from the prescribing information without reference to anyone at Celgene. Celgene expected the invitations to only be used in the approved form and distributed though approved means. Those that were sent out by Celgene complied with the relevant requirements.

The invitation was emailed twice in early March 2016 to all of the aesthetics company's customers who appeared on its electronic database. Details of the number of customers who received and opened the email invitation were provided. Celgene was working to identify how many of these recipients were not health professionals; the aesthetics company had estimated that the proportion might be up to 50%.

November 2015

Celgene stated that its investigation revealed that the same KAMs had similarly used the aesthetics company to invite dermatologists to attend the meeting in November 2015 which did take place. Celgene assumed that some of the recipients of the emailed invitation would not have been health professionals. On that occasion the invitation and associated meeting materials were certified in accordance with Celgene's SOP. That invitation was also modified by the aesthetics company before sending with the result that the prescribing information was removed. Again these changes were made without reference to Celgene; the company was attempting to clarify this point in relation to both meetings as its investigation proceeded. There was no written agreement in place to define the services to be provided by the aesthetics company.

Records showed that there were 13 attendees at the November 2015 meeting in addition to three speakers (consultant dermatologists), the two Celgene KAMs and representatives of the aesthetics company. The attendees included three dermatologists, one rheumatologist, four clinic directors, one GP, two dentists, one MSc student, and a theatre manager. Email exchanges suggested that the aesthetics company provided attendees with gifts and samples of products that it sold. Celgene has been informed by the aesthetics company that the gifts provided included pens, product information and small sample tubes (4x 2g). These were of no monetary value to the aesthetics company. No promotional aids or samples of Celgene products were distributed by the Celgene KAMs.

Celgene stressed that its investigation was at a preliminary stage and was continuing.

Corrective actions

Celgene stated that it had cancelled the March 2016 meeting, instructed the aesthetics company not to send any more communications about Celgene meetings or other activities and asked it to forward any emails about the March meeting to Celgene. It had also withdrawn all relevant meeting materials and disciplinary procedures were ongoing.

Preventative actions

Celgene submitted that by 30 April 2016 it would have reviewed all meetings organized by the staff involved, briefed field-based staff with regard to the need for signed written agreements to be in place with all third parties providing services for or on behalf of Celgene and fully reviewing distribution lists prior to mailing of meeting invitations. It would also have completed an investigation of training records of all field-based commercial staff and provided refresher training for all field-based staff on the Code, the Celgene Meetings SOP and email policy. Finally it would have reviewed all written procedures to ensure sufficient clarity on compliance with the Code. Updates and training would be provided as identified and needed.

Celgene stated that it was greatly concerned by this matter and remained committed to ensuring that all its employees operated within the framework of the Code at all times.

Celgene was asked to provide further comments in relation to the requirements of Clauses 4.1, 4.10, 15.2 and 26.1 of the 2015 Code and in addition comments in relation to Clauses 2, 9.1, 14.1 and 18.1 of the 2015 Code.

RESPONSE

Celgene explained that in mid-2015 it decided to engage with dermatologists in private practice in a particular area. With the approval of his/her

manager, one of the KAMs introduced his/her colleague, the KAM responsible for relationships with doctors in that area, to the aesthetics company. The aesthetics company's products were all regulated as cosmetics rather than medicines. The KAM and his/her contact at the aesthetics company had previously worked together at a pharmaceutical company and had both passed the ABPI examination for representatives. The KAM suggested to his/her manager that it would be worth exploring whether the aesthetics company could help Celgene forge links with dermatologists working in private healthcare.

November 2015 meeting

The two Celgene KAMs and the aesthetics company together planned a joint promotional meeting which Celgene funded. The KAM responsible submitted all of the meeting arrangements (venue, speakers, speaker briefs, honoraria, catering) to Celgene's electronic meetings approval system (FAST) together with the agenda and the invitation. The KAM described the collaboration with the aesthetics company in the submission in general terms. The collaboration was also described on the invitation submitted for approval, which carried Celgene's logo and the aesthetics company's logo in equal prominence. The foot of the invitation stated 'This meeting is organized and funded by Celgene Limited in association with [the aesthetics company]'.

The meeting arrangements, the agenda and the invitation were approved by the KAM's manager and electronically certified by Celgene's signatories. Copies of the certificates were provided. The meeting title was 'An evening on psoriasis for the private dermatologist'. Two lectures were planned entitled 'Recent Advances in Treating Psoriasis - Oral therapy a new hope?' and 'Delivering Skin Fitness'. The speakers [and the chairman] were NHS dermatology consultants, at least two of whom maintained private practices local to the meeting venue.

Celgene posted, handed or emailed the invitation to doctors working in the dermatology field who it considered might be interested in attending. Celgene also sent the invitation to the aesthetics company, with the intention that it would use it to invite health professionals working in the private dermatology sector. The Celgene KAMs believed that this had been made clear in informal discussions about the meeting arrangements. It appeared, however, that the aesthetics company emailed the agenda for the meeting, rather than the certified invitation, to its database of around 3,000 customers. The agenda did not refer to Otezla and no prescribing information was attached.

Celgene was informed during the course of this investigation that the aesthetics company maintained an electronic database of its customers and that about half of them were doctors, nurses and dentists, the remainder were likely to be qualified beauty therapists owning, managing or working in private skin clinics. The aesthetics company's database had largely been built up from contacts made at trade exhibitions; the company had explained that it had many UK customers in the private health sector and tended to market its products to private skin and beauty clinics where the public could buy them only on the recommendation of the practitioners in those clinics. The aesthetics company did not routinely sell products directly to the public and in order to buy its products, a purchaser would generally be required to show that they were either a doctor, a dentist, a nurse or a qualified beauty therapist.

When the meeting arrangements were being made neither the Celgene KAMs nor anyone else at Celgene knew about the nature of the database or that the invitation would be addressed to people on the database. Celgene's intention, as reflected in the approval system, was to only invite consultant dermatologists and pharmacists.

Shortly before the meeting, the aesthetics company emailed the Celgene KAMs to state that it would bring bags, literature, pens and promotional samples of its products used for the relief of certain skin symptoms to the meeting. The KAM responsible for the meeting recalled a subsequent conversation with the aesthetics company in which he/she explicitly stated that no samples should be brought to the meetings. There was no written record to this effect.

Around 20 people attended the meeting including both KAMs, their manager and representatives from the aesthetics company. The attendance list kept by Celgene listed 13 names. In the course of the investigation Celgene verified that all except three of the 13 attendees were doctors, dentists or nurses. The KAM understood that the three other attendees worked in a business role in private skin clinics.

The aesthetics company left bags bearing the logo of one of its products on the chairs at the end of the meeting. The bags were promotional and cost around £1.30 to produce. Each bag contained:

- 4 x 2g sample sachets of a skin product with a wholesale price of 50p each. This 2g size was not available as a retail product.
- 1 x 10g trial size tube of another skin product. The 10g size was not available as a retail product. 100g of the product retailed at £35.95
- The aesthetics company's brochure.
- A pen costing approximately 23p, bearing the logo for one of the aesthetics company's products.

In response to a request for further information about the content of the bags, Celgene submitted that each contained a brochure, a pen and identified the samples:

- 2 x 2ml sample sachets (30ml had a recommended retail price (rrp) £77.52)
- 2 x 2g sample sachets (50g, rrp £63)
- 1 x 10g sample (100g, rrp £35.95).

The KAMs and their manager saw the bags but did not look into them or take one home; they all assumed that the bags contained only promotional pens and literature for the aesthetics company's products.

The meeting was well received and the KAMs, with the approval of their manager, decided to arrange another in collaboration with the aesthetics company. The KAMs and their manager did not, at the time, identify any concerns regarding the relevance of participants at the meeting.

Planned March 2016 meeting

The meeting invitation was submitted into the ZINC system which Celgene used for the approval of promotional materials whilst the meeting arrangements were submitted through FAST, Celgene's e-approval system for meetings arranged by KAMs. The investigation revealed that one of the final approvers in the FAST system for this meeting was not a final signatory. None of the materials approved by this person for this meeting were issued, and of course the meeting did not go ahead.

Neither the FAST nor the ZINC submissions referred to the collaboration and the invitation stated that 'This meeting is funded and organized by Celgene Limited'.

The title of the meeting was 'An Evening for the Private and NHS dermatologist'. The final invitation was approved and certified electronically on 29 February 2016. The printed version was certified on 11 March 2016. Celgene posted or emailed the invitation to the same list of dermatologists to whom it had sent the first invitation.

Celgene stated its investigation revealed that, contrary to its SOP, the invitation seemed to have been sent by one of the KAMs to the aesthetics company on 26 February 2016, before the second (non-medical signatory) had reviewed it. This invitation was, however, identical to the version that was subsequently certified. The aesthetics company emailed the KAMs to ask 'OK to send it to the database?'. The KAMs replied that it was and did not anticipate the possibility that the invitation would be sent to people other than health professionals.

Celgene explained that the aesthetics company was unable to attach the pdf version of the certified invitation to an email and so without consulting Celgene, cut and pasted the invitation into the body of the email. The cut and paste removed the black outlined box at the bottom of the invitation containing information on adverse event reporting.

One of Celgene's regional medical liaisons (RMLs) notified the compliance director on Friday 18 March 2016 that an invitation from the aesthetics company had been sent to his/her personal email address. In a previous scientific role, the RML had attended trade exhibitions where the aesthetics company had exhibited and he/she had signed up to receive mailings from it.

The following Monday a preliminary investigation revealed information that raised concerns regarding to whom the invitations had been sent. Celgene immediately cancelled the meeting and withdrew the printed materials emailing the relevant field force. Celgene also instructed the aesthetics company to notify the two of its customers who had accepted the invitation that the meeting was cancelled. Celgene had written confirmation that the aesthetics company had emailed these two people cancelling the meeting.

Celgene submitted that the invitations which it approved and distributed for both meetings complied with Clause 4.1. The invitation sent out by the aesthetics company in March 2016 also complied with Clause 4.1. The invitation sent out by the aesthetics company for the November 2015 meeting, whilst not referring to Otezla by name, did not contain the prescribing information listed in Clause 4.2 of the Code.

Celgene submitted that the invitations which it approved and distributed for both meetings complied with Clause 4.10. The invitation sent out by the aesthetics company for the November 2015 meeting, whilst not referring to any medicine by name, did not contain the statement on adverse event reporting required by Clause 4.10. The invitation sent out by the aesthetics company in March 2016 did not contain the statement on adverse events required by Clause 4.10.

The invitation posted and emailed by Celgene for the November 2015 meeting was issued in its final form. It was certified electronically by Celgene's two signatories. However, the printed version was not separately certified.

The invitation posted and emailed by Celgene for the March 2016 meeting was certified electronically by Celgene's two signatories before it was emailed by Celgene. The printed version, which was identical to the electronic version, was separately certified on 11 March 2016, after it had been posted.

Neither of the invitations sent out by the aesthetics company for the meetings in November 2015 and March 2016 were certified by Celgene. The aesthetics company appeared to have inadvertently altered the materials after they had been electronically certified by Celgene, not appreciating the importance of maintaining the documents in the exact form in which they had been received.

Celgene regretfully accepted that its representatives had failed to comply with all relevant requirements of the Code. Failing to check the nature of the aesthetics company's database was clearly careless. However, neither of the KAMs, nor indeed anyone else at Celgene, ever thought that anyone other than appropriate health professionals or other relevant decision makers would receive the invitations. In the absence of any indication or evidence that there were any representations made that were intentionally misleading, inaccurate, disparaging, in poor taste or outside the terms of Otezla's marketing authorization, Celgene would not characterize the representatives' conduct as unethical.

The meeting in November 2015 was a jointly hosted promotional meeting by Celgene and the aesthetics company. The aesthetics company gave promotional samples of its products to the attendees, most of whom were already its customers. The samples were relevant to the practices of the attendees and

were intended to provide them with an opportunity to evaluate the products for recommendation to their patients and customers.

The KAMs stated that they were unaware that the aesthetics company had distributed samples of its products. One of the KAMs also stated that he/she expressly asked the company not to do so. There was no indication that the samples were provided as an inducement to prescribe, administer, recommend, buy or sell any medicine, but rather to provide the aesthetics company's contacts with an opportunity to evaluate the products for recommendation to their patients and customers.

The invitation sent out by the aesthetics company for the November meeting consisted only of the meeting agenda, listing the titles of the lectures and bearing the logos of Celgene and of the aesthetics company.

The invitation sent out by the aesthetics company for the March 2016 meeting referred to Otezla by name and included the claim: '… the potential place of Otezla (apremilast) in the treatment of psoriasis'.

Both invitations were sent to the people whose names appeared in the aesthetics company's database. Celgene was informed by the aesthetics company that about half of these were health professionals as defined by the Code. A significant proportion of the remainder might be owners or business managers of clinics where patients with skin conditions were treated.

Celgene accepted that the aesthetics company's database should not have been used to send out any invitations as Celgene could not make its own checks on the nature of the recipients. This was especially so given that Celgene intended to only invite health professionals involved in the treatment of psoriasis patients.

Celgene submitted that it operated within a comprehensive compliance structure comprising policies, SOPs and electronic tools such as ZINC and FAST. All of Celgene's relevant managers and field force had been trained on the Code, and this training was regularly updated. Celgene regretfully conceded that, despite this, it had failed to maintain its own high standards in the organisation and execution of these two meetings. An outline of the corrective and remedial measures that Celgene had taken and intended to implement rapidly to ensure that high standards were maintained in the future was provided.

Celgene stated that all the corrective actions outlined above were completed by 31 March:

1 Cancellation of meeting due to be held in March 2016. Celgene emailed a cancellation notice to all those whom it had invited and asked the aesthetics company to notify the two people who had replied directly to its mailing that the meeting was cancelled.
2 Aesthetics company instructed not to send any more communications about Celgene meetings or other activities. This was orally agreed on 23 March 2016 and confirmed via review and agreement of meeting minutes.
3 Emails received by the aesthetics company about the March meeting to be forwarded to Celgene. This was orally agreed on 23 March 2016 and confirmed via review and agreement of meeting minutes. No such emails were forthcoming after 23 March.
4 Withdrawal of all relevant meeting materials. Celgene also conducted a formal withdrawal of materials associated with this meeting in accordance with written procedures. Celgene provided a copy of this withdrawal notification and confirmation of successful withdrawal completion.
5 Disciplinary proceedings were ongoing.

The preventative actions as defined above to be completed by 30 April 2016:

1 Review all meetings organised by those involved in the two meetings:

Celgene stated that a detailed review of the records of the 9 relevant meetings showed that no others were conducted jointly with other companies, or that anyone other than health professionals were invited to attend (or attended) them. There were 3 instances where the final approval of the meeting and associated materials had been given by a medical final signatory plus a person who was not a final signatory and one instance where a meeting invitation was generated but not certified in its final physical form. Certification of all slides sets used at these meetings had not been robustly performed. There were important lessons learned from these findings, and remedial action had already ensured that only appropriate final signatories could be final approvers. Training on the relevant updated Celgene SOPs would address the need for robust certification of materials.

2 Clear briefing to all Celgene field-based staff:

i) A reminder that signed written agreements were to be in place with all third parties providing services for, or on behalf of, Celgene. A certified briefing had been distributed to all staff who might interact with third party providers or materials or activities governed by the Code which included all field-based staff (commercial and medical), national sales managers, commercial operations, scientific and medical advisors, market research staff, external affairs teams, and product managers. This information would be incorporated in the imminent update of Code-related SOPs (see point 5 below).

ii) Full review of distribution lists prior to mailings of meeting invitations. A briefing entitled 'Dissemination of promotional material via email' had been certified. After further consideration during the preparation of this briefing, the scope was widened to include all promotional material, not just emailed meeting invitations. This briefing had been distributed to all staff who might email promotional material, including all field-based staff (commercial and medical), national sales

managers, commercial operations, scientific and medical advisors, market research staff, external affairs teams, and product managers. This information would be incorporated in the imminent update of Code-related SOPs (see point 5 below).

3 Investigate training records of all field-based commercial staff:

Following its voluntary admission, Celgene had widened the scope of this preventative action to include review of the training records of all staff involved in the generation, review and approval of promotional materials and meetings. According to Celgene procedures, training was assigned in its global electronic training tool and delivered either online or via an instructor-led course. All assigned training was tracked on a monthly basis and any non-compliance was routinely flagged to relevant line managers by the chief compliance officer. The UK affiliate training compliance rate was 81% training complete as of 31 March 2016. The training assignments for each job role had been evaluated. As a result of this review, the processes for developing and delivering training would be updated by the end of June 2016, including reinforcing the requirement for a robust training programme for all staff.

4 Refresher training for all field-based staff:

i) The Code – When Celgene identified this specific non-compliance, a project was already ongoing to deliver on-line Code training to head-office and field-based staff. This training was rolled-out on 30 March, and was closely tracked to ensure it was completed by end April 2016. Additionally more detailed role-specific Code on-line training was scheduled for completion in May.

ii) The Celgene meeting SOP – this SOP had been reviewed and was being updated. Once the final version was signed, it would be trained to everyone involved in the organisation, approval and delivery of meetings.

iii) Celgene email policy – This action had been appropriately addressed through the action taken in 2ii above.

5 Review of all written procedures to ensure sufficient clarity on compliance with the Code.

Updates and training to be provided as identified and needed. The SOPs which addressed the generation and approval of materials and approval of meetings and subsistence had been reviewed in detail by experienced personnel. Changes were currently being incorporated, and when formally signed off, these SOPs would be trained to all relevant personnel before end April 2016.

Celgene submitted that it had an excellent record of compliance and had not had to answer any complaints to the PMCPA since it was established in 2006. [Post Consideration note: Celgene had received a complaint where no breach of the Code was ruled Case AUTH/2454/11/11] Celgene's failures on this isolated occasion were inadvertent and related to involvement with a third party with whom it had not worked before. Celgene hoped that the promotional activities that were the subject of its voluntary admission would not bring discredit upon, or reduce confidence in, the pharmaceutical industry. Celgene immediately made its best efforts to put remedial and preventative actions in place once the failures in its processes came to light.

Celgene submitted that its investigation had provided a salutary lesson in the importance of constant vigilance in the operation of compliance checks and controls even where, as was clear here, staff had acted with the best intentions to uphold the values embodied by the Code.

In response to a request for further information Celgene submitted that it was not its practice to appoint third parties on the basis of an informal verbal agreement. Appropriate preventative actions would be implemented to address that point.

An introduction to the aesthetics company was made via one of the KAMs who had previously worked with an employee of the aesthetics company in another pharmaceutical company. An initial meeting took place to discuss the potential to collaborate in a meeting, where the aesthetics company's role would be to invite private dermatologists with whom it had a relationship. An email from the KAM to the aesthetics company dated 7 September 2015, documented that a meeting took place in early September, and referred to plans for an evening meeting as 'an approach to engaging with the [stated area] private dermatologists'. This email set out that Celgene would organise the venue and contact a potential chair and one potential speaker for the meeting, and the aesthetics company was asked to liaise with a second potential speaker. A proposed agenda was included, and the email concluded with a statement, 'between us all we can put on a really interesting and enjoyable meeting and with [the aesthetics company] contacts in the private sector we should secure a quality audience'. This email referenced a planned follow-up meeting on 18 September 2015. No written record of that meeting had been identified.

Celgene submitted that it was not aware of the use of a database for the November meeting. For the March meeting, although emails provided evidence that the KAMs knew about the proposed use of a mailing database, Celgene had discovered no evidence that the professional status of customers on the aesthetics company's database was discussed. Appropriate preventative actions would be implemented to ensure that this did not happen again.

Celgene explained that for the November meeting, the invitation and agenda were internally approved on 14 October 2015, and the KAM responsible for the meeting was notified by the FAST system by automated email on the same day. Following that approval, one KAM emailed the invitation and agenda to the aesthetics company on 20 October and the other KAM also emailed the invitation to the aesthetics company on 22 October. Only the

two KAMs involved in the meeting were included in these email exchanges. There were subsequent email exchanges with the two KAMs indicating that the aesthetics company then used the agenda as an 'invitation' which it emailed on 13 November 2015. The March meeting was approved in the FAST system on 18 February 2016, and the KAM responsible for the meeting was notified by the FAST system by automated email the same day. The meeting invitation was certified electronically in ZINC, with the final certification of the final physical form completed on 11 March 2016. The invitation was sent from the responsible KAM to his/her peers who included the other KAM involved in this meeting on 26 February 2016, and this second KAM forwarded the invitation to the aesthetics company on 26 February 2016 (copy provided). Only the two KAMs involved in the meeting were included in these email exchanges.

Celgene submitted that as per its SOP, Generation and Approval of Quality Materials (UKIR-SOP-COP-001), the originator of an item ensured the ZINC certificate was signed before materials were released noting the additional requirement for a signatory to certify hard copy material in the final form before release.

Meetings and Subsistence (UKIR-SOP-COP-002) required KAM-led speaker meetings (so-called Type B meetings) to be approved in the e-meetings approval system, FAST. The e-meetings approval user guide (UKIR-WP-COP-001) clarified that once a meeting was approved in FAST, the KAM received an email notification and could then send out the invitation and agenda.

Standard invitations for speaker meetings were typically automatically generated using a FAST template. For the March meeting, an agency was engaged to design the invitation which was reviewed and certified in ZINC. In parallel, the KAM worked directly with the design agency to prepare the invitation, and had received an electronic copy of the final invitation directly from the design agency. The invitation was therefore already in his/her possession before its final certification (albeit this version was identical to that which was subsequently certified in ZINC) and was distributed before final certification by the KAM to his peers and line manager, and one of his KAM peers then forwarded this to the aesthetics company.

Celgene provided copies of the emails responding to the aesthetics company's request for permission to send the invitation to its database – 26 February 2016. The emails from Celgene to the aesthetics company were written by the two KAMs organising the meeting, and both copied in the other KAM. No other Celgene employees were included in these email exchanges.

Celgene submitted that in investigatory interviews, the final signatories commented that they did not recall thinking about the meaning of 'drive recruitment'. Neither of the KAMs endorsed that an email should be sent to anyone other than a relevant health professional, and no one at Celgene understood the breadth of the distribution by the aesthetics company.

Celgene explained that the Meetings and Subsistence SOP required signatories to review KAM-led meetings within FAST and approve/reject as appropriate based on Code compliance, and the e-meetings work practice also required commercial and medical final signatories to review the meeting for compliance and quality and to ensure it addressed business needs. In the investigatory interviews with the meeting approvers, they explained that the November meeting approval form (in FAST) did not raise any concerns at the time, and no questions were raised. A copy of the certificate, which was generated in FAST, approving the November 2015 meeting was provided.

Celgene submitted that the three dermatologists and the rheumatologist were invited by Celgene to the November 2015 meeting, and with the exception of the rheumatologist, all of the attendees were also invited by the aesthetics company.

In interviews, the KAMs and their manager, all of whom were at the November meeting, stated that delegates at that meeting were appropriate, being either health professionals or clinic managers fulfilling a similar role to business managers in the NHS. The KAMs and their manager did not observe any behaviour which indicated that some of the delegates were not relevant attendees at the meeting.

The details of the budgeted expenses were entered into FAST by one of the KAMs and approved by his/her line manager and final signatories prior to meeting approval. Actual costs for the meeting were paid by the two KAMs. One paid for the room hire, and the other paid for the subsistence. The expense reports coded the meetings as per internal policy as 'meetings', receipts from the venue were attached. Celgene's policy did not require the meetings attendance sheet or names of individual attendees to be attached to expense reports for such speaker meetings. The attendance sheet was uploaded as required to the FAST meetings approval system after the meeting took place. Relevant expense reports for the November meeting were provided.

Celgene submitted that during the initial investigation into this incident, it was identified from email correspondence that bags might have been distributed at the meeting. Further communication with the aesthetics company confirmed that bags were in fact distributed, and Celgene requested details of the exact contents from the aesthetics company on 24 March 2016. This information was provided and is stated above.

During interviews, the KAMs and their manager stated that they did not see the contents of the bags and did not take one home. The aesthetics company shipped the bags to the venue and put them on the delegates' chairs at the beginning of the meeting.

Celgene provided copies of the following email exchanges which referred to the gifts and samples provided at the November meeting:

- 12 November 2015 from the aesthetics company to the two KAMs asking if the bags could be sent to the meeting venue
- 12 November 2015 from the aesthetics company with KAM in copy describing items to be distributed at November meeting
- 16 November 2015 from the aesthetics company to KAMs discussing the items to be distributed at the November meeting.

The emails from the aesthetics company dated 12 and 16 November described the proposed contents of bags, and queried to whom they could be sent to at the meeting venue. Celgene had not discovered a responding email following these communications. In investigatory interviews, one of the KAMs stated that he/she verbally told the aesthetics company that product samples could not be provided at the meeting.

Celgene submitted that before 1 October 2015, its Meetings and Subsistence SOP did not require speaker slides to be uploaded into FAST for review prior to a meeting. The November meeting was submitted for approval on 18 September and approved on 14 October.

Celgene explained that the slides used by one of the speakers at the November meeting were from a previously certified slide kit. The full slide kit was provided together with the relevant certificate. The selection of slides presented on the evening was not uploaded to FAST or reviewed in advance of the meeting, and there was no certificate for the selection of slides used. In addition, the slides presented by the second speaker were also not uploaded into FAST or reviewed in advance of the meeting, and had no certificate. Both sets of slides used on the evening were provided.

The director and the business development manager from the aesthetics company attended the meeting in November to meet and greet their customers, support the consultant dermatologist and help facilitate the event.

Celgene submitted that both of the KAMs and their manager had passed the ABPI examination, and their certificates were provided together with their training records.

Celgene had a written procedure to review and approve this type of speaker meeting. This procedure was applied for the review of this meeting. However, Celgene had discovered through this incident that it needed to improve its governance procedures and actions were ongoing to address the matter.

PANEL RULING

The Panel noted that mid-2015, Celgene decided to engage with private practice in a particular area but that it had little experience in communicating with dermatologists working outside the NHS. In its response, Celgene had not provided any documentation to show how it planned to manage that process of engaging with new customers.

The Panel assumed that as a result of the decision to target private practice, the two meetings at issue (November 2015 and March 2016) were planned jointly by local field-based staff and the aesthetics company. An initial planning meeting between one of the KAMs and the aesthetics company took place on 4 September 2015 with regard to the November 2015 meeting. In an email dated 7 September to the aesthetics company the KAM stated 'I'm not sure this kind of thing has ever been done before …'. The email also referred to using the aesthetics company's contacts to 'secure a quality audience'. That email was copied to the other KAM and to his/her first- and second-line managers. It was thus clear from the outset that senior staff within Celgene knew that, as stated in the email, the KAM was proposing a 'unique collaborative venture' and intended to invite contacts of the aesthetics company. The Panel considered that the email should have prompted mangers to urgently and proactively investigate the proposed arrangements, the reputation/nature of the aesthetics company and the proposed relationship between the parties to ensure compliance with the Code. In the Panel's view, to know about the proposals but fail to guide more junior staff in an activity with which the company was unfamiliar, particularly when those staff appeared to be engaging a third party provider with whom Celgene had not worked before, was extremely poor.

The Panel considered that the lack of guidance was further compounded by the fact that although the meetings approval form for the November meeting stated that the aesthetics company would 'help drive recruitment', none of the signatories thought to question what that meant or would entail. The Panel noted Celgene's submission that when the meeting arrangements were being made, no-one in the company knew about the nature of the aesthetics company's database or that invitations would be sent to those on the database. The company acknowledged that this was careless.

The Panel noted that Celgene funded the meetings and distributed some of the invitations. It appeared that the KAMs who had organised the meetings had, through the personal contact of one of them and with the knowledge of more senior staff, used the aesthetics company to distribute at least some of the invitations. The director and the business development manager from the aesthetics company attended the November 2015 meeting. The March meeting was cancelled when Celgene was alerted by one of its staff that the invitation had been sent to his/her private email address even though he/she was not a health professional. The collaboration between Celgene and the aesthetics company was informal and appeared to have been wholly arranged by junior staff. There was no written agreement detailing the arrangements and the responsibilities of the parties. The relationship between Celgene and the aesthetics company was described in various ways. The approved copy of the invitation for the November meeting stated 'This meeting is organised and funded by Celgene Limited in

association with [the aesthetics company]' whereas that for the March meeting stated 'This meeting is organised and funded by Celgene Limited' with no reference to the aesthetics company. The invitation sent by the aesthetics company for the November meeting stated '[aesthetics company] in conjunction with Celgene' at the beginning and 'This meeting is organised and funded by Celgene Limited in conjunction with [aesthetics company]' at the end. The invitation sent by the aesthetics company for the March meeting was headed with '[Aesthetics company] in collaboration with Celgene' and contained the statement 'This meeting is organised and funded by Celgene Limited'.

November 2015 meeting

The Panel noted that following approval of the invitation, which included the agenda, for the November meeting, the KAM responsible for the meeting was notified by email the same day and in that regard appeared to have been sent a copy of the approved document. Six days later the KAM attached a copy of the approved invitation to an email addressed to the aesthetics company but made no reference to the utmost importance of using that material as approved. Indeed the KAM stated 'I also had a play with a word document which you might want to use as an agenda?' It was that word document which the aesthetics company emailed out. Thus the invitation sent out by the aesthetics company, for a promotional meeting, had not been certified as required by the Code. A breach of Clause 14.1 was ruled. Although the document did not refer to Otezla by name, it did detail a presentation entitled 'Recent Advances in Treating Psoriasis – Oral therapy a new hope?' In the Panel's view this was an indirect reference to Otezla (first authorized in January 2015) and that, together with the fact that the meeting would promote Otezla, triggered the requirements of Clause 4. As there was no prescribing information included, the Panel ruled a breach of Clause 4.1. There was also no statement regarding the reporting of adverse events and so the Panel ruled a breach of Clause 4.10.

With regard to the invitation for the November meeting sent by Celgene, the Panel noted the company's submission that although the electronic version was certified in its final form, the printed version, whilst identical to the electronic version, was not checked and signed in its final form until after it was posted. The Panel ruled a breach of Clause 14.1 in that regard.

The Panel noted that Clause 26.1 stated that prescription only medicines must not be advertised to the public. The Panel noted that the meeting approval form for the November meeting stated that the aesthetics company would 'help drive the recruitment for the meeting'. In that regard the Panel noted its concerns above that Celgene had not appeared to do anything to find out what that meant or would entail. The company had not determined exactly who would be invited to the meeting by the aesthetics company which, it could be assumed, would also want some benefit out of the meeting. This was particularly important given that the products marketed by the aesthetics company were all cosmetics and so its customer base was different to and broader than health professionals or other relevant decision makers as defined in the Code.

The Panel noted Celgene's submission that the aesthetics company had emailed an invitation to the November meeting to its database of 3,000 customers of which only approximately 50% were health professionals. In that regard the Panel was concerned to note that the professional status of the customers on the aesthetics company database had never been discussed. As noted above, the document provided to the aesthetics company did not refer to Otezla directly but it did refer to recent advances in treating psoriasis and question whether oral therapy was a new hope. The Panel noted that Otezla was not the only oral therapy for the treatment of psoriasis. The invitation referred to Celgene as described above. Although the document had been sent to those who were not health professionals, on balance the Panel did not consider that its content was such that Otezla had been promoted to the public. No breach of Clause 26.1 was ruled.

The Panel noted that Clause 18.1 stated that no gift, pecuniary advantage or benefit might be supplied, offered or promised to members of the health professions or to administrative staff in connection with the promotion of medicines or as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine, subject to the provisions of Clauses 18.2 and 18.3. The Panel noted that the aesthetics company provided delegates with bags bearing the logo of one of its products. The bags were promotional and cost around £1.30 to produce. Each bag contained a number of sample packs of skin products marketed by the aesthetics company. Although none of the sample packs provided were available as a retail product, and each only had a nominal value to the company, they would nonetheless, have a perceived value to the recipients. Based on the retail cost of the products provided, the Panel calculated that the recipients had received just under £19 worth of skin care products together with a pen bearing the logo of one of the products and a large, silver, branded bag (approximate cost, £1.30) in which to put the samples, pen (23p) and promotional literature. The Panel considered that the provision of these items meant that attendees had been given gifts in connection with the promotion of Otezla and a breach of Clause 18.1 was ruled. That the items did not relate to Otezla was irrelevant as they were provided at an Otezla promotional meeting. Further, given that the attendees included a rheumatologist, two dentists and a theatre manager, the Panel queried Celgene's statement that the samples of skin care products distributed at the meeting were relevant to the practice of the attendees.

The Panel noted that it was unclear as to when the bags had been distributed at the meeting. Celgene had stated that they were put on chairs at the end of the meeting, but also that they were put on chairs at the beginning of the meeting. The Panel noted that there had been some correspondence to the KAMs from the aesthetics company about the provision of the bags and to whom they should

be sent at the meeting venue. There was no written response from the KAMs stating that such bags should not be provided and it appeared the aesthetics company had got some contact details for sending the bags to the venue. The aesthetics company copied one of the KAMs in to an email which specifically referred to bags being sent to the venue. Celgene had submitted that one of the KAMs had verbally, and explicitly, told the aesthetics company that product samples could not be provided at the meeting; it did not appear that the KAM had tried to stop the provision of bags. In the Panel's view this was wholly inadequate. The Panel considered that whether the bags had been distributed at the beginning or end of the meetings, the KAMs responsible for the meeting should have stopped their distribution. To not have done, having apparently told the aesthetics company that samples could not be distributed but knowing that they had been sent, was poor. Further, the Panel noted with concern Celgene's submission that the KAMs and their manager saw the bags but did not look into them or take one; they all assumed that the bags contained only promotional literature for the aesthetics company's products and pens – despite previous discussions and one email from the aesthetics company clearly referring to a full size of one product and 10g of another being in the bag (it appeared that the full size product was not included). In the Panel's view the KAMs and their manager were likely to have seen delegates looking at the contents of the bag and queried why they did not identify the bags themselves as being in breach of the Code.

March 2016 meeting

With regard to the March meeting, the Panel again noted Celgene's submission that the email invitation for the March 2016 meeting was certified before use. As with the November invitation, the printed version, whilst identical to the electronic version, was not checked and signed in its final form until after it was posted. The Panel ruled a breach of Clause 14.1 in that regard.

The Panel noted Celgene's submission that one of the KAMs, who had worked with a design agency to develop the invitation to the meeting, had been sent, from the agency, an electronic copy of the final document which he/she sent to his/her peers one of which was the other KAM who then forwarded it to the aesthetics company. That document had not been certified. The aesthetics company then, without consulting Celgene, cut and pasted the invitation into the body of an email and in doing so removed the black outlined box at the end of the invitation containing information on adverse event reporting. The Panel thus ruled a breach of Clause 4.10. The invitation sent by the aesthetics company had not been certified and a breach of Clause 14.1 was ruled. The Panel noted that as prescribing information had been included, there was no breach of Clause 4.1.

The Panel noted Celgene's submission that the invitation for the March meeting emailed by the aesthetics company, did not include the inverted, black, equilateral triangle in the prescribing information. In the Panel's view, however, that symbol should have appeared in the introductory comments of the email as that was the most prominent display of the product (Otezla) name. Celgene, however, had not been asked to consider the requirements of Clause 4.11 of the 2015 Code and so the Panel could make no ruling in that regard.

The Panel noted that the invitation referred to Otezla and included prescribing information. The Panel noted that although the meeting had been cancelled, the aesthetics company had, as before, emailed the invitation to 3,000 of its customers of which, according to Celgene, only approximately 50% were health professionals. The Panel noted that one of the people to get that invitation was one of Celgene's own staff who was not a health professional but who in a previous role, had attended trade exhibitions where the aesthetics company had exhibited and had signed up to receive mailings from it. The Panel considered that a member of the public had thus received the email and in that regard had received promotional material about Otezla, a prescription only medicine. A breach of Clause 26.1 was ruled.

Overall

The Panel was concerned about the activities of the KAMs and their manager as outlined above. In the Panel's view almost every aspect of the arrangements for the meetings at issue either showed a flagrant disregard for the requirements of the Code or a profound lack of knowledge. The Panel considered that the KAMs and their manager had failed to maintain a high standard of ethical conduct in the discharge of their duties and had not complied with the requirements of the Code. A breach of Clause 15.2 was ruled.

The Panel noted its comments and rulings above and considered that the company had failed to maintain high standards. A breach of Clause 9.1 was ruled.

The Panel considered that overall the conduct of many company employees had fallen short of competent care leading to multiple breaches of the Code. The Panel considered that the company's conduct was such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was extremely concerned that this case highlighted multiple and serious compliance failings at all levels within Celgene including the actions of first and second-line field staff, the failure to properly manage those staff, use of uncertified materials, non-adherence to company SOPs, lack of action by those approving meetings and the extremely informal arrangements for the engagement of third parties. In the Panel's view there appeared to be a laissez-faire or reckless attitude to compliance by many within Celgene and so it decided, in accordance with Paragraph 8.2 of the Constitution and Procedure, to report Celgene to the Appeal Board for it to decide whether further sanctions were required.

During its consideration of this case the Panel noted that Otezla was a prescription only medicine indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who had a contraindication

to, or were intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA). Otezla was also indicated in the treatment of psoriatic arthritis. The attendees at the November meeting had included three dermatologists, one rheumatologist, four clinic directors, one GP, two dentists, one MSc student and a theatre manager. Given that Clause 11.1 of the Code required material only to be sent or distributed to those categories of persons whose need for, or interest in, it could be reasonably assumed, the Panel questioned the relevance of Otezla to the dentists and the theatre manager in particular. In that regard the Panel was concerned at Celgene's submission that when interviewed the KAMs and their manager stated that the delegates were appropriate.

The Panel queried whether the health professionals who were emailed by the aesthetics company, had given prior permission to receive promotional emails as required by the Code.

The Panel noted Celgene's submission that one of the speakers at the November meeting used slides selected from a previously approved slide kit. Neither that selection of slides nor the second speaker's slides were uploaded onto the meetings approval system or reviewed in advance of the meeting. The Panel noted the requirements of Clause 14.1 that all promotional material must be certified before use, but considered that the use of uncertified slides went beyond the voluntary admission and so it made no ruling in that regard.

The Panel requested that Celgene be advised of its concerns above.

COMMENTS FROM CELGENE ON THE REPORT FROM THE PANEL

Celgene submitted that it took compliance very seriously and was committed to the highest standards of compliance and ethical conduct. This had been demonstrated through a ten year history of no Code challenges prior to this voluntary admission. [Post meeting note: Celgene had received a complaint where no breach of the Code was ruled (Case AUTH/2454/11/11)].

Celgene accepted that there were failings in its management of this meeting and associated materials, and that the company's procedures and execution should be improved. Nevertheless, Celgene submitted that what had occurred in this case did not represent the compliance culture at Celgene. The language used by the Panel to describe Celgene's employees' intentions was not supported by any of the evidence before it.

Celgene submitted that there was not a 'laissez-faire or reckless attitude to compliance by many within Celgene' as stated by the Panel. Upon discovery, Celgene immediately conducted a thorough investigation of this matter involving compliance, human resources and legal functions at local, regional and global levels. There was no evidence to suggest deliberate non compliance with the Code or a reckless attitude towards it. On the contrary, all of the employees involved were genuinely dismayed when they discovered the consequences of their individual actions.

Celgene submitted that the facts that led to this voluntary admission came to light when a field-based employee notified the compliance team. Within ten days of this notification, following an initial investigation, the senior management team decided to make a voluntary admission to the PMCPA; a company with a 'flagrant disregard' for the Code would not have done so. Self-reporting showed a respect for the Code and self-regulation. It also demonstrated a desire to encourage compliance internally and, through transparent reporting, publicly demonstrated that Celgene, as a member of the ABPI, took the Code seriously.

Celgene submitted that it had conducted a thorough review of what went wrong, including an open and honest investigation with all employees concerned. Celgene reiterated that it had also deployed a detailed corrective and preventative action (CAPA) plan and noted that it had ensured that there were adequate resources to deliver against this plan, including more frequent internal reviews of its systems going forward.

Celgene submitted that most of the rulings were directly linked to the failure to properly monitor the activities of the third party. Clearly, Celgene was responsible for the actions of third parties in these circumstances. Celgene was currently reviewing its procedures and systems related to third party contracting to ensure that such failures could not happen again.

Celgene had urgently addressed the certification failures and submitted that its systems were now robust. The other shortcomings that had resulted in multiple breaches in this case had been addressed within a comprehensive CAPA plan.

In summary, although there were lapses, Celgene submitted that the facts determined through investigation did not show recklessness or a pervasive 'laissez-faire' attitude toward compliance. To the contrary, as soon as this matter came to Celgene's attention, it immediately investigated and concluded that a voluntary admission would be consistent with the expectation placed on ABPI member companies, in keeping with the spirit of the Code.

At the consideration of the report the representatives from Celgene apologised for the significant failings in this case and submitted that the company was doing everything to prevent this from happening again. Celgene gave brief details of its culture which it submitted was built on a set of strong global values. By way of background Celgene submitted that its heritage was in rare and life threatening diseases in oncology and haematology. In early 2015, Celgene had launched an inflammation and immunology franchise with dermatology, a new therapeutic area. This new franchise had: overlap between regulated and non-regulated environments; almost 50% increase in employees (50 additional); increased commercial activity – new therapeutic area, new clinical customers – with rapid increase

in volume of materials for approval. Celgene's understanding of what went wrong included a mixture of process failure and third party oversight failure.

Celgene gave further details of its CAPA plan which included *inter alia*, a schedule of self-audit, recruitment of additional members for the compliance team, third party review of all compliance processes including newly updated processes, Code re-training of all employees and a signatory forum.

Celgene asked the Appeal Board to consider whether the language used by Panel was a fair reflection of the facts and its compliance culture. There was no evidence that there was any intent to run meetings in a non-compliant way.

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board noted that this case had arisen from a voluntary admission and it was grateful for the company's apology at the hearing of the report; the company had started to implement a CAPA plan. The Appeal Board further noted Celgene's submission that its heritage lay in haematology, but that in early 2015 dermatology had taken the company into a new therapeutic area and this had been accompanied by a rapid increase in the number of employees and commercial activity. The Appeal Board nonetheless noted that very basic mistakes had been made by a number of staff, including signatories and the KAMs' manager, and it was extremely concerned by Celgene's admission at the consideration of the report that two senior managers, the director of medical affairs and the business unit director, had both known about the meeting that had gone ahead. The Appeal Board noted that the engagement with private dermatologists via an aesthetics company was a new venture for Celgene; the company should have immediately recognised that there would be a number of Code and compliance issues to address. What should have been obvious and potential problems appeared to have been ignored and mistakes had been made at all levels within the company; in that regard the Appeal Board was concerned about Celgene's supervision of its staff and oversight of the meetings at issue.

Despite Celgene's quick reaction once it was aware of the matters at issue and its voluntary admission, the Appeal Board decided, given its serious concerns noted above, to require in accordance with Paragraph 11.3 of the Constitution and Procedure, an audit of Celgene's procedures in relation to the Code. On receipt of the audit report, the Appeal Board would consider whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

Celgene was audited in October 2016 and on receipt of the audit report in November the Appeal Board noted Celgene's acknowledgement that leadership oversight had been deficient and that staff had been given too much autonomy. The Appeal Board was concerned about the poor quality of training. The culture of trust and empowerment was not supported by appropriate checks and balances. It appeared that the importance and significance of the compliance challenges were down played. The company appeared not to have a positive, pro-active culture of compliance.

On receipt of further information in December 2016, and on noting key dates in 2017 for compliance objectives etc, the Appeal Board decided that the company should be re-audited in May 2017. On receipt of the report for the re-audit the Appeal Board would decide whether further sanctions were necessary.

Celgene was re-audited in May 2017 and on receipt of the re-audit report in June the Appeal Board noted that although some progress had been made the report highlighted a number of issues and concerns to be addressed.

On receipt of further information in July 2017 regarding, *inter alia*, Celgene's compliance plan and despite requesting further updated responses, the Appeal Board decided that the company should be re-audited in January 2018. On receipt of the report for the re-audit the Appeal Board would decide whether further sanctions were necessary.

Celgene was re-audited in February 2018 and on receipt of the report the Appeal Board considered that Celgene had made progress. The Appeal Board was very concerned about some of the issues being found however it noted that Celgene UK was proactively dealing with issues as they arose. The Appeal Board noted that Celgene had a comprehensive compliance action plan for 2018 to address recommendations from the re-audit which stated that progress had already been made. The global company appeared not to be checking with Celgene UK regarding meetings and activities despite the SOPs requirement that it should. The Appeal Board considered that, on the basis that issues continued to be addressed, the compliance plan followed, and all staff continued to take a proactive, positive and personal role in compliance, no further action was required.

Complaint received	**1 April 2016**
Undertaking received	**4 July 2016**
Appeal Board Consideration	**21 July 2016, 11 November, 8 December, 22 June 2016, 22 July 2017, 18 April 2018**
Interim Case Report first published	**7 October 2016**
Case completed	**18 April 2018**

CASE AUTH/2961/6/17

INDIVIOR v MARTINDALE

Promotion of Espranor and information to the public

Indivior complained about the promotion of Espranor oral lyophilisate (buprenorphine) by Martindale Pharmaceuticals. The materials at issue were two detail aids, a patient leaflet and a website. Indivior marketed Subutex (buprenorphine sublingual tablets). Both Espranor and Subutex were indicated for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

The detailed response from Martindale is given below.

Indivior noted that the landing page to the Espranor website included the claim 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment'. The claim was directly visible to all visitors ie patients and health professionals worldwide. At the bottom of the homepage, the options to enter the website as 'a UK health professional' or 'not a health professional' were visible. The 'not a health professional' option opened a new page which appeared to be a general page for patients whether taking Espranor or not. Indivior was concerned that the website was promotional and encouraged patients to request Espranor and that important safety information from the summary of product characteristics (SPC) with regard to Espranor not being directly interchangeable with other buprenorphine products, was not addressed.

The Panel noted that the patient section of the website stated that it was for 'patients interested in opioid substitution therapy (OST) and Espranor' and considered that its audience was therefore wider than just patients who had been prescribed the product as submitted by Martindale. The website was open access and the homepage would potentially be seen by a broad audience. This was not unacceptable so long as the website complied with the Code and relevant parts were suitable for the general public. The Panel noted that the website was directed at not only health professionals and those who had been prescribed the medicine but also the general public. Irrespective of the intended audience, the open access homepage should be suitable for the general public. The Panel noted that the claim in question 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment' would be seen by this wide audience and considered that it promoted a prescription-only medicine to, *inter alia*, members of the public and encouraged them to ask their doctor to prescribe it. Breaches of the Code were ruled.

The Panel noted that the part of the website which stated that it was for patients interested in OST and Espranor, contained information about Espranor and a link to the patient leaflet, rather than general information about OST and all relevant treatments. In the Panel's view, this section of the website might be generally suitable for patients for whom Espranor had been prescribed, rather than the general public and it encouraged the general public to seek a prescription for it. A breach of the Code was ruled.

The Panel noted Indivior's concern that the section of the website for patients interested in OST and Espranor' did not include important safety information, identified in the SPC, such as 'Espranor is not directly interchangeable with other buprenorphine products'. The Panel noted that the webpage in question gave top line information about Espranor and stated that readers should speak to their doctor if they had any specific questions about their treatment. A reference to the Yellow Card Scheme appeared at the bottom of the page. A link to the patient information leaflet (PIL) was provided and this included the warning 'Espranor is not interchangeable with other oral buprenorphine products and the dose of Espranor may differ from the dose of other buprenorphine products'. The Panel noted its comments above about the unclear nature of the intended audience and its rulings of breaches of the Code. The page in question described Espranor as a new wafer form of buprenorphine and referred to its use as a substitute for opiate drugs such as morphine or heroin. The Panel noted Martindale's submission about the vulnerable nature of those being treated for opioid dependence and that any change to medication would cause anxiety. The Panel considered that the statements about Espranor might encourage patients to consider interchangeability. The Panel considered that the web page should stand alone as regards the medicine's risk/benefit profile and compliance with the Code and could not rely on the PIL in that regard. Readers would not necessarily click on the link. In addition, the Panel noted the emphasis in the EU Risk Minimisation Plan for Espranor that it should not be swapped for sublingual buprenorphine, or vice versa, without health professional advice. Given the prominence given to the interchangeability warning in the PIL, that the webpage appeared to be directed at, *inter alia*, patients and the points raised above including the vulnerable nature of such patients, the Panel considered the omission of such information meant that this section was not presented in a balanced way. A breach of the Code was ruled.

Indivior noted that the claim 'This renders the buprenorphine dose impossible to remove from the mouth once administered' appeared in one detail aid and 'No delay, No diversion, No nonsense buprenorphine' appeared in the other.

Indivior stated that misuse (intentional and inappropriate use not in accordance with the authorised product information which could be accompanied by harmful physical or psychological effects) and diversion (the unsanctioned supply of regulated medicines from legal sources to the illicit drug market, or to a user for whom the drugs were not intended) of medicines used in opioid use disorder was a well-known and accepted adverse event that occurred with opioid agonists, including buprenorphine.

Indivior noted that in response to a query related to the claim' 'impossible to remove from the mouth once administered' Martindale referred to the SPC which stated: 'Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue'. Indivior alleged that the claim was exaggerated, misleading, inaccurate and not supported by the evidence provided; it was harmful to prescribers and patients as it created the illusion that it was not possible to remove the medication once on the tongue.

The Panel noted that it had asked both parties to define, *inter alia*, 'dispersal', 'dissolution', 'disintegrate' and 'dissolve'. The parties' definitions were not wholly dissimilar. However, the Panel queried whether Martindale had applied sufficient rigour to the consistent application of the terms throughout the materials such that their meanings were clear. The Panel noted that this matter was further complicated as the use of certain terms also appeared to be inconsistent in the various studies and public documents.

The Panel noted that the claims at issue 'This renders the buprenorphine dose impossible to remove from the mouth once administered' and 'No delay, No diversion, No nonsense buprenorphine' implied that there was absolutely no possibility that a dose could be removed from the mouth following supervised administration (diversion) which was not so. The Espranor SPC stated 'Removal of Espranor from the mouth following supervised administration is *virtually* impossible due to its rapid dispersal on the tongue' (emphasis added) which implied that that there was a potential for the dose to be removed from the mouth following its supervised administration. The Panel further noted clinical data (Strang *et al* 2017) regarding the disintegration time of Espranor ie that time when 'the tablet could no longer be removed intact'. 96.3% of Espranor administrations achieved partial disintegration on the tongue in ≤ 15 seconds' and 'the median time for complete [Espranor] tablet disintegration was 2 minutes ...'. This meant that 3.7% of administrations took longer than 15 seconds to achieve partial disintegration leaving potential for the dose to be removed. By 2 minutes, Espranor had completely disintegrated in 58% of administrations. In four recordings either partial or complete disintegration was noted at 15 minutes.

The Panel noted the qualified statement in a clinical study that a benefit of the reduced time to disintegration with Espranor was 'the *reduced potential* for concealment and diversion' (emphasis added). The Panel considered that the claims in question 'No diversion.' and 'This renders the buprenorphine dose impossible to remove from the mouth once administered' were too dogmatic and implied there was absolutely no possibility of diversion, however small, and that was not so. This implication was compounded in relation to the latter claim as it appeared beneath the unqualified heading 'Espranor *prevents* the most common route of diversion' (emphasis added). The Panel considered that the claims in question were misleading and could not be substantiated, breaches of the Code were ruled.

The Panel further noted Indivior's allegation that the information about adverse events (in this case misuse and diversion of buprenorphine) did not reflect the available evidence. The Panel considered that the claims in question might potentially be harmful to patients as doctors might assume that it was absolutely impossible for patients to remove the dose which was not necessarily so. However, the clause cited by Indivior related to the requirement that claims about adverse reactions must reflect available evidence and not state that there were no adverse reactions, toxic hazards or risks of addiction or dependency. The Panel noted Indivior's submission that, *inter alia*, diversion was a well-known and accepted adverse event with opioid agonists including buprenorphine. The Panel noted diversion was not listed in Section 4.8, Undesirable effects, of the Espranor SPC. In the Panel's view, the claims in question did not fall within the remit of the cited clause and so it ruled no breach of that clause.

Indivior stated that Martindale had been unable to provide data to support a number of claims that Espranor instantly disintegrated when placed on the tongue eg '…buprenorphine that instantly disintegrates on the tongue …'. In fact, the evidence it provided showed that this was not the case. Indivior noted that conflicting claims were presented side-by-side in the PIL which stated 'Instant Disintegration', followed by 'Average time to complete disintegration (median): 2 minutes', further confusing patients. Indivior alleged that the claims were inaccurate, misleading and misrepresented the data which was unsubstantiated by the published evidence. Indivior further noted that the SPC stated 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds'.

The Panel noted its general comments above about the definition and inconsistent use of, *inter alia*, 'disintegration'. It considered its comments above about diversion were relevant to the claims now at issue about instant disintegration.

The Panel considered that most of the claims made for instant disintegration were too dogmatic and implied that the tablets completely disintegrated instantly on every administration which was not so. Context was important. Further information should be given about disintegration times, the meaning of the term and clinical study results so that readers could properly assess the claims. In the Panel's view, 5 of the 6 claims in question were each misleading and could not be substantiated; breaches of the Code were ruled.

The Panel noted that further information about partial disintegration time and dissolution time vs sublingual buprenorphine was provided alongside the claim 'Instant disintegration' on page 3 of the one of the detail aids. In that regard the Panel considered that the context was such that this claim was materially different to the others at issue. However, on balance, the Panel considered that the prominent claim 'Instant disintegration' was misleading insofar as it gave the immediate visual impression that tablets completely disintegrated instantly on each administration and that was not necessarily so. This immediate impression was not capable of substantiation. Breaches of the Code were ruled.

Indivior noted that it had highlighted above the importance of misuse and diversion in patients receiving OST. Martindale had not provided evidence to support claims that Espranor eliminated or prevented the opportunity for removal of the medicine. A video on the Espranor website showed that the product remained on the tongue and available for removal for at least the eight seconds; the product was shown largely unchanged on the tongue. The SPC stated: 'Removal of Espranor from the mouth following supervised administration is *virtually* impossible due to its rapid dispersal on the tongue' (emphasis added). Indivior did not accept that this statement could be converted into the claim that the product 'eliminates' the opportunity for diversion. Indivior alleged that such claims were inaccurate, misleading and not substantiated.

The Panel noted its general comments and rulings above in relation to instant disintegration and diversion claims. The Panel noted that it might be difficult for a patient to remove Espranor from the mouth once administered but considered that it was misleading to state that Espranor and its 'instant disintegration' completely eliminated the opportunity for such removal. The Panel considered that such claims were too dogmatic. Insufficient information was given to enable a reader to assess the data. The Panel further noted the SPC statements above and considered that the claims at issue were misleading and not capable of substantiation; breaches of the Code were ruled. Indivior referred to the claims 'Espranor is not interchangeable with other buprenorphine products' which appeared on the website and 'Espranor was not directly interchangeable with other forms of buprenorphine' which appeared in each of the detail aids. Indivior stated that efficacy data confirmed that 'Espranor is not interchangeable with other buprenorphine products'. This was prominently featured on the packaging the SPC and PIL (either in bold, or in a boxed warning) and so should be similarly displayed on all materials to enable prescribers and patients to make informed choices. Indivior did not consider that Martindale had not gone to sufficient lengths to highlight that Espranor was not interchangeable with other buprenorphines used in OST; the text was not sufficiently prominent and this important information was not provided early enough in all of the materials in question and was not in the patient leaflet at all. Indivior alleged that Martindale had brought discredit upon the industry by underplaying a key prescribing issue and thus misleading prescribers.

The Panel noted that a boxed warning that Espranor was not interchangeable with other buprenorphine products was included in Section 4.2 of the SPC. A boxed warning appeared at the beginning of Section 2 (What you need to know before you take Espranor) of the PIL which read 'Espranor is not interchangeable with other oral buprenorphine products and the dose of Espranor may differ from the dose of other buprenorphine products'. This latter boxed warning was also part of the labelling on the product packaging as referred to in the PAR. The Panel noted that the EU Risk Management Plan discussed the prevention of error due to the wrong medication and noted the higher bioavailability of buprenorphine from Espranor than from Subutex. Medication errors were listed as an important potential risk in the summary of safety concerns.

The Panel disagreed with Indivior's contention that the warning in question should make it clearer that Espranor was not interchangeable with other buprenorphines used in OST. The Panel noted that some other buprenorphine products were licensed to treat, *inter alia*, moderate to severe cancer pain and severe pain which did not respond to non-opioid analgesics. The Panel noted Espranor's licensed indication, substitution treatment for opioid dependence, and that each item at issue was either promotional material for the product or for patients who had been prescribed it and discussed its licensed use. The Panel thus did not consider that the non-interchangeability warning at issue needed to qualify the reference to buprenorphines by stating that it applied to those used in OST. High standards had been maintained on this point. No breach of the Code was ruled.

The Panel disagreed with Martindale's submission that the warning in one of the detail aids, 'Espranor is not directly interchangeable with other forms of buprenorphine', stood out as the header because it was highlighted in blue. The Panel noted that all five subheadings on the page were in the same pale blue font. Two main headings were in purple font and the text was otherwise black. The Panel considered that the pale blue font colour and the overall design of the page, including the position of the warning in question as the subheading to the final paragraph at the bottom of the page, meant that it was not sufficiently prominent. Although, as submitted by Martindale, the warning in the Espranor SPC was in the same size as the rest of the text on that page, it was also within a box and 'Not

interchangeable with other buprenorphine products' was emboldened. The Panel considered that the warning should have been made more prominent given the therapy area, the vulnerable nature of the patients and its prominence in the SPC. A breach of the Code was ruled.

The Panel noted that the warning 'Espranor is not directly interchangeable with other buprenorphine products' was in the other detail aid followed by the prescribing information. Despite the use of emboldened font within the warning, the Panel considered that it should have been presented earlier in the detail aid given that the preceding pages discussed how Espranor delivered buprenorphine in OST more effectively than hard, compressed, sublingual formulations and compared its dissolution time to that of Subutex. The Panel considered that its comments above about the need for the warning to be more prominent were relevant here. High standards had not been maintained. A breach of the Code was ruled.

With regard to the Espranor website, the Panel noted that although the warning in the SPC had been reproduced in full and was within an outlined box, it was only presented towards the end of the health professional section. As above the Panel considered that it should have been presented earlier; high standards had not been maintained and a breach of the Code was ruled.

The Panel noted that Indivior had also alleged that the warning was not sufficiently prominent on page 15 of the website which comprised prescribing information. In this regard, the Panel noted that the prescribing information did not include the SPC. The Code dictated the content of prescribing information which included precautions and contraindications and warnings issued by, *inter alia*, the licensing authority which were required to be in advertisements and it also required prescribing information to be provided in a clear and legible manner. There was no reference in the relevant clauses about prominence of particular elements of the prescribing information. The Panel noted that the warning, 'Espranor is not interchangeable with other buprenorphine products' was in the same font size as the rest of the prescribing information within the Dosage and administration section. It was underlined as were 10 other phrases or sentences in the first column of prescribing information. It was not prominent such that it caught the reader's eye. Although the Panel considered that it would have been helpful if the warning had been visually more prominent in the absence of a specific direction or requirement of the Code, on balance, it did not consider that the company had failed to maintain high standards. No breach of the Code was ruled.

The Panel noted that the absence of the warning on the patient section of the website was covered by its ruling above.

With regard to the patient leaflet the Panel noted its relevant comments above including the content of the EU Risk Minimisation Plan and in particular noted the vulnerability of the patients and considered that in these particular circumstances it was important to ensure that all relevant information was made available. The Panel considered that the failure to include the verbatim warning (or similar) in the patient information leaflet was such that high standards had not been maintained. A breach of the Code was ruled.

The Panel noted the vulnerability of the patient population and that the highlighted warning was a prominent part of the SPC, PIL and the product pack. The Panel noted its comments above on the lack of prominence given to the warning across several materials and that it was not on the patient materials at issue at all. The Panel noted that prejudicing patient safety was given as an example of an activity likely to be in breach of Clause 2 of the Code. A breach of that clause was ruled.

Indivior alleged that Martindale misrepresented dissolution and disintegration data for Subutex when comparing it with Espranor, implying that there were greater differences in dissolution time to that shown by the head-to-head data. According to Indivior, Martindale also suggested that the difference was clinically important without providing any supportive evidence. Indivior referred to the SPC and clinical data and stated that dissolution and disintegration were not comparable nor interchangeable in this context. Indivior alleged that Martindale was misleading with this comparison; it had distorted the data, exaggerated and given undue emphasis to the benefits of Espranor compared with Subutex.

The Panel noted Indivior's submission that the SPC for Subutex stated 'The tablet should be kept under the tongue until dissolved, which usually occurs within 5 to 10 minutes'. The Espranor SPC stated that 'The oral lyophilisate should be … placed whole on the tongue until dispersed, which usually occurred within 15 seconds, and then absorbed through the oromucosa. Swallowing should be avoided for 2 minutes ... Patients should not consume food or drink for 5 minutes after administration'. The SPC further noted that physicians must advise patients that the oromucosal route of administration was the only effective and safe route of administration for Espranor. If the oral lyophilisate or saliva containing buprenorphine were swallowed, the buprenorphine would be metabolised and excreted and have minimal effect. The Panel noted its comments above about the clinical data regarding disintegration and diversion.

In relation to the website claim 'Unlike conventional hard compressed buprenorphine sublingual tablets which take up to 10 minutes to dissolve, Espranor instantly disintegrates within 15 seconds of being placed on the tongue resulting in rapid dissolution (median time 2 minutes)', the Panel noted that the latter part of the claim 'resulting in rapid dissolution (median time 2 minutes)' appeared at the top of the following page on the version provided by the complainant. The Panel noted its ruling of a breach of the Code in relation to a claim about instant disintegration within 15 seconds above. The Panel noted the reference to 5-10 minutes in the

Subutex SPC and considered that readers would probably compare the stated 'instant disintegration' of Espranor with the stated 'up to 10 minutes' dissolution time for the comparator. The Panel noted Indivior's submission that dissolution and disintegration were not comparable in this context and noted the parties' definition of terms. The Panel queried whether 'up to 10 minutes' was a fair reflection of the Subutex SPC. Those readers who saw the entire claim, which concluded on page 4, might compare Espranor's median dissolution time of 2 minutes with 'up to 10 minutes' for Subutex. The Panel considered that the claim in question 'Unlike conventional hard compressed buprenorphine sublingual tablets which take up to 10 minutes to dissolve, Espranor instantly disintegrates within 15 seconds of being placed on the tongue resulting in rapid dissolution (median time 2 minutes)' exaggerated the differences between the products and was misleading in this regard. The claim could not be substantiated. Breaches of the Code were ruled.

In relation to the website claim 'Buprenorphine is currently only available as hard compressed sublingual tablets which take up to 10 minutes to dissolve,' the Panel noted that whilst the claim itself did not refer to Espranor, the preceding paragraphs discussed Espranor and referred to its 'rapid dissolution' and 'Instant disintegration ...'. Closely similar claims about instant disintegration had been ruled in breach of the Code above. The Panel noted its comments above about the Subutex SPC and the phrase 'up to 10 minutes'. In the Panel's view, readers were invited to compare the stated 'up to' 10 minutes' dissolution time of the comparator with the stated instant disintegration of Espranor which were misleading and exaggerated the differences between the products. This comparison was incapable of substantiation. A breach of the Code ruled.

The Panel noted that the claim 'Conventional, hard, compressed, sublingual buprenorphine tablets take up to 10 minutes to dissolve' on the front page of one of the detail aid immediately followed the claim 'Espranor oral lyophillsate has been specifically designed to disintegrate instantly and dissolve rapidly when placed on the tongue'. This preceding claim, including the phrase 'disintegrate instantly', had been ruled in breach of the Code above. The emboldened unqualified claims on the front page of the detail aid included 'No delay. No diversion'. The Panel noted its comments above about the Subutex SPC and the phrase 'up to 10 minutes'. The Panel considered readers were invited to compare the stated 'up to' 10 minute dissolution time for Subutex with the stated instant disintegration of Espranor which gave a misleading and exaggerated comparison of the two which could not be substantiated. Breaches of the Code were ruled. The Panel noted that the claim 'In the UK, licensed buprenorphine is currently only available as hard-compressed sublingual tablets, which take up to 10 minutes to dissolve and may compromise supervised administration' was in the introductory section of one of the detail aids that discussed barriers to buprenorphine use (page 3). Whilst the preceding page and subsequent sections on the page in question discussed Espranor, the Panel noted that the only relevant statement in relation to Espranor across both pages was the first bullet point at the top of page 2 which read 'Espranor oral lyophilisate is a novel freeze dried wafer formulation of buprenorphine which disintegrates instantly and rapidly when placed on the tongue'. As noted above, claims about instant disintegration had been ruled in breach of the Code. The Panel noted the detailed information given across pages 2 and 3 of the A4 detail aid. Other than the aforementioned bullet point, there was no other mention of disintegration and dissolution. Visually no prominence was given to the aforementioned bullet point at the top of page 2 such that the Panel considered, on the balance of probabilities, that the claim in question on page 3, 'In the UK, licensed buprenorphine is currently only available as hard-compressed sublingual tablets, which take up to 10 minutes to dissolve and may compromise supervised administration' would not be read in light of the first bullet point on the preceding page and thus not a comparison with it. The design of the page was relevant. The Panel ruled no breach of the Code.

In relation to the allegation about the comparison on page 3 of the other detail aid, the Panel noted the page was prominently headed 'Espranor: rapid by design'. Beneath the left-hand column and the prominent subheading 'Instant disintegration' a clock face depicted that 96% of Espranor patients vs 72% with Subutex (p=0.0002) had partial disintegration (no longer removable from the mouth) at ≥15 seconds. The figure of 96% was prominent and in the same purple font as the claims 'rapid by design and instant disintegration'. The right-hand column was headed 'Rapid dissolution' beneath which the average time to complete disintegration (median) was visually depicted showing Espranor as 2 minutes and Subutex as 10 minutes, p<0.0001. The data was referenced to the Espranor SPC and Strang *et al* (2015). The Panel noted its comments on this page above. The Panel noted its comments above on the wording in the Subutex SPC. The Panel noted that the bar chart did not reflect the range of 5-10 minutes within which Subutex usually dissolved as stated in its SPC. The Panel noted that there were differences between the products in relation to disintegration and dissolution in favour of Espranor. The prominent subheading 'Instant disintegration' had previously been ruled in breach of the Code. The Panel noted that more comparative data was given on this page than for the claims at issue above. Nonetheless, the Panel considered that the failure to fairly reflect the Subutex SPC in conjunction with the prominent claim 'instant disintegration' meant that the comparison was misleading and exaggerated the differences between the products. The comparison was not capable of substantiation. Breaches of the Code were ruled.

The Panel noted the allegation that Martindale suggested that the above comparisons were clinically relevant which was not supported by the data. However, the Panel noted that whilst

claims had to be capable of substantiation, the burden was on Indivior to show that, on the balance of probabilities, such claims were not clinically relevant. It had not identified any data and Martindale had not responded to this point. The Panel noted that the studies before it in relation to different matters in this case included discussion of supervision times. In the Panel's view, Indivior had not discharged the burden of proof. The Panel ruled no breach of the Code.

Indivior noted claims regarding the reduced supervision time afforded by Espranor and that in support of such claims Martindale had referred to an excerpt of its clinical study report which was a key reference for multiple claims in its materials, but this had not been provided in a full enough form to confirm or deny the claim. It surmised: 'The faster speed of disintegration with [Espranor] *will* reduce the supervision time required compared to [sub-lingual buprenorphine], providing a greater convenience for both the patient and clinician, and the *potential for reduced supervision costs* in both the healthcare and prison systems' (emphasis added). Indivior did not consider that there was evidence to support the claims and again noted that the Espranor SPC stated '… Swallowing should be avoided for 2 minutes … Patients should not consume food or drink for 5 minutes after administration' which increased the required supervision time to at least 5 minutes.

The Panel noted Indivior's reasoning that, given wording in the Espranor SPC, supervision time should be at least 5 minutes. In the Panel's view, the aim of supervision was to ensure that the patient did not remove a dose for diversion. It was well-known that patients removed doses of buprenorphine from supervised consumption in creative ways.

The Panel considered that its comments above about the time taken to achieve partial and complete disintegration and diversion were relevant here.

The Panel noted Martindale's submission that there was no statement in the SPC to suggest supervision for 5 minutes to ensure that food was not consumed after taking Espranor; the only reference to supervision was during the initiation of treatment. Daily supervision of dosing was recommended to ensure proper placement of the dose on the tongue and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

The Panel noted that Strang *et al* (2017) concluded that 'Espranor's rapid disintegration and consequent greater ease of supervised dosing may increase the feasibility of buprenorphine treatment in busy community and custodial settings when supervised dosing is considered important. This now needs to be explored clinically'. The authors subsequently stated that 'hopefully rapid-dissolving variants of buprenorphine may increase the range of settings in which buprenorphine can safely be delivered such as settings where it is unrealistic to expect full supervision of dosing over several minutes'. These contexts would warrant attention in future studies. The Panel noted that the page of the clinical study report that had previously been disclosed to Indivior was more dogmatic, it stated 'The faster speed of disintegration with [Espranor] will reduce the supervision time required compared to the comparator, providing a greater convenience for both the patient and clinician, and the potential for reduced supervision costs in both the healthcare and prison systems'.

The Panel noted that there were differences between the products which were relevant to supervision time. The Panel considered that the phrase 'reduces the time required.' had to be considered in the context in which it was used.

The Panel noted that the website claim 'Rapid dissolution reduces the time required for supervised administration' was one of two bullet points and appeared immediately above the claim 'Instant disintegration eliminates the opportunity for removal from the mouth once administered' which was ruled in breach of the Code above in relation to the elimination claim. In addition, the phrase 'instant disintegration' was closely similar to matters ruled in breach of the Code above. In the Panel's view, the context including the unqualified claim about instant disintegration and elimination implied that the reduction in time required for supervision would be greater than it in fact was. In this regard, the claim 'Rapid dissolution reduces the time required for supervised administration' was misleading and incapable of substantiation. Breaches of the Code were ruled.

In relation to the claim 'Instant disintegration of Espranor reduces the time required by pharmacists for supervised self-administration of buprenorphine' in one of the detail aids, the Panel considered that its comments in relation to the first claim above applied here. 'Instant disintegration' was part of the claim at issue. Breaches of the Code were ruled.

The Panel noted that the third claim 'Minimises supervision time and reduces potential diversion for misuse.' was a prominent claim at the bottom of page 3 of the other detail aid on the same page as matters ruled in breach of the Code above in relation to comparative dissolution times and the claim 'Instant disintegration'. The Panel considered that the term 'minimises' was different to the term 'reduces'. It implied reduction to an almost irreducible amount. In the Panel's view, this implication was compounded by the other claims ruled in breach on the page. Overall, the Panel considered the claim misleading and incapable of substantiation. Breaches of the Code were ruled.

Indivior referred to the claim 'Equivalent safety and efficacy to sublingual buprenorphine' which appeared on page 8 of one of the detail aids and to 'Clinical trials show that Espranor is as effective as conventional compressed sublingual forms of buprenorphine at treating opioid dependence with a comparable safety profile' which appeared on the website. Indivior submitted that these claims

were in contrast to the statement '56.5% of patients reported mild AEs [adverse events] with Espranor compared with 7.7% of patients taking [sublingual buprenorphine]' found in both detail aids. Indivior also noted that Strang *et al* (2017) stated '… more AEs and Treatment-Emergent AEs with [Espranor] (mostly "mild")' and 'However, a greater proportion of [Espranor] subjects experienced at least one AE and similarly for TEAE (73.9 and 69.6%, respectively) compared to the [sublingual buprenorphine] group'. Indivior was concerned that Martindale had misrepresented the safety data on its website. It also noted that Martindale had additional risk minimisation measures stipulated in its risk management plan, as stipulated in the Public Assessment Report (PAR). Martindale did not address these in any of the materials Indivior had seen. Indivior further noted that there was no safety information in the patient leaflet.

The Panel noted that the first claim at issue was a subheading and read 'Equivalent safety and efficacy to sublingual buprenorphine'. It appeared on page 8 of one of the detail aids. The Panel noted Martindale's submission that the key safety concern facing any new formulation of buprenorphine was respiratory depression and the Espranor safety study which aimed to investigate this concern stated that whilst administration of Espranor did not result in a higher risk of respiratory depression when compared to sublingual buprenorphine a higher number of mild treatment-emergent adverse events (TEAEs) were reported in the Espranor group. Strang *et al* (2017) stated that a greater proportion of Espranor subjects experienced at least one AE and similarly for TEAE (73.0 and 69.6% respectively).

The Panel noted that although information about the greater incidence of mild adverse events with Espranor vs Subutex appeared on page 6 of the detail aid, the claim at issue 'Equivalent safety and efficacy to sublingual buprenorphine' appeared on page 8. The Panel considered that the claims and data on page 8 had to be able to stand alone in relation to the requirements of the Code and, in this regard, considered that the phrase 'Equivalent safety …' was not a fair overall reflection of the adverse event data given the difference in the incidence in mild adverse events and was misleading in this regard. The claim was incapable of substantiation and did not reflect the available evidence. Breaches of the Code were ruled.

The second claim at issue on page 7 of the website read 'Clinical trials show that Espranor is as effective as conventional compressed sublingual forms of buprenorphine at treating opioid dependence with a comparable safety profile' and was referenced to Strang *et al* (2015). There was no further discussion of the products' adverse event profiles. The Panel considered that its comments immediately above about the adverse event data applied here. The Panel considered that the claim at issue was not a fair reflection of the adverse event data in relation to mild adverse events. The claim was incapable of substantiation and did not reflect the available evidence. Breaches of the Code were ruled.

The Panel noted Martindale's submission that the patient leaflet was for those prescribed Espranor as a 'how to administer' guide and provided details of how to report side-effects. The patient would also have the Espranor patient information leaflet with the full list of adverse events. The Panel noted that the leaflet had to be able to stand alone with regard to the requirements of the Code. It was headed 'This leaflet is intended for patients that have been prescribed Espranor'. No information about the product was given other than a diagrammatic illustration of its administration and information on how to report side effects. Given its limited circulation to patients for whom the product had been prescribed and specific purpose to illustrate administration, the Panel, on balance, did not consider that it was necessary to include safety data as alleged. No breach of the Code was ruled.

Indivior presumed that Martindale chose to use its clinical study report to reference significant claims in its materials because Strang *et al* (2017) was not available at the time. Indivior asked a number of times for fully marked up references to support the claims. Martindale subsequently sent 6 out of at least 123 pages of the study report, which did not support the claims referenced, around 5 weeks later. Indivior was concerned that some claims were taken from extracts of the preamble of the study report and not from any data itself, and that other claims supported by the study report would require verification. Indivior had not seen the full report and was concerned at the length of time taken to receive final comments from Martindale.

Indivior was very concerned at the strength of some of the claims given that they appeared to be based on opinion and summation rather than data or peer-reviewed evidence.

The Panel noted that the Code required that substantiation for any information, claim or comparison must be provided as soon as possible, and certainly within ten working days, at the request of members of the health professions or other relevant decision makers. The Panel noted that the relevant clause had not been raised and so Martindale not been asked to comment on it and the Panel could make no rulings in that regard.

The Panel noted Indivior's concern with regard to the strength of some claims but also noted that Indivior had not identified the claims at issue; it was not for the Panel to identify the claims. In the Panel's view, it did not have a valid complaint to consider and thus ruled no breach of the Code.

Overall, Indivior alleged that high standards had not been maintained with regard to the launch campaign for Espranor. Indivior submitted that the alleged breaches were overall very serious and some in particular brought discredit upon, and reduced confidence in, the pharmaceutical industry. With regard to dependency therapy the NHS was under significant resource constraints, making it particularly important for the pharmaceutical industry to provide credible evidence based information to prescribers and patients alike about its products. Indivior alleged a breach of Clause 2.

The Panel noted its comments and rulings above and considered that Martindale had failed to maintain high standards; a breach of Clause 2 had also been ruled above.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. Examples of activities that were likely to be in breach of Clause 2 included, *inter alia*, prejudicing patient safety and/or public health.

The Panel noted its rulings of breaches and comments above. The Panel noted the vulnerability of the patient population and the therapy area. The Panel noted Indivior's reference to the need for evidence-based information and, in this regard, noted the difficulties of undertaking studies in this patient population. The Panel noted the small study size, Espranor n=23 and sublingual buprenorphine, n=13 and that it was unblinded. The Panel considered that further information about the study should have been provided in the materials to enable the reader to assess the data. This was particularly so given the strong unqualified nature of some of the claims at issue. In addition, the Panel considered that the cumulative effect of advertising Espranor to the public and encouraging patients to ask for it, implying that there was absolutely no possibility of diversion, and claims in relation to reduced supervision time due to the instant disintegration of Espranor, which was not so, prejudiced patient safety and a further breach of Clause 2 was ruled.

Indivior complained about the promotion of Espranor (oral lyophilisate) by Martindale Pharmaceuticals Limited. Indivior marketed Subutex (buprenorphine sublingual tablets). Both Espranor and Subutex were indicated for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

At issue were two Espranor detail aids, one entitled 'Product Overview (ADD/11/2016/122)', the second entitled 'Straight to the Point (ADD/01/2017/130)'; a patient leaflet (ADD/12/2016/127) and an Espranor website, www.espranor.com (ADD/01/2017/133).

Martindale noted that in its correspondence Indivior referred to the use of the product names Xprenor and Espranor. To clarify, the original market authorization (MA) holders of this product made the initial submission to the Medicines and Healthcare products Regulatory Agency (MHRA) under the brand name Xprenor. The submission was subsequently withdrawn and Martindale, who took over as the market authorization holder, performed both safety studies under the name of Xprenor. The UK and Indian studies in the clinical study report were also carried out as per MHRA guidance, using the product name Xprenor. However, a trademark conflict was subsequently discovered, so the product name was changed to Espranor in 2015. Hence the product originally named Xprenor in the clinical studies was subsequently licensed and launched as Espranor.

Indivior stated that after inter-company dialogue which dated back to 1 March 2017, it was unable to accept Martindale's responses and therefore submitted a complaint.

1 Promotion to the public on the Espranor website

The landing page of the Espranor website (espranor.com), was headed 'Welcome to Espranor (Buprenorphine oral lyohilisate)' followed by 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment'. The following paragraph stated 'This site provides information on Espranor for UK-based healthcare professionals and patients. Please select from the buttons below to tailor the content to your needs'. The options given were 'I am a UK healthcare professional' and 'I am NOT a healthcare professional'.

The page that the reader was taken to if they selected 'I am NOT a healthcare professional' was headed 'This website is for patients interested in opioid substitution therapy and Espranor'.

COMPLAINT

Indivior noted that the landing page to the Espranor website (last accessed 23 June 2017) included an unreferenced claim 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment'. This claim was directly visible to all visitors to the website ie patients and health professionals worldwide. When a reader scrolled down on the homepage, the options to enter the website as 'a UK health professional' or 'not a health professional' were visible at the bottom.

Indivior stated that the 'not a health professional' section linked to a new page which appeared to be a general page for patients whether they were on Espranor or not. This 'general patient' section of the website on page 17 was entitled 'This website is for patients interested in opioid substitution therapy and Espranor'. Indivior was concerned that the website was promotional and encouraged patients to request Espranor, rather than make an informed decision in consultation with their health professional. Indivior was also concerned that important safety information, identified in the summary of product characteristics (SPC), such as 'Espranor is not directly interchangeable with other buprenorphine products', was not addressed on this page.

Indivior stated that Martindale was advertising directly to the public. In Indivior's view the website encouraged patients to ask for Espranor, rather than assist patients already on Espranor. As highlighted in matters below, Indivior considered that the claim 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid

dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment' was misleading and not supported by evidence, in breach of Clauses 7.2, 26.1 and 26.2.

RESPONSE

Martindale refuted Indivior's allegation of breaches of the Code and submitted that the Espranor website was created for health professionals and patients who had been prescribed Espranor. The landing page clearly stated that it 'provides information on Espranor for UK based healthcare professionals and patients'. There was a clear button to select the appropriate page relevant to the viewer. This website would only be accessed by someone who knew the name Espranor by receiving a prescription for it. It was never intended for anyone who had not already received a prescription for Espranor. The website directed patients to speak to their doctor if they had any specific questions about their health or treatment. There was no link from the Martindale Pharma website to the Espranor website, so members of the public would not accidentally find this website when they sought information about the company or its products.

Martindale strongly refuted the allegation that it was advertising directly to the public and submitted that statements on the patient page were supported by clinical data.

Patients already on opioid substitution therapy (OST) were clearly dependent on their current medication. They were vulnerable and any change in their medication was likely to cause anxiety. It was well recognised that in any consultation with a health professional, a patient would only retain approximately 50% of the verbal information they were given. The aim of the website was to provide relevant information for those patients who had already been prescribed a new OST product, in this case Espranor.

In response to a request for further information, Martindale reiterated that the website was created for health professionals and patients who had been prescribed Espranor; it provided information for UK based health professionals and patients and would only be accessed by someone who knew the name Espranor by receiving a prescription for it. The website was not intended for those who had not already been prescribed Espranor. There was no link from the Martindale Pharma website to the Espranor website, so members of the public would not accidentally find this website when seeking information about the company or its products.

Martindale further submitted that there were currently no materials given to health professionals regarding the Espranor website. Health professionals would only be told about the website if they asked if there was one.

Martindale submitted that the name Espranor was not derived from the word buprenorphine and hence would not be intuitively found. An OST patient who was prescribed Espranor was likely to Google the name which would lead them to the website which was not mentioned on the Martindale Pharma website.

Martindale aimed to create a user friendly website, that acknowledged that the patient was interested enough to have found the name of their new medication. Martindale submitted that the patient group accessing the website was one and the same (being prescribed Espranor and interested enough to use it).

PANEL RULING

The Panel noted that this point solely concerned the website. The Panel noted that the page numbers on the printed version of the website provided by the complainant differed to those on the printed version provided by Martindale. At all points in its ruling the Panel referred to the page numbers as they appeared in the version provided by the complainant.

The Panel noted Indivior's concern that the claim 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It was licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment' on the Espranor website landing page promoted Espranor to the public and encouraged members of the public to ask for it.

The Panel noted Martindale's submission that the website in question would only be accessed by someone who knew the product name Espranor after receiving a prescription for it. The Panel noted that the patient section of the website stated that it was for 'patients interested in opioid substitution therapy and Espranor' and considered that its audience was therefore wider than just patients who had been prescribed the product. The Panel noted that the website was open access and the homepage would potentially be seen by a broad audience. This was not unacceptable so long as the website complied with the Code and relevant parts were suitable for the general public: the supplementary information to Clause 28.1, 'Access' was relevant. The Panel noted that the website was directed at not only health professionals and patients for whom the medicine had been prescribed, but also the general public. Irrespective of the intended audience, the open access homepage should be suitable for the general public. The Panel noted that the claim in question on the landing page 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment' would be seen by this wide audience and considered that it promoted a prescription-only medicine to, *inter alia*, the public and encouraged them to ask their doctor to prescribe it. Breaches of Clauses 26.1 and 26.2 were ruled.

In relation to that part of the website which stated that it was for patients interested in OST and Espranor, the Panel noted that it contained information about Espranor and a link to the patient leaflet rather than general information about OST and all relevant treatments. In the Panel's view, this section of the website might be generally suitable for patients for whom Espranor had been prescribed, rather than the general public and it encouraged the general public to seek a prescription for it. A breach of Clause 26.2 was ruled.

The Panel further noted Indivior's concern that the claim 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment' was misleading and not supported by evidence. Indivior did not provide detailed allegations or evidence in support but referred to later complaints. Martindale had not responded to this matter at point 1. It was not possible to consider the complaint on this matter at this point in the absence of detail from either party. The matter in relation to the phrase 'instant disintegration' and Clause 7.2 was thus covered by the Panel's ruling at point 3 below. The Panel noted that Indivior had not cited Clause 7.3 in relation to substantiation.

The Panel noted Indivior's concern that page 17 of the website headed 'This website is for patients interested in opioid substitution therapy and Espranor' did not include important safety information, identified in the SPC, such as 'Espranor is not directly interchangeable with other buprenorphine products'. The Panel noted that the webpage in question gave top line information about Espranor including its indication and administration and stated that readers should speak to their doctor if they had any specific questions about their treatment. A reference to the Yellow Card Scheme appeared at the bottom of the page. A link to the patient information leaflet (PIL) was provided for further information on the following page in a section entitled 'Resources'. The PIL included the warning 'Espranor is not interchangeable with other oral buprenorphine products and the dose of Espranor may differ from the dose of other buprenorphine products' in an outlined box at Section 2 on the first page. The Panel noted its comments above about the unclear nature of the intended audience and its rulings of breaches of the Code. The page in question (page 17) described Espranor as a new wafer form of buprenorphine and referred to its use as a substitute for opiate drugs such as morphine or heroin. The Panel noted Martindale's submission about the vulnerability of OST patients and that any change to medication would cause anxiety. The Panel considered that the statements about Espranor might particularly encourage patients to consider the issue of interchangeability. The Panel considered that the page ought to be capable of standing alone as regards the medicine's risk/benefit profile and compliance with the Code and could not rely on the patient information leaflet in that regard. Readers would not necessarily click on the link. In addition, the Panel noted that the EU Risk Minimisation Plan discussed medication errors noting the higher bioavailability of buprenorphine in Espranor compared with Subutex. The Risk Minimisation Plan included a patient guide, page 2 of which featured a boxed statement which included the warning that 'You should not swap Espranor for sublingual buprenorphine, or the other way around, without your health professional's advice. Given the prominence given to the interchangeability warning in the PIL, that the content of the page appeared to be directed at, *inter alia*, patients and the points raised above including the vulnerability of those patients, the Panel considered the omission of such information meant that this section was not presented in a balanced way. In the Panel's view, the non-interchangeability warning did not necessarily need to be reproduced verbatim however, closely similar information should be conveyed. A breach of Clause 26.2 was ruled.

2 Diversion claims

Claim 'This renders the buprenorphine dose impossible to remove from the mouth once administered' appeared in page 8 of the 'Product Overview' detail aid.

Claim 'No delay, No diversion, No nonsense buprenorphine' appeared in page 1 of the 'Straight to the Point' detail aid.

COMPLAINT

Indivior stated that misuse (intentional and inappropriate use not in accordance with the authorised product information which could be accompanied by harmful physical or psychological effects) and diversion (the unsanctioned supply of regulated medicines from legal sources to the illicit drug market, or to a user for whom the drugs were not intended) of medicines used in opioid use disorder was a well-known and accepted adverse event that occurred with opioid agonists, including buprenorphine. It was well-established that patients removed doses of buprenorphine from supervised consumption in creative ways. Larance *et al* (2011) showed that 23% of OST patients reported having removed a supervised dose and for those on buprenorphine, 90% of doses had been removed directly from the patient's mouth. This was seen equally with a tablet and with wafer/film formulations. This data highlighted the significant challenge health professionals, payors and carers faced with diversion of opioid medication.

Indivior noted that Martindale had not provided evidence to support the claims. In response to queries related to the claim 'This renders the buprenorphine dose impossible to remove from the mouth once administered', Martindale referred to the SPC which stated: 'Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue'. Indivior alleged that the claim was not only exaggerated, but was not supported by the evidence

provided. Indivior stated that this information was harmful to prescribers and patients as it created the illusion that it was not possible to remove the medication once on the tongue.

Indivior submitted that Martindale's claim, the phrase 'No diversion' was not substantiated with any evidence or clinical trial data. Indivior did not consider that the claims were accurate and, as such, they were misleading and not substantiated by clinical evidence. Information about adverse events (in this case misuse and diversion of buprenorphine) did not reflect the available evidence. Indivior alleged breaches of Clauses 7.2, 7.4, 7.6 and 7.9.

RESPONSE

Martindale submitted that Larance *et al* was an Australian study, which used products from other companies. The entire basis of the Espranor product development related to the oral lyophilisate technology, producing 'instant dissolution' as per Seager (1998). This was developed to specifically target the misuse and diversion issues encountered with existing licensed buprenorphine products. Larance *et al* was published before Espranor was licensed. Indivior submitted that the results of this study could not, therefore, be presumed to apply to the Espranor oral lyophilisate formulation. As stated earlier, the formulation of Espranor was specifically developed to provide clinicians and patients with a clinically effective formulation of OST which would reduce the risk of diversion and abuse. The data contained in the Clinical Study Report confirmed the rapid disintegration of the formulation when it touched the tongue, minimising the risk of diversion through the removal of a supervised dose.

Martindale noted that, as an oral lyophilisate, Espranor needed careful handling; each individual freeze-dried 'oral lyophilisate' of buprenorphine was foil wrapped in a blister. Once the blister was opened, it was recommended that the oral lyophilisate was placed on the tongue immediately as the wafer was very sensitive to moisture and susceptible to disintegration. Espranor oral lyophilisate was able to be handled with dry hands. Once the oral lyophilisate touched saliva on the tongue, 96.3% partially disintegrated in ≤15 seconds rendering it unable to be removed from the mouth (this was because it would have dissolved in saliva). The definition of partial disintegration according to the Clinical Study Report was that the formulation could no longer be removed from the mouth.

This was represented in the SPC with the following wording:

> 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds, and then absorbed through the oromucosa' and "Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue"'.

The study protocol, which Martindale had not provided to Indivior as it was commercially sensitive in its entirety, referred to a paper by Seager, which was the basis of the product development for Espranor. This paper stated the following with regard to the Zydis technology and the 'instant disintegration: The Zydis fast-dissolving dosage form was a unique freeze dried medicinal tablet, made from well-known and acceptable materials. When Zydis units are put into the mouth, the freeze dried structure disintegrates instantaneously releasing the drug which dissolved or dispersed in the saliva'.

Martindale provided Indivior with page 116 of the Clinical Study Report headed 'Discussion and Conclusions' which contained the following information, which was also provided to Indivior:

> 'This study demonstrates that the Xprenor tablet starts to disintegrate on the tongue in ≤15 seconds in 96.3% of administrations, with a median time to complete Xprenor tablet disintegration of 2 minutes compared to 10 minutes with Subutex. The faster speed of disintegration with Xprenor will reduce the supervision time required compared to Subutex, providing a greater convenience for both the patient and clinician, and the potential for reduced supervision costs in both the healthcare and prison systems.'

Taking the study data into account, it was difficult to see how the product would be removed from the mouth when in 96.3% of administrations the product had started to disintegrate on the tongue in ≤15 seconds. If the product could not be removed from the mouth, it could not be diverted.

In response to a request for further information Martindale provided the following dictionary definitions with references for dispersal, dissolution, disintegration and dissolving:

A Disperse: (Chemistry) Distribute (small particles) uniformly in a medium Synonym: Dissolve

B Dissolution:
- The action or process of dissolving or being dissolved
- Disintegration; Decomposition

Synonym(s): Dissolving, Disintegration

C Disintegrate: Break up into small parts as a result of impact or decay Synonym: Dissolve

D Dissolve: (with reference to a solid) become or cause to become incorporated into a liquid so as to form a solution Synonym(s): Disintegrate, Disperse.

Martindale noted that its clinical study report defined time to partial disintegration as no longer able to remove from the mouth.

FURTHER INFORMATION FROM INDIVIOR

In response to a request for information, Indivior clarified its understanding of the terms: dispersal, dissolution, disintegration and dissolving.

Indivior assumed that the Panel was referring to these in relation to the unresolved complaints below and what Indivior believed was the direct marketing of some of those claims to patients on the patient website:

- Unresolved Complaint 2: Impossible to remove and NO Diversion;
- Unresolved Complaint 3: Instant disintegration (multiple claims)
- Unresolved Complaint 4: Instant disintegration eliminates the opportunity for removal from the mouth.

Indivior stated that it was in that context that it was responding. Indivior noted that given the context in which the terms were used, it had analysed and interpreted the meaning of such words in the context of what might be understood by the general public and health professionals on reading such terms and, in a more specific context, to assess whether this provided any further clarity.

Indivior stated that the reader of the material was likely to be a patient affected by opioid use disorder, a carer of such a patient, or a health professional involved in the care of such patients applying their general understanding without reference to specific medical definitions (such as those in relation to bioequivalence mentioned below). Thus, Indivior considered that a general definition of these terms was best understood, assessed and defined by the Oxford English Dictionary definitions as detailed below:

1 Dispersal (n): The action or process of distributing or spreading things [or people] over a wide area.
2 Dissolution (n): The action or process of dissolving or being dissolved.
3 Disintegration (n): The process of coming to pieces.
4 Dissolving (v-dissolve): (with reference to a solid). Become or cause to become incorporated into a liquid so as to form a solution.

Notwithstanding the above, Indivior had specifically analysed the relevant terms in a medical context to assess any alternate interpretation to provide further clarity.

- **Dissolution**

  The EMA Guideline on the Investigation of Bioequivalence used the term 'dissolution' and Indivior considered that the associated specific medical definition was 'the rate of drug release from a dosage form'; hence medicines could be described in terms of dissolution time, or dissolution profile. In this context, Indivior noted that the Espranor Public Assessment Report (PAR) confirmed that '[Espranor's] bioequivalence to [Subutex] has not been demonstrated' but Martindale had received a biowaver and a requirement to place a boxed warning on packaging stating 'Espranor is not interchangeable with other buprenorphine ...'. As such, there was a different dissolution of the Espranor product compared to the mono-buprenorphine sublingual tablets.

- **Dissolving and Disintegration**

  Indivior believed the term 'dissolving' to be intrinsically linked to the term 'dissolution'; they seemed impossible to separate (as seen by the Oxford English Dictionary definitions). Indeed, 'dissolving' might be seen as the process to achieve 'dissolution'. Accordingly, Indivior did not believe there to be any material differences between 'dissolving' and 'dissolution', nor in the way Martindale used the terms.

  The Espranor Public Assessment Report (PAR) used the terms 'dissolving' and 'disintegration' seemingly interchangeably and as a general principle, Indivior did not take issue with that (indeed the pivotal paper, Strang *et al* 2017 provided earlier used the terms interchangeably). Moreover, given the meaning of 'disintegration' highlighted above, 'the process of coming to pieces', it was logical that 'disintegration was a necessary part of (if not a pre-requisite for) 'dissolving'. Accordingly, whilst it was possible that from a medical point of view there might be subtle differences between 'dissolving' and 'disintegration'; given the general public understanding highlighted above, and the context in which such statements were used by Martindale, Indivior did not believe such differences were material.

  However, Indivior noted that the disputed Martindale claims were not supported by the PAR. The report highlighted that the mean time for complete disintegration was 2 minutes. Hence, as identified in complaints 3 and 4, references to 'instant disintegration' could not be supported.

- **Dispersal**

  In a medical context and building on the general public understanding, Indivior considered it logical to interpret 'dispersal' as meaning the physical distribution/dissemination of a medical material following administration. Accordingly, this was slightly different from 'dissolving', 'dissolution' and 'disintegration'. Indivior stated that in applying logic, one could conclude that dispersal could only occur following the dissolution, dissolving or disintegration of the relevant material to some extent, and might only be completely dispersed following complete dissolution, dissolving or disintegration.

  Indivior stated that through the above, it could be seen that (save for the technical definition associated with 'Dissolution' taken from EMA bioequivalence testing) there was little difference between the medical and general understanding of these terms.

Impact of definitions in context

A Infer a relationship of dissolution (which implied bioequivalence)/disintegration and subsequent benefits

Indivior noted that Martindale made disputed claims that were associated with the 'instant disintegration' claims (unresolved complaint 4 in its letter of 26 June 2017) for example, 'eliminating the opportunity for removal from the mouth once administered' and 'instant disintegration eliminates the opportunity for removal ...' amongst other such claims. Indivior was concerned that the reader would believe these disputed claims, and infer benefit which was associated with bioequivalence (and dissolution/ disintegration).

B Confusion as to the instant properties of Espranor

Indivior noted that the words being assessed had been used interchangeably by Martindale in its materials. Whilst arguably such use was not in line with the EMA definition, the concern was that the use of such terms inferred a relationship to bioequivalence and subsequent benefits which were not substantiated, particularly with reference to 'instant' which could not be substantiated.

Indivior believed that in Martindale claiming Espranor's instant dispersal, dissolution, disintegration and dissolving, Martindale made the association that the product had been completely taken, as if it were ingested or impossible to divert; this implication was self-evident from the claims 'impossible to remove from the mouth once administered' and 'No delay, No Diversion'. However, this was not substantiated:

a) Espranor's PAR acknowledged that the mean time for complete disintegration was 2 minutes; and
b) It was acknowledged the active ingredient (buprenorphine) in fact remained on the tongue for up to 15 minutes before 'complete disintegration' [Strang *et al* 2017, figure 2].

Whilst Indivior believed that the differences in time above related to the differences between disintegration of the physical delivery system/film and the disintegration of the buprenorphine itself, it was evident that neither of these were 'instant'. As such, the indication that the product had been completely taken as if ingested or impossible to divert was consequently erroneous.

In that context, Martindale used the above terms in relation to Espranor without drawing a distinction between the dispersal, dissolution, disintegration and dissolving of the physical delivery system used to administer the active ingredient and the dispersal, dissolution, disintegration and dissolving of the active ingredient itself. Notwithstanding that reference to 'instant' dispersal, dissolution, disintegration and dissolving was not substantiated, the implications of Martindale's use of such terminology in relation to Espranor, especially when predicated by reference to 'instant', was that there was instant dispersal, dissolution, disintegration and dissolving of the medicine; when in reality, the active ingredient (the fundamental issue and aspect most liable to misuse and diversion) did not benefit from such instant dispersal, dissolution, disintegration and dissolving.

C Misleading impact on the risk of misuse and diversion of the Espranor product and active ingredient

Indivior noted that building on the above, Martindale went further and claimed that Espranor was 'As easy to administer and take as methadone', which was a liquid for ingestion, and therefore incorrectly inferred that Espranor could not be diverted or removed from the mouth. It was noted that Martindale made indirect (and in some cases) associations with terms that implied bioequivalence (ie dissolution, which was used interchangeably with the other terms) with mono-buprenorphine/Subutex sublingual tablets and also stated that Espranor 'renders the buprenorphine dose impossible to remove from the mouth once administered' and so clearly claimed that with Espranor it was not possible to divert the active ingredient, however, it was also acknowledged that, in fact, it remained on the tongue for up to 15 minutes before 'complete disintegration'; [Strang *et al* 2017, Figure 2].

Indivior being aware that the mono-buprenorphine was a highly desirable medication that was often diverted and misused and, in its experience, took 5-10 minutes to dissolve in the mouth, was concerned that health professionals and carers would be misled by the claims that Martindale was making which were unsubstantiated by evidence. It was unclear how 'instant dissolution', even if it were true of the physical delivery system itself, would prevent someone from removing the 'dispersed'/'dissolving'/'dissoluted'/'disintegrated' product from the tongue with active ingredient (and/ or saliva containing such active ingredient), and misusing it, or diverting it.

PANEL RULING

The Panel noted that it had asked both Martindale and Indivior to define certain terms including dispersal, dissolution, disintegrate and dissolve. The parties' definitions were not wholly dissimilar. However, the Panel queried whether Martindale had applied sufficient rigour to the consistent application of the terms throughout the materials such that their meanings were clear. The Panel noted that this matter was further complicated as the use of certain terms also appeared to be somewhat inconsistent in the various studies and public documents. In this regard, the Panel noted Indivior's submission that dissolving and disintegration were used seemingly interchangeably in the Espranor PAR and Strang *et al* (2017). The Panel, of course, was only concerned with the materials produced by Martindale which had to comply with the Code.

The Panel noted that the parties referred to Strang *et al* (2015), the Clinical Study Report (2014) and Strang *et al* (2017). The Panel noted that all three related to the same study data. Strang *et al* (2015) was a presentation based on data from the Clinical Study Report and the published 2017 paper was the published record of the Clinical Study Report and bore the same EudraCT number. The Panel noted that the materials at issue appeared to pre-date the publication of the 2017 paper although not its

submission for publication in 2016. The Panel noted that materials had to reflect evidence available at the point of certification. Papers published subsequently were relevant if it meant that materials no longer complied with the Code and required amendment/ withdrawal. In this regard, Strang *et al* (2017) did not appear to be new data – it summarised and was the published record of the 2014 Clinical Study Report.

The Panel considered that its general comment above at point 1 about the page numbers applied to the website by the complainant were relevant here. The Panel adopted the page numbering applied by the complainant.

The Panel noted that the claims at issue 'This renders the buprenorphine dose impossible to remove from the mouth once administered' and 'No delay, No diversion, No nonsense buprenorphine' implied that there was absolutely no possibility that a dose could be removed from the mouth following supervised administration (diversion) which was not so. At Section 4.4, Special Warnings and Precautions For Use, Diversion, the Espranor SPC stated 'Removal of Espranor from the mouth following supervised administration is *virtually* impossible due to its rapid dispersal on the tongue' (emphasis added) which implied that that there was a potential for the dose to be removed from the mouth following its supervised administration. The Panel further noted that Strang *et al* (2017) defined disintegration as the point when 'the tablet could no longer be removed intact' and stated that over all periods, 96.3% of [Espranor] administrations achieved partial disintegration on the tongue in ≤ 15 seconds' and 'The median time for complete [Espranor] tablet disintegration was 2 minutes ...'. This meant that 3.7% of administrations took longer than 15 seconds to achieve partial disintegration leaving potential for the dose to be removed. By 2 minutes, Espranor had completely disintegrated in 58% of administrations. According to the Clinical Study Report on which Strang *et al* (2017) was based, there were four recordings of either partial or complete disintegration at 15 minutes. The Clinical Study Report also differed from Strang *et al* in that partial disintegration was defined as 'no longer able to remove from the mouth'. The reason for the difference was not explained in either publication. The authors' discussion in the published paper referred to 'remarkably rapid disintegration with complete disintegration by 3 minutes for more than 75% of Espranor administrations ...'. The authors also noted that on the first days some anxious patients had very dry mouths resulting in slower disintegration.

The Panel noted its comments above. The Panel noted that the definition of disintegration in Strang *et al* (2017) only referred to the impossibility of removing the intact tablet and in this regard noted Indivior's comment about removing the disintegrated product or saliva containing the dissolved product. The Panel noted the qualified statement in the Clinical Study Report that a benefit of the reduced time to disintegration with Espranor was 'the *reduced potential* for concealment and diversion' (emphasis added). Similarly, on page 3 of the Straight to the Point detail aid the qualified phrase '... reduces potential diversion for misuse' appeared. The Panel considered that the claims in question 'No diversion.' and 'This renders the buprenorphine dose impossible to remove from the mouth once administered' were too dogmatic and implied there was absolutely no possibility of diversion, however small, and that was not so. This implication was compounded in relation to the latter claim as it appeared beneath the unqualified heading 'Espranor *prevents* the most common route of diversion' (emphasis added). The Panel considered that the claims in question were misleading and could not be substantiated, breaches of Clauses 7.2 and 7.4 were ruled in relation to each claim.

Clause 7.6, as raised by Indivior, stated that when promotional material referred to published studies, clear references must be given. Clause 7.6 applied to references to published material, including the use of quotations, tables, graphs and artwork. The Panel noted that Indivior had not identified the reference/s in the material to published studies. It was not for the Panel to identify the references for Indivior. In the Panel's view, it did not have a valid complaint to consider and thus ruled no breach of Clause 7.6.

The Panel further noted Indivior's allegation that the information about adverse events (in this case misuse and diversion of buprenorphine) did not reflect the available evidence. The Panel considered that the claims in question might potentially be harmful to patients as doctors might assume that it was absolutely impossible for patients to remove the dose which was not necessarily so. However, Clause 7.9 of the Code related to claims about adverse reactions reflecting available evidence and not stating that there were no adverse reactions, toxic hazards or risks of addiction or dependency. The Panel noted Indivior's submission that, *inter alia*, diversion was a well-known and accepted adverse event with opioid agonists including buprenorphine. The Panel noted diversion was not listed in Section 4.8, Undesirable effects, of the Espranor SPC. In the Panel's view, the claims in question did not fall within the remit of Clause 7.9, they related to the likelihood of the product's diversion rather than adverse reactions and risk of dependency etc which might arise after administration of the product post diversion and ruled no breach of that Clause accordingly.

3 Instant disintegration claims

Claim 'Espranor allows instant disintegration and rapid dissolution when placed on the tongue'. This appeared on the home page of the website. Indivior also referenced alongside this claim 'disintegrate instantly' and 'instant disintegration' which each appeared in the 'Straight to the Point' detail aid on pages 1 and 2 respectively.

Claim 'Espranor oral lyophilisate is a novel freeze-dried wafer formulation of buprenorphine which disintegrates instantly and rapidly dissolves when placed on the tongue' which appeared on page 2 of the Product Overview detail aid.

Claim '… has been specifically designed to disintegrate instantly and dissolve rapidly when placed on the tongue' which appeared on the front page of the 'Straight to the Point' detail aid.

Claim 'Instant disintegration of Espranor reduces the time required by pharmacists for supervised self-administration of buprenorphine' which appeared on page 8 of the 'Product Overview' detail aid.

Claim Espranor instantly disintegrates within 15 seconds …' which appeared on page 3 of the website. Alongside this claim Indivior referred to 'Instant disintegration' on page 3 of the Straight to the Point detail aid.

Claim '… buprenorphine that instantly disintegrates on the tongue …' which appeared on page 6 of the website. Alongside this claim Indivior referred to 'dissolve instantly' which appeared on page 17 of the website.

COMPLAINT

Indivior stated that Martindale had been unable to provide data to support claims that Espranor instantly disintegrated when placed on the tongue. In fact, the evidence it provided showed that this was not the case. Martindale referred to Strang *et al* (2015) which stated '[Espranor] completely disintegrating within 2 minutes in 58% of administrations' and later provided Strang *et al* (2017) which stated 'Over all periods, 96.3% of [Espranor] administrations achieved partial disintegration on the tongue in ≤15' with a quotation including a question mark in figure 2 stating 'Partial or complete disintegration at 15 s?'. Indivior reproduced a figure from Strang et al (2017) which showed that complete disintegration occurred at 15 minutes. The same figure was also included in the 'Product Overview' detail aid.

Indivior stated that Martindale referred to the proprietary Zydis technology website which was the basis of its product and stated 'The Zydis ODT (orally dissolving tablet) fast-dissolve formulation, is a unique, freeze-dried oral solid dosage form that *disperses almost instantly in the mouth* – no water required' (emphasis added) and Seager (1998) to support the instant disintegration claim. Martindale took no account of the fact that the active ingredient buprenorphine was also present in Espranor, and that there was no data to show that buprenorphine together with Zydis technology resulted in 'instant disintegration'. In fact, complete disintegration of Espranor took 15 minutes according to Martindale's own data.

Indivior noted that conflicting claims were presented side-by-side in the PIL which stated 'Instant Disintegration', followed by 'Average time to complete disintegration (median): 2 minutes', further confusing patients.

Indivior considered that the claims were inaccurate, misleading and misrepresented the data which was unsubstantiated by the published evidence in breach of Clauses 7.2, 7.4 and 7.6.

Given the data Martindale provided, Indivior was furthermore confused that the SPC stated 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds'.

RESPONSE

Martindale submitted that the Espranor oral lyophilisate formulation had characteristics that were very different to that of a tablet. It was a fragile, freeze-dried 'wafer' which had been individually foil wrapped in a blister. Once the blister was opened, it was suggested that the oral lyophilisate was placed on the tongue immediately, as the wafer was very sensitive to moisture and susceptible to disintegration. Espranor oral lyophilisate was to be handled with dry hands. It was clear, therefore, that once the oral lyophilisate touched saliva on the tongue, 96.3% partially disintegrated in ≤15 seconds rendering it unable to be removed from the mouth (this was because it would have dissolved in saliva). The definition of partial disintegration, according to the Clinical Study Report, was that the formulation could no longer be removed from the mouth. Martindale submitted that the study data supported the claim, in the context of both the fragile structure of the wafer and the definition of partial disintegration. This was represented in Section 4.4 of the SPC which stated that 'Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue'. Martindale noted that this wording was reviewed and approved by the Medicines and Healthcare products Regulatory Agency (MHRA) based on the study data.

As stated earlier, Seager (1998), which was the basis of the product development for Espranor, stated the following with regards to the Zydis technology and the 'instant disintegration':

> The Zydis fast-dissolving dosage form is a unique freeze dried medicinal tablet, made from well-known and acceptable materials. When Zydis units are put into the mouth, the freeze dried structure disintegrates instantaneously releasing the drug which dissolves or disperses in the saliva.

Martindale noted that Indivior stated that there was no data to show that buprenorphine with the Zydis technology resulted in instant disintegration. However, the first time point measured in the Espranor Phase II study was 15 seconds, no data was available prior to this time point, as it was not measured. According to the published study results, 'Oral disintegration time of (Espranor) and [a sublingual buprenorphine], was measured by direct observation, measuring (a) time to disintegration (i.e., tablet could no longer be removed intact) and (b) time until completely dissolved'.

At 15 seconds, results showed that 96.3% of Espranor administrations achieved partial disintegration on the tongue vs 71.8% with the competitor, ($p < 0.001$). The definition of partial

disintegration, according to the Clinical Study Report, was that the formulation could no longer be removed from the mouth.

Section 4.2 of the Espranor SPC stated:

> 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds, and then absorbed through the oromucosa. Swallowing should be avoided for 2 minutes. The oral lyophilisate should be taken immediately after opening the blister. *Patients should not consume food or drink for 5 minutes after administration'.* (emphasis added).

Martindale noted that this wording was reviewed and approved by the MHRA based on the study data.

PANEL RULING

The Panel noted its general comments at point 2 above including the parties' definition of relevant terms and the adoption of website page numbers in the printed version provided by the complainant. The Panel also noted that its comments at point 2 above about diversion were relevant to the claims presently at issue about instant disintegration.

The Panel noted that this matter was further complicated by apparently inconsistent use of the term disintegration. For instance, as noted by Indivior, the patient information leaflet referred to both instant disintegration and that the average time taken to complete disintegration was 2 minutes. The Panel, as stated at point 2 above, was only concerned with the materials produced by Martindale.

The Panel noted that the Clinical Study Report and Strang *et al* (2017) stated that 'over all periods, 96.3% of [Espranor] administrations achieved partial disintegration on the tongue in ≤ 15 seconds' and 'The median time for complete [Espranor] tablet disintegration was 2 minutes ...'. The data showed that at 2 minutes, [Espranor] had completely dissolved in 58% of administrations. The Panel also noted that, as stated at point 2 above, the Clinical study report showed that there were four recordings of partial or complete disintegration at 15 minutes.

In addition, the Panel noted that the voice-over on the video on the health professionals section of the website 'How to Dispense in a Supervised Setting' stated that 'You may want to offer your patient a small drink of water as this aids the dissolving of Espranor, once administered'.

The Panel considered that the six claims listed above for instant disintegration (save the claim 'Instant disintegration' in the 'Straight to the Point' detail aid mentioned above, alongside the fifth claim) were too dogmatic and implied that the tablets completely disintegrated instantly on every administration which was not so. Context was important. Further information should be given about disintegration times, the meaning of the term and the study so that readers could properly assess the claims. In the Panel's view, the claims in question were each misleading and could not be substantiated. The Panel ruled breaches of Clauses 7.2 and 7.4 in relation to each claim in question.

The Panel noted that further information was provided alongside the claim 'Instant disintegration' on the left-hand side of page 3 of the 'Straight to the Point' detail aid. Immediately beneath the claim in question it stated '% of individuals with partial disintegration (no longer removable from the mouth): ≤15 secs' above a depiction of a clock face highlighting 15 seconds. Adjacent to this was the claim '96% vs 72% with Subutex'. The right-hand side of the same page beneath the subheading 'Rapid dissolution' depicted a bar chart showing that that the average time to complete dissolution with Espranor was 2 minutes vs 10 minutes with Subutex. The Panel considered that the context was such that this claim was materially different to the other claims at issue. Further information had been provided. However, on balance, the Panel considered that the prominent claim 'Instant disintegration' was misleading insofar as it gave the immediate visual impression that tablets completely disintegrated instantly on each administration and that was not necessarily so. This immediate impression was not capable of substantiation. A breach of Clauses 7.2 and 7.4 was ruled.

Clause 7.6, as raised by Indivior, stated that when promotional material refered to published studies, clear references must be given. Clause 7.6 applied to references to published material, including the use of quotations, tables, graphs and artwork. The Panel noted that Indivior had not identified the reference/s in the material to published studies. It was not for the Panel to identify the references for Indivior. In the Panel's view, it did not have a valid complaint to consider and thus ruled no breach of Clause 7.6.

4 Elimination of the opportunity for removal from the mouth

Claim 'Eliminating the opportunity for removal from the mouth once administered' which appeared on page 4 of the website.

Claim 'Instant disintegration eliminates the opportunity for removal …' which appeared on page 7 of the website.

Claim 'Espranor prevents the most common route of diversion' which appeared on page 8 of the 'Product Overview' detail aid.

COMPLAINT

Indivior highlighted earlier the importance of the issue of misuse and diversion in patients receiving OST. Indivior noted that Martindale had not provided evidence to support the claim with regard to how the opportunity for removal of the drug was 'eliminated'. A review of the video on the Espranor website showed that even without the active ingredient buprenorphine present, the product remained on the tongue and appeared to be available for removal for at least the eight seconds the product was shown largely unchanged on the tongue. Martindale

referred to the SPC which stated: 'Removal of Espranor from the mouth following supervised administration is *virtually* impossible due to its rapid dispersal on the tongue' (emphasis added). There was no evidence to substantiate this statement. Indivior did not accept that this statement could be converted into the claim that the product 'eliminates' the opportunity. Indivior alleged that the claims made were inaccurate, misleading and were not faithfully substantiated by the clinical evidence and that Martindale was in breach of Clauses 7.2 and 7.4.

RESPONSE

Martindale provided Indivior with several references to substantiate the claims above, none of which were accepted as outlined below:

Martindale noted that the oral lyophilisate needed careful handling. Each individual freeze dried 'oral lyophilisate' of buprenorphine was individually foil wrapped in a blister. Once the blister had been opened, it was suggested that the oral lyophilisate was placed on the tongue immediately, as the wafers were very sensitive to moisture and susceptible to disintegration. Espranor oral lyophilisate were to be handled with dry hands. It was clear, therefore, that once the oral lyophilisate touched saliva on the tongue, 96.3% partially disintegrated in ≤15 seconds rendering it unable to be removed from the mouth. This was represented in the SPC, with the following wording:

> 'Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue.'

Seager (1998), which was the basis of the product development for Espranor, stated the following with regards to the Zydis technology and the 'instant disintegration': The Zydis fast-dissolving dosage form was a unique freeze-dried medicinal tablet, made from well-known and acceptable materials. When Zydis units were put into the mouth, the freeze dried structure disintegrated instantaneously releasing the drug which dissolved or dispersed in the saliva.

It was important to note that the first time point measured in the Espranor Phase II study was 15 seconds, no data were available prior to this time point as it was not measured. According to the published study results, 'Oral disintegration time of [Espranor] and [a sublingual buprenorphine] was measured by direct observation, measuring (a) time to disintegration (i.e., tablet could no longer be removed intact) and (b) time until completely dissolved'. 'At 15 seconds, results showed that 96.3% of [Espranor] administrations achieved partial disintegration on the tongue vs. 71.8% with [a sublingual tablet], ($p < 0.001$)'. The definition of partial disintegration according to the Clinical Study Report was that the formulation could no longer be removed from the mouth.

PANEL RULING

The Panel noted its general comments at point 2 and, in addition, its comments and rulings in points 2 and 3 above and considered that they were relevant here.

The Panel noted that it might be difficult for a patient to remove Espranor from the mouth once administered but considered that it was misleading of Martindale to state that Espranor and its 'instant disintegration' (and at claim 3 above, in conjunction with its rapid dissolution) completely eliminated the opportunity for such removal. The Panel considered that each claim was too dogmatic. Insufficient information was given to enable a reader to assess the data. The Panel further noted that the SPC stated 'Removal of Espranor from the mouth following supervised administration is *virtually impossible* due to its rapid dispersal on the tongue' (emphasis added). The Panel therefore considered that claims 1-3 above were each misleading and were not capable of substantiation and therefore ruled breaches of Clauses 7.2 and 7.4 in relation to each.

5 Lack of visibility of interchangeability information

Claim 'Espranor is not interchangeable with other buprenorphine products' which appeared on pages 10 and 15 of the website.

Claim 'Espranor is not directly interchangeable with other forms of buprenorphine'. This appeared on page 2 of the 'Product Overview' detail aid and page 4 of the 'Straight to the Point' detail aid.

COMPLAINT

Indivior stated that the Martindale efficacy data confirmed that 'Espranor is not interchangeable with other buprenorphine products'. This was prominently featured on the packaging and the SPC and PIL (either in bold, or in a boxed warning) and as such, should be similarly and prominently featured on all materials so that prescribers and patients could make informed choices.

Indivior stated that Martindale had made some concessions and changes to the website following Indivior's initial request. Currently, Martindale placed this warning as set out above.

Indivior, however, considered that Martindale had not gone to sufficient lengths to highlight that Espranor was not interchangeable with other buprenorphines used in OST, did not make the text prominent enough and did not provide this important information early enough in all of the materials seen to date. Further, this information was not present in the patient leaflet.

Indivior did not consider that the display of safety information for a new product was prominent enough, despite the changes to the website. Indivior alleged that Martindale had purposefully misled prescribers by underplaying a key prescribing issue and had thus brought discredit upon the industry in breach of Clauses 2, 7.9 and 9.1.

RESPONSE

Martindale submitted that in the product overview, which was the focus of Indivior's initial complaint, the warning from the SPC that 'Espranor is not directly interchangeable with other forms of buprenorphine' was highlighted in blue in the text so that it stood out as the header. This sentence was presented on page 2 of the 'Product Overview'. Page 1 did not contain any claims other than the title of the document and the name of the product. In addition, the warning in the Espranor SPC was mentioned on the 'Product Overview' under the header 'Espranor is not directly interchangeable with other forms of buprenorphine' in a size that was no different to the rest of the text on that page.

The text 'Espranor is not directly interchangeable with other forms of buprenorphine' was included on the website in a box in the health professional pages. For the patient there was a direct link to the SPC and the PIL and page 1 of the PIL contained the safety information in a box in a similar manner to that presented in the SPC.

With regards to the appropriate risk minimisation measures in this context, Martindale had extensive discussion with the MHRA about a post-authorization safety study which involved four questionnaires. In August 2016 the MHRA finally agreed that it would be extremely difficult to gather any useful additional clinical data other than through a good pharmacovigilance system. It was satisfied with all the warnings in the SPC, PIL and carton.

With regards to the patient leaflet, this was not part of the inter-company dialogue. Martindale noted that this material had a clear header that stated 'This leaflet is intended for patients that have been prescribed Espranor'. Espranor was a prescription-only medicine. Patients receiving this leaflet would have been prescribed Espranor and informed by their health professional that 'Espranor is not directly interchangeable with other forms of buprenorphine'. Martindale agreed that health professionals needed to be aware that 'Espranor is not directly interchangeable with other forms of buprenorphine', hence this information was prominently featured in all materials, the SPC, PIL and packaging.

PANEL RULING

The Panel noted that the warning 'Espranor is **not interchangeable with other buprenorphine products**. **Different buprenorphine products** have different bioavailability. Therefore, the dose in mg can differ between products. Once the appropriate dose has been identified for a patient with a certain product (brand), the product cannot be readily exchanged with another product' appeared as a boxed warning at Section 4.2 of the SPC. A boxed warning appeared at the beginning of Section 2 (What you need to know before you take Espranor) of the patient information leaflet which read 'Espranor is not interchangeable with other oral buprenorphine products and the dose of Espranor may differ from the dose of other buprenorphine products'. This latter boxed warning was also part of the labelling on the product packaging as referred to in the PAR. The Panel noted that the EU Risk Management Plan discussed the prevention of error due to the wrong medication (Section SVI.4 Potential for medication errors) noting the higher bioavailability of buprenorphine from Espranor than from Subutex. Medication errors were listed as an important potential risk in the summary of safety concerns.

The Panel noted that Indivior had cited Clause 7.9 which related to claims and information about adverse reactions. It also required that companies could not state that a product had no adverse reactions, toxic hazards or risks of addiction or dependency. The matters raised at this point did not relate to adverse events or other matters covered by Clause 7.9. The Panel considered that Clause 7.9 was not relevant and thus considered the matters raised under Clause 9.1 which had been cited. No breach of Clause 7.9 was ruled in relation to each claim.

The Panel considered that its general comment above at point 1 about the page numbers applied to the website by the complainant were relevant here. The Panel adopted the page numbering applied by the complainant.

The Panel disagreed with Indivior's contention that the warning in question should make it clearer that Espranor was not interchangeable with other buprenorphines used in OST. The Panel noted that some other buprenorphine products were licensed to treat, *inter alia*, moderate to severe cancer pain and severe pain which did not respond to non-opioid analgesics. The Panel noted Espranor's licensed indication, substitution treatment for opioid dependence, and that each item at issue was either promotional material for the product or for patients who had been prescribed it and discussed its licensed use. In such circumstances, the Panel did not consider that the non-interchangeability warning at issue needed to qualify the reference to buprenorphines by stating that it applied to those used in opioid substitution therapy. High standards had been maintained on this point. No breach of Clause 9.1 was ruled.

The Panel disagreed with Martindale's submission that the warning on page 2 of the 'Product Overview' detail aid 'Espranor is not directly interchangeable with other forms of buprenorphine' stood out as the header because it was highlighted in blue text. The Panel noted that all five subheadings on the page were in the same pale blue font. Two main headings were in purple font and the text was otherwise in black font. The Panel considered that the pale blue font colour and the overall design of the page, including the position of the warning in question as the subheading to the final paragraph at the bottom of the page, meant that it was not sufficiently prominent. Although, as submitted by Martindale, the warning in the Espranor SPC was in a size that was no different to the rest of the text on that page, it was also within a box and the phrase 'not interchangeable with other buprenorphine products' was emboldened. The Panel considered that the warning should have been made more prominent given the therapy area, the vulnerable nature of the

patients and its prominence in the SPC. A breach of Clause 9.1 was ruled.

The Panel noted that the warning 'Espranor is **not directly interchangeable** with other buprenorphine products was on page 4 of the 'Straight to the Point' detail aid followed by the prescribing information. Although 'not directly interchangeable' was emboldened within the warning, the Panel considered that the warning should have been presented earlier in the detail aid given that the preceding pages discussed how Espranor delivered buprenorphine in OST more effectively than hard, compressed, sublingual formulations and compared its dissolution time to that of Subutex. The Panel noted its comments above about the need for the warning to be more prominent and considered that those reasons were relevant here. High standards had not been maintained. A breach of Clause 9.1 was ruled.

In relation to page 10 of the website, the Panel noted that although the warning in the SPC had been reproduced in full and was within an outlined box, it was only presented on page 10, towards the end of the health professional section of the Espranor website. The Panel considered that it should have been presented earlier for the same reasons as stated above in relation to each of the detail aids; high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that Indivior had also alleged that the warning was not sufficiently prominent on page 15 of the website which comprised prescribing information. In this regard, the Panel noted that the prescribing information did not include the summary of product characteristics. Clause 4.2 dealt with the content of prescribing information which included precautions and contraindications and warnings issued by, *inter alia*, the licensing authority which were required to be in advertisements. Clause 4.1 required prescribing information to be provided in a clear and legible manner. There was no reference in either Clause 4.1 or 4.2 about prominence to particular elements of the prescribing information. The Panel noted that the warning in question 'Espranor is not interchangeable with other buprenorphine products' was in the same font size as the rest of the prescribing information within the Dosage and administration section. It was underlined as were 10 other phrases or sentences in the first column of prescribing information. It was not prominent such that it caught the reader's eye. Although the Panel considered that it would have been helpful if the warning in question had greater visual prominence in the absence of a specific direction or requirement in Clauses 4.1 and 4.2 of the Code, on balance, it did not consider that the company had failed to maintain high standards. No breach of Clause 9.1 was ruled.

The Panel noted that the absence of the warning on the patient section of the website was covered by its ruling at point 1 above.

The Panel noted that Indivior was also concerned that the warning was not included in the patient leaflet, a double-sided A5 sheet intended for patients who had been prescribed Espranor. Page 1 dealt with reporting of side-effects and page 2 explained how to administer Espranor. The Panel noted its relevant comments including the content of the EU Risk Minimisation Plan and ruling of a breach of the Code at point 1 above in relation to the failure to include the warning on the patient section of the website. The Panel noted, in particular, the vulnerability of these patients and considered that in these particular circumstances it was important to ensure that all relevant information was made available. The Panel considered that the failure to include the warning in the patient information leaflet was such that high standards had not been maintained. In the Panel's view, the non-interchangeability statement from the SPC did not necessarily need to be reproduced verbatim, however, closely similar information should be conveyed. A breach of Clause 9.1 of the Code was ruled.

The Panel noted the vulnerability of the patient population and that the highlighted warning was a prominent part of the SPC, PIL and the product pack. The Panel noted its comments above on the lack of prominence given to the warning across several materials and that it was not on the patient materials at issue at all. The Panel noted that prejudicing patient safety was given as an example of an activity likely to be in breach of Clause 2. A breach of Clause 2 was ruled.

6 Misleading comparison with Subutex and dissolution time

Claim 'In the UK, licensed buprenorphine is currently only available as hard-compressed sublingual tablets, which take up to 10 minutes to dissolve and may compromise supervised administration'. This appeared on page 3 of the 'Product Overview' detail aid.

Claim 'Unlike conventional hard compressed buprenorphine sublingual tablets which take up to 10 minutes to dissolve'. This appeared on page 3 of the website.

Claim 'Buprenorphine is currently only available as hard compressed sublingual tablets which take up to 10 minutes to dissolve'. This appeared on page 7 of the website.

Claim 'Conventional, hard, compressed, sublingual buprenorphine tablets take up to 10 minutes to dissolve'. This appeared on page 1 of the 'Straight to the Point' detail aid.

In addition, the visual comparison of the disintegration and dissolution times of Subutex and Espranor on page 3 of the 'Straight to the Point' detail aid was the subject of complaint.

COMPLAINT

Indivior alleged that Martindale misrepresented the Subutex data when comparing it with Espranor implying that there were greater differences in

dissolution time to that shown by the head-to-head data. Martindale also suggested that the difference was clinically important without providing any supportive evidence. The Subutex SPC stated 'The tablet should be kept under the tongue until dissolved, which usually occurs within 5 to 10 minutes'. The Espranor SPC stated that Espranor was dispersed '… which usually occurs within 15 seconds, and then absorbed through the oromucosa. Swallowing should be avoided for 2 minutes …. Patients should not consume food or drink for 5 minutes after administration'. As highlighted earlier under point 3, Strang *et al* (2017) showed that complete disintegration occurred at 15 minutes. Thus, according to the SPC, a reasonable supervision time was at least 5 minutes after administration of Espranor, which was not substantially different to 5-10 minutes for Subutex and even longer if factoring in the complete disintegration time of Espranor of 15 minutes as highlighted in Strang *et al* (2017). Dissolution and disintegration were not comparable nor interchangeable in this context.

Indivior alleged that Martindale was misleading with this comparison, distorted the data, exaggerated and gave undue emphasis to the benefits of Espranor compared with the reference product. Indivior alleged that this was in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Martindale submitted that all data that it represented came directly from the Clinical Study Report (MD2012/01XP). This data was published in a peer-reviewed journal (Strang *et al* 2017). The text to which Indivior referred clearly stated that hard compressed sublingual tablets took 'up to 10 minutes' to dissolve. Nowhere in the Espranor materials did it state 'it takes 10 minutes' for sublingual tablets to dissolve. There was a clear distinction here and Martindale submitted that the statement was fair and in line with the references provided.

The published study results (Strang *et al* 2017) stated the following:

> 'Over all periods, 96.3% of "[Espranor]" administrations achieved partial disintegration on the tongue in ≤ 15 vs. 71.8% with "[a sublingual buprenorphine]" ($p < 0.001$). At 2 min, "[Espranor]" had completely dissolved in 58.0% of administrations versus only 5.1% ("[sublingual buprenorphine]"; $p < 0.0001$). The median time for tablets to completely disintegrate was 2.0 min for "[Espranor]" versus 10 min for "[sublingual buprenorphine]" ($p < 0.0001$).'

These results were presented in the materials in both text form and as figures. Martindale submitted that the reader was not misled in any way as to the results that were presented.

Section 4.2 of the Espranor SPC stated the following:

> 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds, and then absorbed through the oromucosa. Swallowing should be avoided for 2 minutes. The oral lyophilisate should be taken immediately after opening the blister. Patients should not consume food or drink for 5 minutes after administration.'

Martindale noted that it was important to understand that the principle of OST was supervised administration. Supervision was likely to last as long as the buprenorphine product took to dissolve which, in the case of Espranor, was a shorter mean time than that of Subutex. There was no statement suggesting supervision for 5 minutes in the Espranor SPC to ensure that food was not consumed.

The point of avoiding swallowing with Espranor was so that the patient did not swallow saliva containing Espranor before it was absorbed, as otherwise the buprenorphine content would undergo first pass metabolism. This did not mean supervision was required during this time. The same applied to food and drink.

PANEL RULING

The Panel considered that its general comment above at point 1 about the page numbers applied to the website by the complainant were relevant here. The Panel adopted the page numbering applied by the complainant.

The Panel noted Indivior's submission that the Subutex SPC stated 'Administration is sublingual. Physicians must advise patients that the sublingual route is the only effective and safe route of administration for this drug. The tablet should be kept under the tongue until dissolved, which usually occurs within 5 to 10 minutes'. The Panel noted that the Espranor SPC stated that the oral lyophilisate should be taken from the blister unit with dry fingers and placed whole on the tongue until dispersed, which usually occurred within 15 seconds and then absorbed through the oromucosa. Swallowing should be avoided for 2 minutes. The oral lyophilisate should be taken immediately after opening the blister. Patients should not consume food or drink for 5 minutes after administration. The SPC further noted that physicians must advise patients that the oromucosal route of administration was the only effective and safe route of administration for this medicinal product. If the oral lyophilisate or saliva containing buprenorphine were swallowed, the buprenorphine would be metabolised and excreted and have minimal effect. The Panel noted its comments above at points 2 and 3 about the comments and findings in the clinical study report and Strang *et al* (2017).

In relation to the claim 'Unlike conventional hard compressed buprenorphine sublingual tablets which take up to 10 minutes to dissolve, Espranor instantly disintegrates within 15 seconds of being placed on the tongue resulting in rapid dissolution (median time 2 minutes)', the Panel noted that the latter part of the claim 'resulting in rapid dissolution (median time 2 minutes)' appeared at the top of

the following page on the version provided by the complainant. The Panel noted its ruling of a breach of the Code in relation to the phrase 'instantly disintegrates within 15 seconds' at point 3 above (claim 3), which misleadingly implied that Espranor tablets dissolved instantly on each administration which was not so. The Panel noted the reference to 5-10 minutes in the Subutex SPC and considered that readers would probably compare the stated 'instant disintegration' of Espranor with the stated 'up to 10 minutes' dissolution time for Subutex. The Panel noted Indivior's submission that dissolution and disintegration were not comparable in this context and noted the parties' definition of terms at point 2 above. The Panel queried whether 'up to 10 minutes' was a fair reflection of the Subutex SPC. Those readers who saw the entire claim, which concluded on page 4, might compare Espranor's median dissolution time of 2 minutes with 'up to 10 minutes with Subutex'. The Panel noted that for a comparison to be valid, like must be compared with like. The Panel considered that the claim in question 'Unlike conventional hard compressed buprenorphine sublingual tablets which take up to 10 minutes to dissolve, Espranor instantly disintegrates within 15 seconds of being placed on the tongue resulting in rapid dissolution (median time 2 minutes)' exaggerated the differences between the products and was misleading in this regard. A breach of Clauses 7.2 and 7.3 was ruled. The claim was incapable of substantiation. A breach of Clause 7.4 was ruled.

In relation to the claim on page 7 of the website 'Buprenorphine is currently only available as hard compressed sublingual tablets which take up to 10 minutes to dissolve,' the Panel noted that whilst the claim itself did not refer to Espranor, the preceding paragraphs discussed Espranor and referred to its 'rapid dissolution' and 'Instant disintegration ...'. Closely similar claims about instant disintegration had been ruled in breach of the Code at point 3 above. The Panel noted its comments above about the Subutex SPC and the phrase 'up to 10 minutes'. The Panel considered that the reader was invited to compare the stated 'up to' 10 minutes' dissolution time of Subutex with the stated instant disintegration of Espranor. In the Panel's view, this comparison was misleading and exaggerated the differences between the products. A breach of Clauses 7.2 and 7.3 were ruled. This comparison was incapable of substantiation. A breach of Clause 7.4 was ruled.

The Panel noted that the claim 'Conventional, hard, compressed, sublingual buprenorphine tablets take up to 10 minutes to dissolve' on the front page of the Straight to the Point detail aid immediately followed the claim 'Espranor oral lyophillsate has been specifically designed to disintegrate instantly and dissolve rapidly when placed on the tongue'. This preceding claim, including the phrase 'disintegrate instantly', had been ruled in breach of the Code at point 3 above. The emboldened unqualified claims on the front page of the detail aid included 'No delay. No diversion'. The Panel noted its comments above about the Subutex SPC and the phrase 'up to 10 minutes'. The Panel considered that the reader was invited to compare the stated 'up to' 10 minute dissolution time of Subutex with the stated instant disintegration of Espranor. In the Panel's view, this comparison was misleading and exaggerated the differences between the products. A breach of Clauses 7.2 and 7.3 were ruled. The claim could not be substantiated. A breach of Clause 7.4 was ruled.

The Panel noted that the claim 'In the UK, licensed buprenorphine is currently only available as hard-compressed sublingual tablets, which take up to 10 minutes to dissolve and may compromise supervised administration' on page 3 of the 'Product Overview' detail aid was within an introductory section that discussed barriers to buprenorphine use. Whilst the preceding page and subsequent sections on page 3 discussed Espranor, the Panel noted that the only relevant statement in relation to Espranor across both pages was the first bullet point at the top of page 2 which read 'Espranor oral lyophilisate is a novel freeze dried wafer formulation of buprenorphine which disintegrates instantly and rapidly when placed on the tongue'. As previously stated, closely similar claims about instant disintegration had been ruled in breach of the Code. The Panel noted the detailed information given across pages 2 and 3 of the A4 booklet. Other than the aforementioned bullet point, there was no other mention of disintegration and dissolution. Visually no prominence was given to the aforementioned bullet point at the top of page 2 such that the Panel considered, on the balance of probabilities, that the claim in question on page 3 'In the UK, licensed buprenorphine is currently only available as hard-compressed sublingual tablets, which take up to 10 minutes to dissolve and may compromise supervised administration' would not be read in light of, and therefore was not a comparison with, the first bullet point on the preceding page. The design of the page was relevant. The Panel ruled no breach of Clauses 7.2, 7.3 and 7.4 of the Code.

In relation to the allegation about the comparison on page 3 of the 'Straight to the Point' detail aid, the Panel noted the page bore the prominent heading 'Espranor: rapid by design'. Beneath the left-hand column and the prominent subheading 'Instant disintegration' a clock face depicted that 96% of Espranor patients vs 72% with Subutex ($p=0.0002$) at ≥15 seconds had partial disintegration (no longer removable from the mouth). The figure of 96% was prominent and in the same purple font as the claims 'Rapid by design' and 'Instant disintegration'. The right-hand column was headed 'Rapid dissolution' beneath which the average time to complete disintegration (median) was visually depicted showing Espranor as 2 minutes and Subutex as 10 minutes, $p<0.0001$. The data was referenced to the Espranor SPC and Strang et al (2015). The Panel noted its comments on this page at point 3 above. The Panel noted the wording in the Subutex SPC set out above and its comments thereon. The Panel noted that the bar chart did not reflect the range of 5-10 minutes within which Subutex usually dissolved as stated in its SPC. The Panel noted that there were differences between the products in relation to disintegration and dissolution in favour of Espranor. The prominent subheading 'Instant disintegration' had previously been ruled in breach of the Code.

The Panel noted that more comparative data was given on this page than for the claims at issue above. Nonetheless, the Panel considered that the failure to fairly reflect the Subutex SPC in conjunction with the prominent claim 'Instant disintegration' meant that the comparison was misleading as it exaggerated the differences between the products. A breach of Clauses 7.2 and 7.3 were ruled. The comparison was not capable of substantiation. A breach of Clause 7.4 was ruled.

In relation to the allegation that Martindale suggested that the above comparisons were clinically relevant which was not supported by the data, the Panel noted that Indivior bore the burden of proof. Whilst claims made by Martindale had to be capable of substantiation, the burden was on Indivior to show that, on the balance of probabilities, such claims were not clinically relevant. It had not identified any data and Martindale had not responded to this point. The Panel noted that the studies before it in relation to different matters in this case included discussion of supervision times. In the Panel's view, Indivior had not discharged the burden of proof. The Panel ruled no breach of Clause 7.2.

7 Reduces supervision time

Claim 'Rapid dissolution reduces the time required for supervised **administration**'. This appeared on page 7 of the website.

Claim 'Instant disintegration of Espranor reduces the time required by pharmacists for supervised self-administration of buprenorphine'. This appeared on page 8 of the 'Product Overview' detail aid.

Claim 'Minimises supervision time'. This appeared on page 3 of the 'Straight to the Point' detail aid.

COMPLAINT

Indivior noted that in response to its requests on 1 March 2017, Martindale provided evidence to support the claim by reference to an excerpt of its Clinical Study Report, which was a key reference for multiple claims in its materials and had not, so far, been provided in a full enough form to confirm or deny the claim. It surmised: 'The faster speed of disintegration with Xprenor (Espranor) will reduce the supervision time required compared to Subutex, providing a greater convenience for both the patient and clinician, and the potential for reduced supervision costs in both the healthcare and prison systems'. Indivior did not consider that there was evidence to support the claims. The same argument, as identified in the point above, applied in that the Espranor SPC stated '… Swallowing should be avoided for 2 minutes … Patients should not consume food or drink for 5 minutes after administration' which increased the required supervision time to at least 5 minutes. Indivior alleged that these claims were in breach of Clauses 7.2, 7.4, 7.6 and 7.9.

RESPONSE

Martindale submitted that it had provided Indivior with page 116 of the clinical study report; the heading on this page was 'DISCUSSION AND CONCLUSIONS', which was clearly not a preamble to the study report as Indivior suggested but contained the key study findings:

> 'This study demonstrates that the Xprenor tablet starts to disintegrate on the tongue in ≤15 seconds in 96.3% of administrations, with a median time to complete Xprenor tablet disintegration of 2 minutes compared to 10 minutes with Subutex. The faster speed of disintegration with Xprenor will reduce the supervision time required compared to Subutex, providing a greater convenience for both the patient and clinician, and the potential for reduced supervision costs in both the healthcare and prison systems.'

Martindale noted that Indivior was concerned about the advice in the SPC regarding food or drink after Espranor administration. Section 4.2 of the Espranor SPC stated the following:

> 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds, and then absorbed through the oromucosa. *Swallowing should be avoided for 2 minutes*. The oral lyophilisate should be taken immediately after opening the blister. *Patients should not consume food or drink for 5 minutes after administration'* (emphasis added).

Martindale submitted that it was important to understand that the principle of OST was supervised administration. Supervision was likely to last as long as the buprenorphine product took to dissolve, which in the case of Espranor was a shorter mean time than that of Subutex. There was no statement suggesting supervision for 5 minutes in the SPC for Espranor to ensure that food was not consumed.

The point of avoiding swallowing with Espranor was so that the patient did not swallow saliva containing Espranor before it was absorbed, as otherwise the buprenorphine content underwent first pass metabolism. This did not mean supervision was required during this time. The same applied to food and drink.

With regard to the supply of the full study report, Martindale provided, in good faith, the relevant pages from the clinical study report, which it considered were sufficient for the issue at hand. Furthermore, the study results were published in March 2017 and a copy of this was provided to Indivior. Martindale considered that Indivior had all the literature it needed to substantiate the claims made concerning the Espranor study results.

PANEL RULING

The Panel noted that its general comment above at point 1 about the page numbers applied to the website by the complainant were relevant here.

The Panel noted Indivior's statement that given the Espranor SPC stated '… Swallowing should be avoided for 2 minutes …. Patients should

not consume food or drink for 5 minutes after administration', this increased the required supervision time to at least 5 minutes.

In the Panel's view, the aim of supervision was to ensure that the patient did not remove a dose for diversion. It was well-established that patients removed doses of buprenorphine from supervised consumption in creative ways.

The Panel considered that its comments at Points 2, 3, 4 and 6 above about the time taken to achieve partial and complete disintegration and diversion were relevant here.

The Panel noted Martindale's submission that there was no statement suggesting supervision for 5 minutes in the SPC for Espranor to ensure that food was not consumed and noted the only reference to supervision was during the initiation of treatment. Daily supervision of dosing was recommended to ensure proper placement of the dose on the tongue and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

The Panel noted that Strang et al (2017) concluded that 'Espranor's rapid disintegration and consequent greater ease of supervised dosing may increase the feasibility of buprenorphine treatment in busy community and custodial settings when supervised dosing is considered important. This now needs to be explored clinically'. The authors subsequently stated that 'hopefully rapid-dissolving variants of buprenorphine may increase the range of settings in which buprenorphine can safely be delivered such as settings where it is unrealistic to expect full supervision of dosing over several minutes'. These contexts would warrant attention in future studies. The Panel noted that the page of the clinical study report that had previously been disclosed to Indivior was more dogmatic, stating 'The faster speed of disintegration with [Espranor] will reduce the supervision time required compared to [sublingual competitor], providing a greater convenience for both the patient and clinician, and the potential for reduced supervision costs in both the healthcare and prison systems'. The Panel noted that Indivior had emphasised 'potential for reduced supervision costs' but considered that cost was not directly relevant to the claims at issue.

The Panel noted that there were differences between the products which were relevant to supervision time. The Panel considered that the phrase 'reduces the time required' had to be considered in the context in which it was used.
The Panel noted that the claim 'Rapid dissolution reduces the time required for supervised administration' was one of two bullet points and appeared immediately above the claim 'Instant disintegration eliminates the opportunity for removal from the mouth once administered' which was ruled in breach of the Code at point 4 in relation to the elimination claim. In addition, the phrase 'Instant disintegration' was closely similar to matters ruled in breach of the Code at point 3. In the Panel's view, the context including the unqualified claim about instant disintegration and elimination implied that the reduction in time required for supervision would be greater than it in fact was. In this regard, the claim in question 'Rapid dissolution reduces the time required for supervised administration' was misleading and incapable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled.

In relation to the second claim at issue 'Instant disintegration of Espranor reduces the time required by pharmacists for supervised self-administration of buprenorphine' in the 'Product Overview' detail aid, the Panel considered that its comments in relation to the first claim above applied here. 'Instant disintegration' was part of the claim at issue. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that the third claim 'Minimises supervision time and reduces potential diversion for misuse.' was a prominent claim at the bottom of page 3 of the 'Straight to the Point' detail aid on the same page as matters ruled in breach of the Code at point 6 above in relation to comparative dissolution times and at point 3 above in relation to the claim 'Instant disintegration'. The Panel considered that the term 'minimises' was different to the term 'reduces'. It implied reduction to an almost irreducible amount. In the Panel's view, this implication was compounded by the other claims ruled in breach on the page. Overall, the Panel considered the claim misleading and incapable of substantiation. A breach of Clauses 7.2 and 7.4 was ruled.

Clause 7.6, as raised by Indivior, stated that when promotional material refers to published studies, clear references must be given. Clause 7.6 applied to references to published material, including the use of quotations, tables, graphs and artwork. The Panel noted that Indivior had not identified the reference/s in the material to published studies. It was not for the Panel to identify the references for Indivior. In the Panel's view, it did not have a valid complaint to consider and thus ruled no breach of Clause 7.6.

The Panel noted that Indivior had cited Clause 7.9 which related to claims and information about adverse reactions. It also required that companies could not state that a product had no adverse reactions, toxic hazards or risks of addiction or dependency. The matters raised at this point did not relate to adverse events or other matters covered by Clause 7.9. The Panel considered that Clause 7.9 was not relevant and thus ruled no breach of Clause 7.9 in relation to each claim cited above.

8 Comparable safety profile

Claim 'Equivalent safety and efficacy to sublingual buprenorphine'. This appeared on page 8 of the 'Product Overview' detail aid.

Claim 'Clinical trials show that Espranor is as effective as conventional compressed sublingual forms of buprenorphine at treating opioid dependence with a comparable safety profile'. This appeared on page 7 of the website.

COMPLAINT

Indivior noted that the claims above were in contrast to the statement '56.5% of patients reported mild AEs with Espranor compared with 7.7% of patients taking Subutex' on page 3 of the 'Straight to the Point' detail aid and page 6 of the Product Overview detail aid which showed large differences in mild adverse events (AEs). Indivior noted that the Strang *et al* (2017) also stated '… more AEs and Treatment-Emergent AEs with "[Espranor]" (mostly "mild")' and 'However, a greater proportion of "[Espranor]" subjects experienced at least one AE and similarly for TEAE (73.9 and 69.6%, respectively) compared to the [Subutex] group'.

Indivior was concerned that Martindale had misrepresented the safety data on the website. It also noted that Martindale had additional risk minimisation measures stipulated in its risk management plan, as stipulated in the PAR. It was noted that Martindale did not take the opportunity to address these in any of the materials Indivior had seen.

Indivior further noted that there was no safety information provided in the patient leaflet.

Indivior alleged that Martindale was in breach of Clauses 7.2, 7.3, 7.4 and 7.9.

RESPONSE

Martindale submitted that licensed buprenorphine had been available in the UK since 1978 and had an established safety profile. The key safety concern facing any new formulation of buprenorphine was respiratory depression and the investigation of this safety concern was the aim of the Espranor safety study, as the MHRA required evidence that the increased bioavailability with Espranor was not associated with an increased risk of respiratory depression. The study confirmed that this was not an issue for Espranor. The 'Product Overview' detail aid contained a full table of the study adverse events for both products. It was clear that there was no significant difference in moderate adverse events between the products, no severe adverse events and no deaths. No patients withdrew secondary to Treatment-Emergent Adverse Events (TEAEs).

Patients in OST were very vulnerable and dependent on receiving their medication regularly. Any change in this medication was likely to cause anxiety. The Espranor safety study was un-blinded, and so the patients were sitting in unfamiliar clinical surroundings taking a new product. They also had a health professional asking them repeatedly how they were feeling. The research team felt that all these factors contributed to the incidence of reporting TEAEs for Espranor, and were confident that the first year of full pharmacovigilance data following launch would be a more accurate representation of the true TEAE incidence. The data was peer reviewed and accepted for publication, and was also accepted by the regulatory authorities, as the licence was issued requiring no additional pharmacovigilance measures. Martindale considered that the results of this study, which had been presented in full in the 'Product Overview', provided the prescriber with a clear picture of the safety profile of Espranor and that this did not contradict the overall conclusion of equivalence between the safety profiles of the products presented.

With regards to the appropriate risk minimization measures in this context, the company had extensive discussion with the MHRA for some months about a post-authorization safety study, which involved four questionnaires. In August 2016 the MHRA finally agreed that it would be extremely difficult to gather any useful extra clinical data other than through a good pharmacovigilance system. It was satisfied with all the warnings in the SPC, PIL and Carton. Martindale submitted that the Patient Leaflet was for patients that had been prescribed Espranor and would have been able to read the PIL. The leaflet was purely 'how to administer Espranor', but it also provided details of how to report side-effects.

In response to a request for further information, Martindale submitted that the Espranor risk management plan was approved during the licensing procedure. The Espranor licence was granted on 22 June 2015. At this stage the MHRA requested a commitment to perform a post-authorization safety study. Martindale had extensive discussion with the MHRA about such a study and submitted two different protocols, which involved four questionnaires. By August 2016 the MHRA had sought external advice and finally agreed that it would be extremely difficult to gather any useful additional clinical data, other than through a good pharmacovigilance system. A post-authorization safety study to monitor the risks of overdose and respiratory depression associated with Espranor was not considered feasible at this stage. The MHRA was satisfied with all the warnings in the SPC, PIL and Carton and Martindale was not asked to produce another risk management plan. The email from the MHRA was provided as well as the risk management post-authorization safety study protocol preliminary assessment report.

PANEL RULING

The Panel considered that its general comment above at point 1 about the page numbers applied to the website by the complainant were relevant here. The Panel adopted the page numbering applied by the complainant.

The Panel noted that the first claim at issue was a subheading and read 'Equivalent safety and efficacy to sublingual buprenorphine'. It appeared on page 8 of the Product Overview detail aid which was headed 'Summary of key points' and introduced a section which summarised efficacy and safety data. The first bullet point beneath the claim in question read 'Two Phase II studies confirmed that in the target patient population Espranor and Subutex were comparable in terms of their safety profile and frequency of reported adverse events' and was referenced to the Espranor PAR. The Panel noted that the PAR referred to two Phase II studies including the Espranor safety study (Strang *et al*

2017). The Panel noted Martindale's submission that the key safety concern facing any new formulation of buprenorphine was respiratory depression and the investigation of this safety concern was the aim of the Espranor safety study. The Panel noted that the study results, as reflected in the PAR, stated that whilst administration of Espranor did not result in a higher risk of respiratory depression when compared to the Subutex, a higher number of mild treatment-emergent adverse events (TEAEs) were reported in the Espranor group. Strang *et al* stated that a greater proportion of Espranor subjects experienced at least one AE and similarly for TEAEs (73.0 and 69.6% respectively). The second Phase II study (conducted in India) referred to was described in the PAR as a supportive study only as the treatment practice, patient population, support network, type of addiction etc in India could be different compared to UK. It did state, however, that the safety results were similar to the UK study.

The Panel noted that the 'Product Overview' detail aid included a table of the reported adverse events for both products on page 6. This reproduced data from a closely similar table in the clinical study report and appeared in a section of the detail aid which discussed treatment-emergent adverse events including the statement '56.5% of patients reported mild AEs with Espranor compared with 7.7% of patients taking Subutex'. Possible reasons for the higher number of mild adverse events for Espranor were discussed above the table including the small study size and the small numbers in the competitor arm and that the study was unblinded. The Panel noted that the claim at issue 'Equivalent safety and efficacy to sublingual buprenorphine' appeared on page 8. The Panel considered that the claims and data on page 8 needed to be capable of standing alone in relation to the requirements of the Code and, in this regard, considered that the phrase 'Equivalent safety ...' was not a fair overall reflection of the adverse event data given the difference in the incidence in mild adverse events. The Panel noted that p values were not stated, or referred to, by either party which might be a reflection of the small study size and its power. The claim in question 'Equivalent safety and efficacy to sublingual buprenorphine' was misleading in this regard as alleged. Breaches of Clauses 7.2 and 7.3 were ruled. The claim was incapable of substantiation and did not reflect the available evidence and breaches of Clauses 7.4 and 7.9 were ruled.

The second claim at issue on page 7 of the website read 'Clinical trials show that Espranor is as effective as conventional compressed sublingual forms of buprenorphine at treating opioid dependence with a comparable safety profile' and was referenced to Strang *et al* (2015). There was no further discussion of the products' adverse event profiles. The Panel considered that its comments immediately above about the adverse event data applied here. In addition, the Panel noted that Strang *et al* (2015) stated there were 'more AEs and TEAEs with Espranor (mostly mild with similar proportions for moderate)'. The Panel considered that the claim at issue 'Clinical trials show that Espranor is as effective as conventional compressed sublingual forms of buprenorphine at treating opioid dependence with a comparable safety profile' was not a fair reflection of the adverse event data in relation to mild adverse events. Breaches of Clauses 7.2 and 7.3 were ruled. The claim was incapable of substantiation and did not reflect the available evidence and breaches of Clauses 7.4 and 7.9 were ruled.

The Panel noted Martindale's submission that the Patient Leaflet was for patients that had been prescribed Espranor as a 'how to administer' guide and provided details of how to report side-effects. The patient would also have the Espranor patient information leaflet with the full list of adverse events. The Panel noted that the leaflet must be capable of standing alone with regard to the requirements of the Code. It was headed 'This leaflet is intended for patients that have been prescribed Espranor'. No information about the product was given other than a diagrammatic illustration of its administration and information on how to report side-effects. Given its limited circulation to patients for whom the product had been prescribed and specific purpose, to illustrate administration, the Panel, on balance, did not consider that it was necessary to include safety data as alleged. The Panel did not consider the omission misleading. No breach of Clause 7.2 was ruled.

9 Provision of marked-up references

COMPLAINT

Indivior stated that Martindale's clinical study report was used to reference significant claims in its materials, presumably as the publication (Strang 2017) was not available at the time. Indivior asked Martindale on 1 March 2017 to provide fully marked up references to support the claims and a few times thereafter. Martindale subsequently sent 6 out of at least 123 pages of the study report, which did not support the claims referenced, around 5 weeks later. Indivior was very concerned that some claims were taken from extracts of the preamble of the study report and not from any data itself, eg the claim 'Rapid dissolution reduces the time required for supervised administration' which was substantiated by Martindale with text from the 'Study Rationale' of the study report, which did not refer to, or provide any evidence or data to, support the claim, but was simply an opinion. Indivior was very concerned that other claims supported by the study report would require verification. Indivior had not had sight of the full report at the time of writing this letter and was concerned at the length of time taken to receive final comments from Martindale on 14 June 2017.

Indivior was very concerned at the strength of some claims made, some of which appeared to be based on opinion and summation rather than data or peer-reviewed evidence. Indivior alleged that Martindale was in breach of Clauses 7.2, 7.3, 7.4 and 7.9.

RESPONSE

Martindale submitted that the Code did not require companies requested for substantiation to provide 'marked-up' references as Indivior suggested.

With regard to the supply of the full study report, Martindale provided, in good faith, the relevant pages from the clinical study report, which it considered were sufficient for the issue at hand. Furthermore, the study results were published in March 2017 and a copy of the published study was provided to Indivior. Martindale considered that Indivior had been provided with all the relevant substantiation needed to critically evaluate the claims concerning the Espranor study results.

Martindale submitted that as soon as it received details of the complaint (27 March), it provided all of the relevant references within 5 working days. Before that it had provided a hard copy of the published Espranor study which contained all the data necessary to address those areas that Indivior was querying.

Martindale submitted that it was unreasonable for a competitor to expect to receive a confidential document such as the full clinical study report. The published paper, which was sent to Indivior on 28 March, contained the dissolution data that seemed to be the essence of the complaint.

PANEL RULING

The Panel noted that Clause 7.5 required that substantiation for any information, claim or comparison must be provided as soon as possible, and certainly within ten working days, at the request of members of the health professions or other relevant decision makers. The Panel noted that, whilst relevant, this Clause had not been raised, Martindale had therefore not been asked to comment on it and the Panel could make no rulings in that regard.

The Panel noted Indivior's concern with regard to the strength of some claims which appeared to be based on opinion and summation, rather than data or peer reviewed evidence. The Panel noted that Indivior had not identified the claims at issue and it was not for the Panel to identify the claims. In the Panel's view, it did not have a valid complaint to consider and thus ruled no breach of Clauses 7.2, 7.3, 7.4 and 7.9.

10 Conclusion

COMPLAINT

Overall, Indivior alleged that Martindale had not maintained high standards with regard to the launch campaign for Espranor and was in breach of Clause 9.1, particularly in relation to complaint number 1, 2, 3, 5, 7, 8 and 9.

Indivior alleged that the breaches were overall very serious, and specifically in the case of complaint numbers 1, 2, 3, 5 and 7, brought discredit upon, and reduced confidence in, the pharmaceutical industry in the field of Addiction Medicine. The Addiction Field in the NHS was under significant resource constraints, making it particularly important for the pharmaceutical industry to provide credible evidence based information to prescribers and patients alike about its products. Indivior stated that the behaviour of Martindale constituted a breach of Clause 2.

RESPONSE

Whilst Martindale accepted there were some unavoidable delays in inter-company dialogue, these delays occurred on both sides. A major obstacle to early resolution was a lack of clarity from Indivior regarding specific claims at issue and not accepting that Martindale were unable to provide Indivior with the full Clinical Study Report as it contained commercially sensitive data.

Martindale remained open and prepared for further inter-company dialogue which it considered had been agreed at the face-to-face meeting at the end of May and were disappointed that Indivior did not pursue this course to its resolution.

Martindale submitted that it hoped that the responses provided would serve to address the issues raised by Indivior and would reassure the PMCPA of its commitment to the highest standards in the promotion of its medicines.

Martindale included hard copies of all references and electronic copies of all references except the Clinical Study Report. This contained company confidential information and Martindale requested that it did not get sent to Indivior.

PANEL RULING

The Panel noted Indivior's general allegation that Martindale had failed to maintain high standards particularly in relation to Points 1, 2, 3, 5, 7, 8 and 9. The Panel noted that Indivior had specifically raised Clause 9.1 at Point 5 above and a breach was ruled in that regard. The Panel noted its comments and rulings at Point 1-4 and 6-8 above and considered that Martindale had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted that Indivior alleged a breach of Clause 2 specifically in relation to Points 1, 2, 3, 5 and 7. The Panel noted that Clause 2 had also been raised at Point 5 above and a breach was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. Examples of activities that were likely to be in breach of Clause 2 as set out in its supplementary information included, *inter alia*, prejudicing patient safety and/or public health.

The Panel noted its rulings of breaches and comments at points 1, 2, 3 and 7 above. The Panel noted the vulnerable nature of the patient population and the therapy area. The Panel noted Indivior's reference to the need for evidence-based information and, in this regard, noted the difficulties of undertaking studies in this patient population. The Panel noted the small study size, Espranor n=23 and Subutex n=13 and that it was unblinded. The Panel considered that further information about the study should have been provided in the materials to enable the reader to assess the data. This was particularly so given the strong unqualified nature of some of the claims at issue. In addition, the Panel considered that the cumulative effect of advertising Espranor to the public and encouraging patients to ask for it,

implying that there was absolutely no possibility of diversion, and claims in relation to reduced supervision time due to the instant disintegration of Espranor, which was not so, prejudiced patient safety and a breach of Clause 2 was ruled.

Complaint received **27 June 2017**

Case completed **2 January 2018**

CASE AUTH/2962/7/17

ANONYMOUS SALES REPRESENTATIVE v PIERRE FABRE

Call rates and certification of meetings

An anonymous representative who promoted Toviaz (fesoterodine) for Pierre Fabre, complained on behalf of a group of representatives about call rates and the certification of meetings. Toviaz was indicated for the treatment of symptoms of overactive bladder syndrome.

The complainant was particularly critical about the conduct of senior staff within the company with regard to the Code and stated that representatives had been instructed to see clinicians more than the average 3 times per year. At a recent sales meeting it was suggested that representatives should not take holidays as they would thus not be selling. The complainant alleged that none of the training used at the meeting had been certified. Similarly, promotional speaker meetings had not been approved or certified but representatives were told to go ahead anyway because the meetings were business critical and the risk was low.

The complainant queried whether an overseas corporate consultant understood UK regulations and whether he/she had sat the ABPI Examination.

The detailed response from Pierre Fabre is given below.

The Panel noted that the sales meeting presentation at issue discussed sales activity and marketing strategy and in this regard it considered that the presentation was briefing material which needed to be certified. Pierre Fabre acknowledged that the presentation had not been certified and in that regard the Panel ruled breaches of the Code.

With regard to overcalling, the Panel noted that during their initial training course the Toviaz representatives had been instructed about the requirements of the Code regarding the number of calls they could make on health professionals. There had been some confusion on this matter at the sales meeting in June 2017 and the representatives had been orally rebriefed at that event and had received approved written instructions but not until August. A presentation at the sales meeting included individual data on sales and bonuses. The data was not set within the context of the number of calls allowed under the Code. In the Panel's view, such data might put pressure on representatives to increase their activity and potentially breach the Code. Despite these concerns and the sales force recording system logged calls such that face-to-face calls could not be differentiated from group calls, the Panel noted that the complainant bore the burden of proof. The Panel considered that it had not been shown on the balance of probabilities that representatives had been instructed to see clinicians more than three times a year on average. There was no evidence of overcalling. No breaches of the Code were ruled. The rulings were upheld on appeal.

The Panel noted that the corporate consultant did not fulfil the definition of a representative; he/she did not call upon health professionals in relation to the promotion of medicines. There was thus no requirement for him/her to take the ABPI Examination and in that regard the Panel ruled no breach of the Code. This ruling was upheld on appeal.

The Panel noted the complainant's concerns that representatives' meetings had not been approved or certified. The Panel noted that the Code required companies to check all meetings to ensure compliance with the Code and to certify those which involved travel outside the UK. The Panel did not consider that the representatives meetings needed to be certified; the arrangements had been documented and approved. No breach of the Code was ruled. This ruling was upheld on appeal

The Panel noted its comments and rulings above and also ruled no breach of Clause 2 of the Code. The complainant's appeal of this ruling was successful; the Appeal Board ruled a breach of Clause 2.

Apart from his/her appeal of the Panel's ruling of no breach of Clause 2, the complainant's appeal was largely unsuccessful as detailed above. However, in submitting his/her reasons for appeal, the complainant noted that in its response, Pierre Fabre had not submitted the whole of the presentation used at the sales meeting. The Appeal Board considered that the additional slides fell within the scope of the complaint and could be considered. The Appeal Board considered that the Panel's rulings with regard to the presentation not being certified applied to the newly submitted slides as acknowledged by Pierre Fabre.

The Appeal Board noted that Pierre Fabre had initially provided an incomplete set of slides from the sales meeting. This omission was a serious matter; it was essential that pharmaceutical companies provided complete and accurate information to the Panel and so the Appeal Board decided that, in accordance with Paragraph 11.3 of the Constitution and Procedure, Pierre Fabre should be publicly reprimanded. The Appeal Board noted that this case had raised serious concerns about Pierre Fabre's compliance structure. However, comprehensive and timely action had been taken including wholesale changes to address the issues highlighted. On balance, the Appeal Board thus decided not to require an audit of the company's procedures.

The complainant stated that part of the sales team working at Pierre Fabre in the Toviaz (fesoterodine) franchise were concerned about representatives' call rates and the certification of meetings. They would like to remain anonymous. Toviaz was indicated for the treatment of symptoms of overactive bladder syndrome. The marketing authorization holder was Pfizer.

COMPLAINT

The complainant explained that the representatives concerned had all joined Pierre Fabre full of enthusiasm six months previously and now regretted that decision. In that regard, the complainant named an employee from an overseas affiliate who had taken up a corporate consulting position in the UK and was now instructing the sales force.

The complainant stated that the representatives had been instructed to see clinicians more than the average 3 times per year. The previous sales manager tried to push back to be in line with the rules, but the Toviaz team was now being instructed verbally to see more than that. The complainant submitted that the activity rate and what was expected would show that the representatives were not in tune with the rules and alleged that senior staff seemed to have a 'nudge-nudge, wink-wink' attitude to the Code. At a recent sales meeting (15/16 June) representatives were told that if they wanted to remain in their roles, they should not take vacation as they would be off-patch (and not selling). This was unacceptable. The complainant stated that none of the training received at the meeting in June seemed to have been certified and that in the representatives' previous roles, all material was thoroughly checked and certified.

The complainant explained that as part of their role, the representatives had been asked to arrange speaker meetings. However, the instructions from senior staff seemed to be different from the rules set out by the Code. None of the promotional meetings had been approved or certified, but the representatives had been told to go ahead anyway as the meetings were business critical and the level of risk was low (presumably the company did not expect to receive a complaint). The complainant stated that the representatives did not feel comfortable as they considered that this was not in line with their procedures and might be in breach of the Code.

The complainant alleged that the overseas corporate consultant did not seem to understand the UK regulations. The representatives would like to know if he/she had sat the ABPI Examination.

The complainant stated that the representatives had approached the PMCPA as a last resort as they could not rely on any internal process to combat such behaviour, especially given the seniority of the staff criticised. The complainant stated that the representatives did not want to endure such unprofessional behaviour and be made to break the rules.

When writing to Pierre Fabre, the Authority asked it to respond in relation to the requirements of Clauses 2, 9.1, 14.1, 15.4, 15.9, if relevant, 16.3 and 22.1.

RESPONSE

Pierre acknowledged that the agenda and certain slides presented at the cycle meeting in June 2017 had not been certified in accordance with the Code, in breach of Clauses 14.1 and 15.9 and also in breach of internal procedures.

Pierre Fabre also submitted that branded materials in these slides included materials that had been pre-approved in accordance with Clause 14.1 and internal procedures. Pierre Fabre acknowledged that some of the oral statements led to initial confusion as to targets regarding calls and contacts of the Toviaz sales team, and to confusion as to entitlement to vacations. When a named senior member of staff was present at the meeting the entitlement to vacations was explained and that there were no changes to the call and contact rates issued by regional business managers (RBMs). The RBMs also orally re-briefed sales targets during the meeting.

Pierre Fabre stated that it had followed up with the individuals concerned regarding the need to strictly comply with the Code and policies and had re-communicated which managers were authorised to instruct Toviaz representatives. The company was also implementing other steps as described below in accordance with the Code and in-house policies.

Pierre Fabre did not consider that there had been a breach of Clause 15.4 at the cycle meeting because:

- the RBMs who were authorised to instruct representatives on call and contact rates provided instructions on call and contact rates which complied with the Code, and orally agreed these instructions with their representatives on 16 June
- oral confirmation of expected call and contact rates which complied with the Code was provided to representatives on 15 June to clarify the confusing information in the slides at issue
- the targets were realistic.

Pierre Fabre submitted that for two speaker meetings held in July 2017 using slide content which had been pre-approved in accordance with the Code, no final signatory approval was provided within the deadlines set by company procedures. Copies of the Zinc documents were provided. For one of the meetings on 7 July, the original intended speaker was replaced by another.

The records documented how signatories checked the proposed speaker meetings described in a detailed 'Meeting Approval Form' and commented on the suitability of the arrangements. Pierre Fabre considered that the educational content was acceptable.

For both these meetings, content such as the slides and the contract for speaker services had been pre-approved. The contract for speaker services was signed before the meeting. This clearly set out a

policy for disclosure. The honoraria agreed with the speakers were consistent with the Code, the venues suitable and costs per person for meals (sandwiches and a buffet meal) on a subsistence basis was reasonable and within the Code.

At the verbal request of each speaker, an invitation letter in standard format containing an agenda was only sent to the speaker. No other invitations or agendas were sent to delegates by the representative.

Based on the above, Pierre Fabre suggested that although its procedures were not fully observed, there was no breach of Clause 22.1 or of the guidance provided on certification of meetings in February 2016. Pierre Fabre denied breaches of Clauses 9.1, 14.1, 15.9 and 22.1 in relation to speaker meetings.

Pierre Fabre stated that by September (allowing for vacation absences and completion of internal disciplinary procedures) it would have completed discussions, and was taking steps to address the breaches of company procedures in accordance with the Code and in-house policies. Further investigations were ongoing.

In relation to the role of the overseas corporate consultant, Pierre Fabre denied a breach of Clause 16.3.

In relation to the matters raised, Pierre Fabre accepted it was in breach of Clause 9.1 as it had not maintained high standards but it did not consider that there had been a breach of Clause 2.

Role of overseas corporate consultant

Pierre Fabre stated that the role of the named employee from an overseas affiliate was to provide advice as a corporate consultant on the marketing of Toviaz in urology. He/she was not a representative, as defined in Clause 1.7; he/she did not call on health professionals or other relevant decision makers in relation to the promotion of medicines. For this reason, he/she was not expected to sit the ABPI examination as required for representatives (Clause 16.3).

Pierre Fabre submitted that the previous UK national sales manager resigned in April 2017 and left in mid-June 2017. Recruitment for a successor was continuing and this successor would be appointed in September 2017. In May and June 2017 representatives received sales data from the Toviaz product manager and from the named corporate consultant. From August the corporate consultant would provide sales data and feedback on Toviaz in Europe and expert advisory services only to the UK managing director.

Pierre Fabre acknowledged that in the weeks between the national sales manager's resignation and 15 June 2017, the corporate consultant had contacted the Toviaz sales force on sales and marketing data analysis, and used the job title 'interim national sales manager' which had caused confusion. After some of the Toviaz sales force voiced their confusion on targets and vacations at the June 2017 cycle meeting, this job title was no longer used.

The Toviaz sales team had been managed since November 2016 by RBMs who had direct authority to brief and instruct their teams. Pierre Fabre provided copies of emails from the corporate consultant regarding sales activity on Toviaz and responses of senior management.

Pierre Fabre also provided copies of slides that accompanied the statements made at the June meeting with information about the promotion of Toviaz in UK and Ireland. The company acknowledged that the slides were confusing and uncertified and so a senior employee orally briefed the representatives on 15 June during the presentation, and then the next day the RBMs re-clarified these briefings with oral instructions. Briefings made by the senior employee and the RBMs were consistent with the Code. When he/she was in attendance at this part of the cycle meeting (until a slide on 'Holiday Periods') the senior employee also explained what was meant by the comments regarding vacations and call rates.

Pierre Fabre stated that with regard to call and contact rates the RBMs, before and on 16 June orally, instructed Toviaz sales teams to set their customer targets as described below. Approved instructions were most recently provided to this sales team on 22 August 2017. This was based on relevant target customers, the average of 180 days a year of field activity and a minimum of 200 customers (targets) in a calendar year: the order of preference to see these targets was:

1 urology consultants/decision makers.
2 obstetrics and gynaecology consultants/decision makers.
3 care of the elderly consultants/decision makers.
4 GPs with an interest in urology overactive bladder.

For Cycles 1-3 the target was to plan to see each of the 200 targets once each cycle. For Cycle 4 RBMs assessed the activity from Cycles 1-3, any targets not yet seen three times would become a priority for Cycle 4, with remaining activity plans focussed on new priority customers identified during the year who had not been seen three times.

Information about vacations was then communicated at the cycle meeting by the RBMs.

Training materials for managers authorised to instruct Toviaz representatives at the cycle meeting were certified and approved before the June 2017 meeting.

Pierre Fabre explained that the planning, review and approval of promotional meetings were covered by and subject to in-house procedures and training. In company training, arrangements for speaker meetings were instructed to be made in accordance with the Code. Training and approved materials were provided on this.

Pierre Fabre stated that representatives could continue to raise any concerns with the RBM or other managers, or anonymously with helplines; the Toviaz representatives did not raise concerns when asked in June 2017 if they had any.

Pierre Fabre submitted that the senior employee regarded compliance with the Code as a key priority and had engaged at all levels across the UK company and a senior employee in European compliance supported him/her in this regard. The corporate consultant was employed by Pierre Fabre Global Region to focus on urology sales data and sales force effectiveness for Toviaz. These two individuals were therefore not employed by the same company and had substantially different roles. The senior employee focussed on activities relating to the UK and Ireland for medicinal products, had contacts with UK health professionals, with managers of UK hospitals and authorities. The other person provided consultancy services, including marketing and data reports on Toviaz business performance and activity, his/her analysis of the data and his/her views on how it might be more effective – only within the Pierre Fabre Group. He/she had no contacts with UK customers. These individuals had received different training and did not benefit from the same incentive schemes.

Furthermore, it was wrong to state that these individuals were conspiring to breach the Code when on 15 June the senior employee instructed all the Toviaz representatives and RBMs to follow the RBM's instructions not the views expressed by the corporate consultant. On other occasions the senior employee had also responded to the corporate consultant's views, though representatives might not have been aware of these responses.

Pierre Fabre stated that its leadership team and senior management were extremely alarmed that breaches of the Code and of its procedures had occurred. The company very much regretted these failings and confusions and the acute disappointment they caused to the complainant. The company acknowledged that Clause 9.1 was breached from the combined breaches of Clauses 14.1 and 15.9 at the cycle meeting and of the breaches of internal procedures at two speaker meetings in July. The company set itself high standards and it acknowledged that in these instances they were not achieved.

Pierre Fabre noted that it insisted on full disclosure of all transfers of value to health professionals; it had established a local compliance network in the UK and had openly encouraged staff to raise questions and report any concerns they might have about the Code or policies, even anonymously. The company stated that it would continue to learn from mistakes in the use of titles.

After careful assessment, Pierre Fabre denied a breach of Clause 2. As required by the Code, the company had clear policies and procedures, it trained and supported its employees and had applied its procedures to identify, report, address and remedy the breaches. The breaches and activities had not led to risks for patient safety and had not brought discredit upon or reduced confidence in the industry.

Pierre Fabre stated that it continued to monitor compliance with the Code and its procedures and further details were provided below on future steps. Senior management had highlighted and would continue to model how compliance with the Code and policies was fundamental to business in the UK.

Pierre Fabre expressed its full and unreserved apologies for the breaches and that its procedures and training did not prevent their occurrence. Senior directors and other managers would continue to set the high standards of the Code in all activities in the UK. More details of steps to model and promote these standards were provided.

Since discovery of the breaches, all immediate steps had been taken to address the breaches and remedy them including calls with management and the sales force about the complaint. Further steps were planned as detailed below. All of the senior management team shared a commitment to ensure the Code continued to be at the core of all its activities.

As of August 2017, Pierre Fabre had internally circulated information about this complaint and the Code. It had re-communicated to the Toviaz sales force a Briefing Document on 2017 Activity.

Future steps and initiatives would include:

- re-train individuals who were found not to comply with compliance with procedures
- continue to raise awareness about the Code, about the importance of certifying and approving all materials for use in promotional meetings as well as with speaker meetings
- appoint Code champions in every function and organizing a Code Awareness Day in 2017
- conducting an internal audit into compliance with the Code in the third of fourth quarter of 2018, and conduct 'spot' checks in the meantime
- take all other steps the UK Leadership Team considered appropriate after review of these breaches and of the outcomes of confidential internal investigations.

With its response Pierre Fabre provided an enclosure on background and facts. The document stated that the marketing authorization holder for Toviaz in the UK was Pfizer Limited. Pierre Fabre was responsible for the promotion of Toviaz in Europe and other markets under the terms of a promotion agreement with Pfizer. In accordance with this agreement, Pfizer and Pierre Fabre were jointly responsible for review and approval of all Toviaz promotional materials, with Pierre Fabre taking responsibility for informing the Pfizer signatory of all relevant items in development and use.

Pierre Fabre was solely responsible for the briefing and training of its staff, including its field force when the content of that briefing or training was not related to Toviaz product information.

Pierre Fabre submitted that if first promoted Toviaz in the UK and Ireland from early December 2016. Representatives who promoted only Toviaz were divided into two regions (North and South). They reported for all instructions and matters to two RBMs who in turn, until mid-June 2017, reported to the national sales manager. In May and June 2017 the regional sales manager reported their own expenses, targets and vacations to the managing director. Representatives and regional managers also received information on marketing messages from the Toviaz product manager and from the sales force effectiveness team.

Representatives were invited by the national sales manager to attend the cycle meeting in June to review market developments, sales progress and to take part in a role play where managers would pretend to be customers meeting their representatives to discuss Toviaz.

Pierre Fabre submitted that the corporate consultant who attended and presented at the meeting on 15 June worked on the promotion of Toviaz, and was the internal expert on marketing in urology and the European and global experience of marketing messages for Toviaz. The Toviaz product manager, attended to support with knowledge and experience of marketing activities by Pierre Fabre in the Republic of Ireland and other EU markets.

Pierre Fabre submitted that the corporate consultant was not authorised to instruct the Toviaz sales force and had no certification or approval authority under the Code. It was common knowledge within Pierre Fabre UK that the individual concerned had not been trained in the UK pharmaceutical industry. He/she was invited to present at the cycle meeting to share information about marketing Toviaz in EU markets and to help prepare representatives for a role play. RBMs were then planning to discuss with representatives their individual and team targets and plans the following day.

Pierre Fabre submitted that before the role play, the corporate consultant presented data on Toviaz activity for April 2017. The regional sales managers understood that this meant slides that had been approved for use at the cycle meeting when in fact they were slides prepared by the corporate consultant and the product manager to review sales progress in April 2017, and to discuss marketing in urology, but not intended to provide instructions to representatives for the purposes of the Code. None of the slides presented by the corporate consultant or the RBMs were circulated to the representatives.

FURTHER INFORMATION FROM PIERRE FABRE

In response to a request for further information Pierre Fabre stated that the investigations extended beyond the scope of the questions raised by the Panel and were being disclosed in the interests of transparency. Pierre Fabre clarified that the breaches were not identified sooner because the staff concerned were not available to authorise access to their email accounts.

Outcome of investigations

Pierre Fabre submitted that it first reviewed all promotional activities for Toviaz in the UK and specifically the compliance of job bags since August 2016 with the Code and company SOPs. This review included instructions given to the sales force, based on interviews with marketing staff who communicated with the sales force and review of emails they sent to the Toviaz sales force. This sales force only promoted Toviaz.

The findings of its global and local compliance team were provided with details and copies of the Zinc documents. Where Pfizer did not certify or examine materials, it was because Pierre Fabre did not send the materials to Pfizer.

Apologies and commitments

On behalf of its senior management in the UK and Europe Pierre Fabre apologised unreservedly that in these instances high standards it set had not been met. The breaches had been brought to the full attention of Pierre Fabre Global Management. It was acknowledged that they should not have occurred. The acting managing director of Pierre Fabre UK, apologised personally that these breaches occurred under previous Pierre Fabre UK leadership.

Pierre Fabre UK submitted that it had and was taking the following steps:

- discontinue the promotion of Toviaz in UK with effect from 21 September 2017 until further notice
- urgent appointment of a national sales manager, a senior marketing manager with significant experience of the Code and a compliance officer
- urgent appointment of a further senior medical advisor
- re-train all staff and sales force on the Code and SOPs, in October 2017
- run an ABPI Code Day
- urgent review of SOPs with new documents issued where appropriate.

Pierre Fabre UK also acknowledged that after the introduction of Zinc and specific SOPs, followed by training on their use, it was disappointing that despite clear attempts by staff to comply with the Code and with SOPs, there were breaches of the Code.

Pierre Fabre submitted that notwithstanding this training, there were errors in complying with its processes which were designed to comply with or be stricter than the Code.

The critical importance of Pierre Fabre's Code of Ethics, the ABPI Code and the EFPIA Code was restated at a presentation on 19 September to all head office staff and representatives.

In response to questions from the Panel, Pierre Fabre stated that the y axis on one of the graphs used at the cycle meeting (slide 20, 'Holidays Period') stated the number of days of vacation requested (after approval from the RBM), for the

period January to end of May 2017. It did not state the number of days' vacation taken. The data taken from the company's sales force reporting system was a snapshot of vacations booked in May 2017. The slide was shown so staff at the meeting could see the vacations booked. It was not intended to reduce absence and 'over-target'. It was shown to encourage representatives who had not yet booked their summer vacation to include this in the sales force reporting system. At the presentation, after this slide created confusion, the senior employee intervened. It should not have been shown without clear explanations.

In relation to questions about when and how the representatives were first briefed about targets, Pierre Fabre submitted that the representatives were briefed on targeting and calls as part of the induction training in November 2016; the briefings and training were approved in accordance with the SOPs. The initial briefing was clear and representatives did not raise questions.

Pierre Fabre submitted that after a clear briefing and detailed training during the induction training in November 2016, it was felt appropriate to provide a further written briefing after confusion arose at the June cycle meeting. This further briefing was certified by 18 August and communicated to the sales force on 22 August 2017. Pierre Fabre referred to the RBMs' explanation that they had, on the morning of 16 June, re-explained key messages to their representatives and how holidays could still be booked as before. They also had agreed action plans with their representatives and presented slides that had been approved in Zinc.

Pierre Fabre submitted that during the initial training period the representatives each received a hard copy of the 2016 Code. In November 2016 it also provided training on Transfers of Value, internal SOPs and the detailed online training. Representatives were also provided with training on the Code in accordance with Pierre Fabre SOPs, including specifically on Clause 15.4.

Pierre Fabre submitted that the meeting application form for the meeting on 7 July 2017 was examined, and included the stamp 'Amend and Resubmit' by a medical reviewer (not a Code signatory) because multiple typographical errors were identified. The marketing reviewer did not add the necessary stamp. However, the arrangements and logistics of the meeting had been accepted prior to the meeting and were considered appropriate under the Code.

Pierre Fabre submitted that with regard to payment of external speakers meetings in July 2017, each speaker at each meeting was paid as agreed in their respective contracts.

With regard to the instructions about the 'meetings in a box', Pierre Fabre submitted that after slides were circulated for information following a verbal briefing, certified slides were circulated on 16 May 2017 and the following instructions were provided by Pierre Fabre UK to representatives: UK/TOV/0417/0037a – First Briefing document after verbal briefings – circulated on 30 June as a version with typographical errors. Pierre Fabre acknowledged that the first briefing was not certified in accordance with its SOPs and with the Code.

Four meetings were held between June and August. Pierre Fabre submitted that the meeting content had been certified and the arrangements examined as required by the Code. However, Pierre Fabre UK SOPs were stricter than the Code as they required certification of the meeting arrangements, and this certification had not been completed.

Pierre Fabre submitted that the statement 'open more doors' contained in an email of 20 February 2017, from the corporate consultant, was aimed at three members of the sales force and was intended to provide support and time of the RBM and head office team. This also included 'one on one' training and support that the representative might need to respond more effectively to customer contacts. The representatives concerned worked in territories with extensive distances between customer centres and complexities for access. RBMs would provide advice. Head office staff would provide support based on their experience of dealing with customers in these regions. For example, one of the representatives did not know that specialist registrars could also be contacted in addition to other urology professionals. This information was provided by his/her RBM. Another form of support was to sponsor hospital meetings if requested in the territories of those representatives, as described in an attachment.

With regard to the targets of one member of staff, Pierre Fabre submitted that he/she did not act as a representative in the UK.

Pierre Fabre submitted that it was not aware that a representative had made more than three unsolicited calls to a particular health professional since Pierre Fabre started to promote Toviaz in December 2016. Pierre Fabre referred to the briefings and slides provided since it started promoting Toviaz.

Pierre Fabre submitted that it was not possible for Pierre Fabre to collate data that distinguished between solicited and unsolicited calls. Its sales force reporting system recorded all of the following as a 'call' in a group total – a 'face to face' meeting, or a 'group' meeting. A review of data on the system showed that between 1 January and 9 September 2017, the sales force reported contacts with 3,878 health professionals in the UK of which 597 were contacted more than three times. This data would include attendance at group meetings, solicited and unsolicited calls. Pierre Fabre submitted that it would continue to monitor reports of representatives and to provide training on the Code and on its instructions.

In conclusion, Pierre Fabre submitted that the decision to discontinue promotion of Toviaz in the UK and to change staff showed how seriously the Pierre Fabre Group had taken the breaches. Pierre Fabre was preparing a detailed remedial plan and was learning from the failings.

Pierre Fabre acknowledged a breach of Clause 9.1 based on the breaches of Clauses 14.1 and Clause 15.9 and of the breaches of its internal procedures.

Pierre Fabre submitted that the group set high standards for all of its teams with regard to the Code and all its procedures. Pierre Fabre acknowledged that they were not met and after conducting necessary investigations it had taken immediate action.

After detailed analysis of the breaches, Pierre Fabre submitted that there was no breach of Clause 2; the company had clear policies and procedures, it had provided training and also tested its employees on their knowledge. Clear standards were set for senior management in the UK. When these standards were not met, after necessary investigations Pierre Fabre had taken action.

Pierre Fabre submitted that it would continue to expect all staff to fulfil their obligations under the Code. It also submitted that there were no risks for patient safety and denied that it had brought discredit upon or reduced confidence in the industry.

Pierre Fabre UK submitted that it continued to monitor compliance with the Code and its procedures and further details were provided on future steps it would take. Senior management has highlighted and would continue to model how compliance with the Code and policies was fundamental to business in the UK.

PANEL RULING

The Panel noted that Clause 15.9 of the Code required companies to prepare detailed briefing material for representatives on the technical aspects of each medicine which they would promote. Briefing material must comply with the relevant requirements of the Code and, in particular, was subject to the certification requirements of Clause 14. Briefing material must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The supplementary information to Clause 15.9 stated that the briefing material referred to in the clause consisted of both the training material used to instruct representatives about a medicine and the instructions given to them as to how the product should be promoted.

The Panel noted that the presentation at issue included slides which discussed sales activity and included comments on the importance of staying in the field, the number of urologists to be seen and the frequency with which they should be seen. The presentation also included slides on the marketing strategy for the UK and Republic of Ireland which included technical aspects of each medicine and claims presented by the product manager. The Panel considered that the presentation was briefing material for representatives and therefore required certification but noted Pierre Fabre's submission that the presentation had not been certified. The Panel thus ruled a breach of Clause 14.1 as acknowledged by Pierre Fabre. This meant that the presentation failed to comply with the Code and thus a breach of Clause 15.9 was ruled. The Panel considered that failing to certify representatives' briefing material meant that high standards had not been maintained and a breach of Clause 9.1 was ruled as acknowledged by Pierre Fabre.

The Panel noted the allegation that representatives had been instructed to see clinicians more than the average 3 times per year. The Panel noted Pierre Fabre's submission that during the initial training course representatives were trained on the Code and company SOPs. The training, dated October 2016, contained information on Clause 15.4 with regard to call and contact rates including an extract from the supplementary information to Clause 15.4 about the number of visits. The Panel further noted Pierre Fabre's submission that the RBMs, before and on 16 June, verbally instructed Toviaz sales teams to set their customer targets based on relevant target customers and an average of 180 days a year of field activity. Given the confusion caused by the presentation at the cycle meeting on 15 June the Panel queried why approved written instructions were not provided to the sales team until 22 August 2017. The Panel noted that the presentation given at the cycle meeting included data on sales on an individual named basis and who had received what bonus which might be seen to put pressure on representatives to increase their activity and potentially breach the Code in doing so. The presented data was not set within the context of the relevant requirements of Clause 15.4 and its supplementary information. In the Panel's view the presentation indirectly advocated a course of action likely to lead to a breach of the Code. The Panel, however, noted Pierre Fabre's submission that verbal briefings in line with the Code were given by a senior member of staff at the meeting on the same day and the RBMs the day after. The company was not aware that a representative had called on a particular health professional more than three times as an unsolicited call since Pierre Fabre started promoting Toviaz in December 2016. The Panel was concerned to note that Pierre Fabre could not distinguish between solicited and unsolicited calls. The sales force reporting system recorded a 'face to face' meeting, or a 'group' meeting as a 'call' in a group total. The Panel queried how in the absence of such differentiation Pierre Fabre could be confident that its representatives complied with the relevant requirements of the Code. The Panel noted that whilst it had some concerns, the complainant bore the burden of proof and considered that he/she had failed to prove on the balance of probabilities that representatives had been instructed to see clinicians more than the average of three times per year. There was no evidence of overcalling. The Panel ruled no breach of Clauses 15.4 and 15.9. This ruling was appealed by the complainant.

Clause 1.7 of the Code defined 'representative' as a representative calling on members of the health professions and other relevant decision makers in relation to the promotion of medicines. Clause 16.3 required that representatives take an appropriate examination within their first year of employment as a representative and pass it within two years of starting such employment.

The Panel noted the corporate consultant's job description and Pierre Fabre's submission that the role was not covered by the definition of representative under Clause 1.7 as the person did not call on health professionals. The Panel considered as the individual did not call upon health professionals in relation to the promotion of medicines there was no requirement to take and pass an appropriate examination. The Panel therefore ruled no breach of Clause 16.3. This ruling was appealed by the complainant.

The Panel noted the complainant's concern that none of the representatives' promotional meetings had been approved or certified. The Panel noted that the supplementary information to Clause 22.1 required that companies ensured that all meetings which were planned were checked to see that they comply with the Code. In addition, meetings which involved travel outside the UK must be formally certified as set out in Clause 14.2. The Panel noted Pierre Fabre's submission that for two speaker meetings held in the UK in July 2017 no final signatory approval was provided within the deadlines set by company procedures. Copies of the Zinc documents were provided. The records documented how signatories checked the proposed speaker meetings described in a detailed 'Meeting Approval Form' and commented on the suitability of the arrangements. The Panel did not consider that these meeting arrangements required certification. The Panel further noted Pierre Fabre's submission that for both these meetings, content such as the slides and the contract for speaker services had been pre-approved, copies of the certificate was provided. The Panel therefore ruled no breach of Clause 14.1. The Panel did not consider that Pierre Fabre had failed to maintain high standards in this regard and no breach of Clause 9.1 was ruled. This ruling was appealed by the complainant.

The Panel noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and was reserved for such circumstances. The Panel noted its comments and rulings above and did not consider that the matter warranted such a ruling. This ruling was appealed by the complainant.

APPEAL BY THE COMPLAINANT

The complainant appreciated the transparency and explanation provided by Pierre Fabre regarding promotional meetings, call rates, and the other associated documentation and now understood this was not in line with company procedure and not in breach of the Code. However, the complainant submitted that some of the information in Pierre Fabre's response was inaccurate as detailed below. The complainant stated that he/she was not a Code expert and left it to the PMCPA to decide if the evidence provided was in breach of Clauses 9.1, 15.4, 15.9, 16.3 or 2.

Role of sales effectiveness

The complainant alleged that Pierre Fabre's statement that the corporate consultant was 'not a sales director', 'did not have the authority to instruct the sales force', had no contact with UK customers' and 'provided consultancy services… for Toviaz' was not entirely true as he/she had instructed the sales team since December 2016, two weeks after it started promoting Toviaz. The complainant provided a copy of an email dated 14 December 2016 to demonstrate the type of communication the representatives were subjected to. This demonstrated that the corporate consultant acted as a sales director (albeit with a different title), especially as the national sales manager was copied into this email who also had to get permission from the corporate consultant before he/she could carry out any activities pertaining to the sales team. The complainant submitted that his/her oncology colleagues also received communication from the corporate consultant (email dated, 27 April 2017). If the individual was a global consultant for Toviaz, why did he/she instruct the Navelbine (oncology) team? Why would a global colleague who was supposed to be providing consultancy support communicate directly with the urology and oncology sales teams, if not in the capacity of a sales director/manager? The complainant alleged that the individual had seen both UK and Irish customers. This also took place during larger meetings, eg the European Association of Urology, March 2017 in London which the individual attended as part of the UK team.

Management of the Toviaz sales team

The complainant stated that when Toviaz was launched in December 2016, the representatives had a national sales manager and an RBM. A representative based outside the UK and was promoted to the RBM to include UK territories in the first quarter of 2017. Since the complaint, this person had been told not to instruct UK representatives until he/she completed the ABPI examination.

The complainant noted slide number 66 of the Business Review Slides were presented as part of the UK's business review on 13 February 2017. The Toviaz slide in question was presented by the corporate consultant; if he/she was not acting as a sales director, what was the intention presenting the slide which indicated which representatives should have their probationary period extended, those that were 'OK Now' and those that should be terminated.

The complainant wanted to understand if the above actions were those of a global consultant that only provided 'consultancy support'. The complainant alleged that he/she had indicated that the consultant was functioning as sales director and had direct involvement with the Toviaz sales team, although the official title might not have reflected that.

Slides and workings of the June cycle meeting – framework and cycle meetings slides

'… [ ] was invited to present at the cycle meeting to share information about marketing Toviaz in EU markets ….'

'… slides prepared by […] to review sales progress in April 2017, and to review sales progress in April 2017, and to discuss marketing in urology, but not

to provide instructions to representatives for the purpose of the Code ….'

The complainant noted Pierre Fabre's statement that the corporate consultant was invited to the meeting. However, to suggest that the individual was invited as a guest was disingenuous at best given that he/she ran the June cycle meeting; he/she oversaw the meeting and had full control. This was also similar to the April cycle meeting in 2017. A significant part of the presentation focused on the calibrage activity presented by the corporate consultant. However, the complainant noted that there were only 2 slides on Calibrage' ('calibration') provided in the enclosure; this was not accurate – there had been at least a dozen. This was a market research activity run by the corporate consultant and a colleague, and the results were shared at the cycle meeting. The complainant was tasked to seek feedback from health professionals about the efficacy of Toviaz and adverse event profiling vs competitors. The representatives were also instructed to use market research results to better focus promotional calls for Toviaz. This summary slide was riddled with typographical errors and poor grammar, eg instead of BBB (blood brain barrier), BBC, and there was reference to sex, etc. The complainant was concerned that the full slide deck was not presented to the PMCPA; probably to downplay the corporate consultant's involvement in the affiliate.

The complainant stated that the representatives had been placed on paid leave and wanted to resume their duties. Although the complainant appreciated the steps taken by Pierre Fabre (replacing the staff), he/she was concerned that there were still inaccuracies around the corporate consultant's role in the UK. The complainant was also surprised by the lack of oversight Pfizer had over the running of Toviaz by Pierre Fabre. Having reviewed the material and evidence provided by both Pfizer and Pierre Fabre, the complainant alleged that there seemed to be a concerted effort by both companies to hide and misrepresent certain facts.

RESPONSE FROM PIERRE FABRE

Pierre Fabre UK, and its European Management and Global Management, apologised unreservedly that Pierre Fabre UK had not yet been able to identify all past breaches of its Code of Ethics and of the Code previously noted. Pierre Fabre also apologised that it had not provided all of the slides that were presented at the June cycle meeting for Toviaz representatives, and thereby misled the Authority on facts that were not the focus of the complaint. The reasons for this partial omission were explained below. Such an omission was unacceptable. Pierre Fabre had also apologised to Pfizer for this omission.

From the outset Pierre Fabre UK had been transparent of its plans to conduct investigations after the complaint was received. Pierre Fabre UK would continue to report to the Authority the breaches of the Code that it identified. The company had also started a process of culture change in the UK and had focused on the recruitment of new senior management in order to achieve change; in parallel it would conduct investigations and self-report as promptly as possible thereafter.

Within two months, Pierre Fabre had made senior interim and permanent appointments and had started to select new leadership. The company had also implemented revised processes and ongoing training programmes to clearly reflect the high standards the Pierre Fabre Group set itself and its teams.

<u>Agreement with Pfizer regarding the promotion of Toviaz and steps taken in September 2017</u>

Pierre Fabre submitted that it had also continued to consult closely with Pfizer.

For both Pfizer and Pierre Fabre, promotion of Toviaz in the UK would not recommence until Pfizer, Pierre Fabre UK, Pierre Fabre Europe & Global, and the interim UK & Ireland compliance officer were satisfied that the compliance culture – which Pierre Fabre Group expected – was fully re-established in the UK. Pierre Fabre submitted that both it and Pfizer had acted responsibly and decisively and with the necessary level of oversight. Both companies would continue to independently monitor progress of the remediation plans implemented in Pierre Fabre.

<u>New management team of Pierre Fabre UK and steps taken since September 2017</u>

Pierre Fabre submitted that it was at the start of a series of steps to re-create and maintain a culture that complied with its code of ethics and with the Code. This would include a new structure, remediation plans, training and other steps. The new structure together with a review of processes, further training and associated culture changes, would help to prevent such breaches in the future.

Pierre Fabre highlighted that senior leadership (interim and permanent) roles had been replaced and that new compliance and senior marketing roles had been created and filled (organogram provided).

Pierre Fabre provided a summary of the ongoing remediation plan. Full cooperation and support for this remediation plan was available from all Pierre Fabre management.

Pierre Fabre submitted that after suspending all promotional activities for Toviaz in the UK, Pierre Fabre UK and Europe had implemented the following since September 2017:

- an interim medical director compliance officer and head of marketing for the UK and Ireland (November 2017)
- the roles of UK & Ireland General Manager and permanent UK head of marketing, medical director and compliance officer would be filled as soon as possible
- a Code refresher for all staff (head-office and field-based) (October 2017)
- more detailed Code training for all staff (head-office and field-based) (November 2017)
- an ABPI Code Day with UK teams (November

2017) (slides provided). Training with relevant European colleagues (December 2017)
- additional internal guidance on working with Pfizer in the UK provided
- remediation plan to include review of current SOPs and new SOPs prepared
- appointment of Code champions (November 2017)
- training for a first member of the Pierre Fabre Europe team to sit the ABPI Examination in 2018.

Admissions after new investigations into allegations of the complainant

After concluding investigations into the key allegations of the complainant, Pierre Fabre set out its findings and admissions below:

- Incomplete slides provided to the Authority – breach of Clause 9.1 and Clause 2.

Pierre Fabre submitted that because the June 2017 cycle meeting slides were not saved within Zinc, and because various versions of these slides were created, in August 2017 Pierre Fabre was unable to identify precisely which slides were presented in June and by whom. The person who had prepared the slides was not available in August for questioning and those who were had different recollections of the slides that were presented.

The senior member of staff decided in August to submit the slides that he/she recalled seeing during the June cycle meeting and to investigate the complainant's allegations. This investigation was planned to enable future self-reporting. The slides the senior member of staff remembered seeing at the June cycle meeting and that were submitted to the Authority included introductory slides about 'calibrage'. Investigations were commenced in September and October 2017 to respond to specific questions from the Authority and to conduct two internal audits. The arrival of the interim UK & Ireland compliance officer provided expert resource to start new investigations. One line of enquiry was into the June cycle meeting. The complainant's statement in his/her appeal identified quotations that were matched to a set of slides which had since been found. Pierre Fabre provided a copy of slides, that appeared to be the set that was presented to the complainant at the June cycle meeting. The slides that were not disclosed in August (slides 35 to 42) raised issues that were not the focus of the complaint. Pierre Fabre set out below the breaches of the Code that it had identified in these slides.

In Pierre Fabre's view the omission of some of the slides was in breach of the spirit of the Code and Clauses 9.1 and 2 and also Pierre Fabre's Code of Ethics. Pierre Fabre noted that it had already accepted breaches of Clauses 15.9, 14.1 and 9.1 of the Code regarding the June `cycle meeting slides.

- Promotion during calibration activities – 24 May to 8 June 2017 – breach of Clauses 15.9, 14.1 and 9.1.

After a review of slides 35 to 42, Pierre Fabre admitted a breach of Clauses 15.9, 14.1 and 9.1, for the promotion of Toviaz in the form of 'Calibrage' (calibration) promotion activities to UK health professionals. Pierre Fabre submitted that 'Calibrage' ('calibration') referred to a 'snapshot' taken by Pierre Fabre sales force effectiveness teams during an internal benchmarking of promotional activity by Toviaz representatives. The purpose was to ensure consistency of message and to identify training needs. Calibration was conducted as follows: representatives conducted usual detailing to customers in accordance with a certified briefing document for the ipad sales aid (including the claim about the four pharmacological properties of Toviaz - UK/TOV/0916/0012b) and a certified document for promotional content in the sales aid - UK/TOV/0916/0012. When a representative considered it appropriate and with the customer's agreement the representative asked: 'What is your opinion about the 4 pharmacological properties of Toviaz that are responsible for 97% of patients being satisfied after 2 years?'. Representatives continued to routinely report the facts of their call with customers as part of their usual daily call reports (date, time, other factual information).

During a calibration, representatives would also be asked to capture qualitative feedback from customers on the key messages for a product. Representatives were free to input as few or as many of the responses of customers as they chose into their calibration reports. Only the feedback selected by representatives, at their discretion, was then logged by them into a database that was distinct from their usual call reporting database. The feedback inserted in the database included only the specialty of customers, and an optional identifier of no more than two characters. Pierre Fabre noted that representatives had been briefed on pharmacovigilance reporting in November 2016. The calibration database was only open for input of feedback by representatives for a finite period. The content of these responses had been re-reviewed by pharmacovigilance personnel in the UK. This data had been archived and would not be reviewed further. It would be destroyed in due course.

Pierre Fabre submitted that documents that recorded the data were entered into the database. The purpose of this promotional activity was to benchmark the effectiveness of a claim with qualitative information obtained in a usual promotional context, not to conduct market research. It was clear to customers that the purpose of a call and a question was promotional. It complemented training and role play that were used to give confidence to representatives in their messaging skills (bearing in mind representatives had only started to promote in December 2016).

The breaches Pierre Fabre had identified with regard to this promotional activity were failures to:

- provide written briefing to representatives (Clause 15.9)
- certify the question to be raised by representatives (Clause 14.1)
- maintain high standards (Clause 9.1).

Pierre Fabre apologised that these breaches occurred. The breaches were analyzed as soon as possible in the circumstances.

Allegations of the complainant in his/her appeal

With regard to specific matters raised by the complainant, Pierre Fabre UK response was as follows:

(a) June cycle meeting slides - omission of slides
Pierre Fabre UK admitted breaches of Clauses 9.1 and 2, as set out above.

(b) and (c) role of sales force effectiveness and call targets

Previous acknowledgements and admissions

Pierre Fabre admitted in August 2017 that an individual from an overseas affiliate had provided sales force effectiveness advice, services and opinions as a corporate consultant to support the business. This led to some representatives being confused as to how this role interfaced with that of the sales director. This confusion increased when the sales director resigned. It had acknowledged that communication with representatives regarding the role of the consultant should have been clearer and that emails and other directions to the representatives should not have occurred.

Pierre Fabre considered that effectiveness of promotion should be followed and tested. At that time Pierre Fabre did not employ resource with such strategic expertise and so such sales force effectiveness services were provided by the corporate consultant. The role of a sales director was operational and did not usually include responsibility for monitoring effectiveness of promotion.

Comments on new documents provided by the complainant

Emails of 14 December 2016 and 27 April 2017

Pierre Fabre provided emails to show that the national sales manager contacted representatives directly to review the end of their probation periods; issued instructions as a sales director would usually write, included his/her own slides in presentations and issued operational instructions to representatives.

European Association of Urology Congress in London on 24-28 March 2017

Pierre Fabre prepared a briefing document (provided) for all participants from the UK, other countries and other divisions of the Pierre Fabre Group, to explain how the Code would apply to customer-facing personnel and other Pierre Fabre resource at international congress. As information about the Pierre Fabre Group was available at the congress the corporate consultant attended as a member of Pierre Fabre corporate, along with other corporate colleagues. However, the corporate consultant might have had contacts with customers who attended the congress. He/she was not considered a promotional resource from his/her attendance records.

Pierre Fabre UK comments on new documents

Pierre Fabre submitted that the slides of a business review of February 2017 (conducted as a telephone conference) might not be the final version and were never used to brief representatives. These slides were not certified as they were for an internal business review.

Calibration activities

Pierre Fabre submitted that these activities were not the subject of the original complaint, but it had admitted the breaches in the above.

Pierre Fabre's commitments and apologies

Promotion of Toviaz in the UK would not recommence until Pfizer and Pierre Fabre were satisfied that the culture of Pierre Fabre and its processes would both secure compliance with the spirit and detail of the Code and of the Pierre Fabre Code of Ethics.

In addition to managing complex remediation plans and audits, Pierre Fabre had continued to admit breaches of the Code that fell within and outside the scope of the complaint, and would continue to further investigate and report breaches that might be identified. The April 2017 cycle meeting documents already fell within the scope of ongoing investigations and would be the subject of self-reporting.

The senior management of Pierre Fabre UK and Pierre Fabre Europe, restated their unreserved apologies that the high standards Pierre Fabre set itself had not been met.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant acknowledged the steps taken by the current Pierre Fabre management and was pleased that the April cycle meeting would be the subject of self-reporting. The complainant also acknowledged the further additional breaches of the Code admitted by Pierre Fabre. However, the complainant submitted that the actions highlighted in the company's latest correspondence would not have been carried out if he/she had not complained.

The complainant was not convinced by the rationale as to why the complete June 2017 cycle meeting slides were not provided to the PMCPA. If there was doubt on the slides presented, why was confirmation not sought by checking with the other managers present during the meeting? Surely not all present would have been unable to recall a significant section of the presentation. Or if the sales team had been approached it would have confirmed the correct version of the slide deck.

The complainant found it difficult to accept that no other personnel either affiliate or global level (Pierre

Fabre and Pfizer) were involved or were unaware of what was happening.

The complainant alleged that Pierre Fabre was disingenuous to state that the business review slides of February 2017 might not have been the final version. What was the final version? The complainant had shared the slides (and emails) to provide evidence that the corporate consultant was more than just a global consultant and had acted as a sales director. Who else could decide if members of the sales team passed or failed their probation?

APPEAL BOARD RULING

The Appeal Board noted that the complainant had made a very broad complaint and although he/she had appealed a number of no breach rulings the appeal did not focus on these or provide the specific reasons for appealing each clause. Instead, the appeal addressed what were alleged to be factual inaccuracies in Pierre Fabre's response to the complaint. In addition, the Appeal Board noted that Pierre Fabre had made a number of admissions as part of its response to the appeal. These were only considered insofar as they came within the scope of the original complaint.

The Appeal Board did not consider that it had any evidence before it to show that the corporate consultant's role was covered by the definition of a representative under Clause 1.7 as he/she did not call on health professionals in relation to the promotion of medicines, thus there was no requirement to take and pass an appropriate examination. The Appeal Board therefore upheld the Panel's ruling of no breach of Clause 16.3. The appeal on this point was unsuccessful.

The Appeal Board noted that the Panel had ruled no breach of Clause 14.1 as the speaker meeting arrangements did not require certification but had been checked. The meeting's material and the speaker contracts had been certified. The Appeal Board did not consider that Pierre Fabre had failed to maintain high standards in this regard and it upheld the Panel's ruling of no breach of Clause 9.1. The appeal on this point was unsuccessful.

The Appeal Board noted the allegation that representatives had been instructed to see clinicians more than the average three times per year and it further noted the Panel's ruling and concerns above on this point. The Appeal Board also noted that whilst there were 597 health professionals who had been contacted more than three times, the company's procedures did not determine whether these were unsolicited or solicited and the complainant had not provided any further evidence on the point. The Appeal Board considered that as there was no new evidence before it to show that there had been overcalling it upheld the Panel's ruling of no breach of Clause 15.4. The appeal on this point was unsuccessful. The Appeal Board also upheld the Panel's ruling of no breach of Clause 15.9. The appeal on these points was unsuccessful.

The Appeal Board noted that although slides 35 to 42 that featured the promotion of Toviaz in the form of 'Calibrage' (calibration) for the June cycle meeting were not seen by the Panel they were part of the evidence that the complainant had seen and complained about. The Appeal Board considered that due to the broad nature of the complaint these slides fell within the scope of the original complaint and could be considered. In that regard, the Appeal Board noted that the version of slides provided by Pierre Fabre in response to the complaint included two slides that referred to 'Calibrage' ('calibration'). The Appeal Board noted that according to Pierre Fabre 'Calibrage' ('calibration') referred to a 'snapshot' taken by its sales force effectiveness teams benchmarking a promotional claim used by Toviaz representatives. The Appeal Board noted that 'Calibrage' ('calibration') required representatives during a promotional call to ask health professionals 'What is your opinion about the 4 pharmacological properties of Toviaz that are responsible for 97% of patients being satisfied after 2 years?' when they considered it was appropriate, and if the customer agreed. Pierre Fabre submitted that in relation to 'Calibrage' ('calibration') it had failed to provide a written briefing to representatives or certify the question. The Panel had ruled that the presentation had not been certified and was thus in breach of Clauses 14.1, 15.9 and 9.1 of the Code. The Appeal Board considered that this ruling applied to the seven newly submitted slides as admitted by Pierre Fabre.

The Appeal Board noted its comments and the rulings of breaches of the Code by the Panel. Taking all the circumstances into account, the Appeal Board considered that Pierre Fabre had brought discredit upon, and reduced confidence in, the pharmaceutical industry and ruled a breach of Clause 2. The appeal on this point was successful.

The Appeal Board noted that the slides for the June cycle meeting provided by Pierre Fabre in response to the complaint were incomplete. Pierre Fabre was only able to provide the correct version of the slides which contained seven additional slides after being advised of the omission by the complainant in his/her appeal. In the Appeal Board's view, this omission was a serious matter. Noting the comments from the complainant, it queried the robustness of the company's original investigation and response on this point. The Appeal Board noted Pierre Fabre's submission that the responsible individual had since left the company. However, the Appeal Board noted and welcomed the fact that Pierre Fabre had taken significant and rapid action and had in place a comprehensive and timely action plan to make wholesale changes to address issues highlighted in this case. However, notwithstanding its comments the Appeal Board considered that it was essential that pharmaceutical companies provided complete and accurate information to the Panel and thus it decided that in accordance with Paragraph 11.3 of the Constitution and Procedure that Pierre Fabre should be publicly reprimanded. The Appeal Board noted that this case had raised serious concerns about Pierre Fabre's compliance infrastructure. Senior

management appeared to be taking this matter seriously and were proactive. It noted its comments above about the comprehensive and timely action plan. On balance, given the immediate steps taken, the Appeal Board decided not to require an audit on the information currently before it. It noted the company's comments about future voluntary admissions.

Complaint received **31 July 2017**

Case completed **5 January 2018**

CASE AUTH/2969/8/17

SENIOR PRACTICE NURSE v ASTRAZENECA

Conduct of a representative

A senior practice nurse complained about the conduct of a medical representative with AstraZeneca UK. The representative was promoting Forxiga (dapagliflozin) which was indicated to improve glycaemic control in adults aged 18 years or over with type 2 diabetes, either as monotherapy or as add-on combination therapy.

The complainant stated that there had been several occasions when the representative had come into surgery asking to see him/her; all of which had been self-presentations at reception with no forwarding or booked appointment. When the representative was advised by the receptionists that the complainant was in surgery seeing patients he/she became quite insistent that the complainant be contacted. The representative was advised to email the complainant directly. The complainant stated that on one occasion he/she had to go into reception in the middle of a minor surgery procedure with a GP to collect a consent form. The representative proceeded to try to talk to him/her in view and ear shot of other patients (after being told that the complainant was busy and needed in surgery) telling him/her that he/she should be changing all diabetic patients from canagliflozin (Invokana, marketed by Janssen) to Forxiga in view of recent surveys linking canagliflozin to increased lower limb amputation.

The representative continued to follow the complainant down the corridor telling him/her how bad canagliflozin was. The complainant stated that he/she was happy to see representatives who wanted to advise him/her about their products but he/she found the AstraZeneca representative to be very unprofessional in his/her approach, basically slagging off her rival company.

The complainant had since spoken to the canagliflozin representative to gain clarification on this matter and had decided to no longer see the AstraZeneca representative as his/her attitude was very threatening and unprofessional.

The detailed response from AstraZeneca is given below.

The Panel noted that according to the complainant his/her receptionist would confirm the representative's frequent visits and that he/she could be quite persistent. The complainant also described the representative's behaviour as threatening and unprofessional. The Panel noted AstraZeneca's submission that the representative did not recall being told that the complainant was in minor surgery when he/she asked to see him/her and denied following the nurse down the corridor in an attempt to continue the conversation. The Panel noted that the complainant confirmed that the representative was fully aware that he/she was in minor surgery and did follow him/her down the corridor which he/she stated was witnessed by receptionists. According to the unsigned statement of the representative's line manager he/she had never witnessed the representative insist on seeing a health professional if told that he/she was busy. In relation to the allegation that the conversation at issue took place within earshot and in full view of patients the Panel noted that the parties' accounts differed. It was not possible to determine where the truth lay. The complainant bore the burden of proof and in this regard the Panel did not consider that the complainant had established a breach of the Code on this point as alleged. No breach of the Code was ruled.

Similarly, in relation to the general allegation that the representative's behaviour was threatening and unprofessional the Panel considered that this had not been established by the complainant and no breach of the Code was ruled on this point.

According to AstraZeneca the named doctor and complainant had given the representative verbal consent to call upon them whenever there were new updates in relation to Forxiga which was why the representative intended to discuss the amputation data with him/her and did not consider that he/she had raised it proactively. The Panel noted that the complainant made no particular comment in this regard but had described the representative's visits as self-presentations at reception with no forwarding or booked appointment. AstraZeneca's HCP Interactions Guidance stated that a 'solicited contact may be recorded if during a prior interaction, the HCP or ORDM had 'given permission to call back at an agreed date and time or specific topic'. It was unclear whether the Guidance covered an open-ended consent to call-back which applied until such consent was withdrawn or otherwise terminated. The Panel made no judgement on the acceptability of open-ended call backs. The Panel was concerned that the guidance did not refer to recording such permission. The Panel was concerned that AstraZeneca was relying on unrecorded verbal consent and the representative's recollection of the same to apparently categorise subsequent calls as solicited. The impression given to health professionals by these arrangements was important bearing in mind the requirements of the Code including that such visits should not cause inconvenience and that the wishes of individuals must be observed. The Panel considered that as a matter of good governance such consent should be recorded internally and in writing to the health professional so that all parties were clear about what had been agreed verbally. It was of particular note that the complainant described the representative's visits as self-presentations and raised concerns about their frequency.

The Panel noted that the HCP Interactions Guidance defined solicited contacts as set out above and stated that a solicited contact might be attendance at a group meeting including HCPs or ORDMs. The following page of the document describing AV/Rep Led meetings stated that these occurred normally with more than one HCP and appeared to suggest that group calls were all solicited by definition. The Panel noted that the representative had recorded meetings with the complainant and a named doctor as a group call on more than one occasion and on one occasion the doctor had not attended, however, it was still recorded as such. The Panel queried whether AstraZeneca's definition of a solicited call or group call or permission to call back satisfied the requirement of a solicited call as referred to in the Code.

The Panel noted that the representative appeared to have called on the complainant four times between January and July. Two calls were described by AstraZeneca as group calls in an internal email dated 29 August summarising the calls at the named surgery, however, AstraZeneca confirmed that only the complainant was present at one of these calls and the second group call did not actually take place. The Panel further noted that the same summary described a meeting with the complainant on 17 January as a 1:1 call, however it appeared that the call report described the call type as group detail. It appeared that the representative called on the complainant three times at the named surgery within the six month period and all were recorded as 'solicited' calls. The Panel noted that the complainant's concerns were broader than calls and contacts and included attendances at reception.

Notwithstanding all of the points outlined above and noting the complainant's burden of proof the Panel considered that there was insufficient evidence to establish on the balance of probabilities whether the number of unsolicited calls on the complainant exceeded 3 on average. The Panel therefore ruled no breach of the Code. Nonetheless, the Panel noted that serious concerns remained about the company's governance in this area, including the poor guidance to representatives about permission from a health professional to call back and unclear guidance about, and poor recording of calls and contacts as set out above. In this regard the Panel considered that the company had failed to maintain high standards. A breach of the Code was ruled. In addition, the Panel noted the poor governance shown by the representative with regards to call recording and the lack of detail therein meant that the representative had failed to maintain high standards and a breach of the Code was ruled.

The Panel noted that there was no record of, or recollection from the representative in question of a discussion about the amputation data on 27 June; the call record was blank and did not detail discussion. The call of 27 June was logged implying that a dialogue had occurred which was in contrast to the representative's recollection. The Panel noted that when questioned how, in general, he/she might discuss the amputation data, the representative noted that he/she always clarified that all SGLT2is had a warning on the respective summary of product characteristics (SPCs) in relation to the risk of amputations and that canagliflozin had more clinical findings on the SPC but it was unknown whether this constituted a class effect.

In relation to the conversation in question the Panel noted that according to the representative's statement during the interaction the complainant asked if there was anything new to discuss about Forxiga; the representative recalled that he/she said that he/she had some safety information on Forxiga and the SGLT2i class but that the word amputation was not used. The Panel noted AstraZeneca's submission that according to the representative canagliflozin was only referred to in order to inform the complainant that he/she should raise any questions about this medicine with the canagliflozin representative. The Panel noted that the complainant and his/her receptionist remembered the representative saying canagliflozin was dangerous and patients should be switched to dapagliflozin.

The Panel considered that whilst it was likely that canagliflozin was discussed it was impossible to establish precisely what was said during the conversation and therefore it was not possible to determine on the balance of probabilities whether the representative had made misleading claims which were incapable of substantiation with regard to the amputation data for Forxiga or canagliflozin. No breaches of the Code were ruled. The Panel did not consider that evidence had been provided by the complainant to show whether on the balance of probabilities the representative had disparaged canagliflozin as alleged and no breach of the Code was ruled.

In relation to the briefing material the Panel noted that the sales force was first briefed about the increased risk of lower limb amputation with canagliflozin in July 2016 to enable the sales force to respond reactively to questions from health professionals about the emerging data in relation to canagliflozin and, *inter alia*, toe amputations. The sales force was specifically instructed that they must not prompt a health professional to ask a question about this. The Panel noted that the briefing stated that the information could be discussed in response to a direct HCP enquiry or proactively with a HCP known to have a safety concern in relation to the SGLT-2 inhibitor class. The briefing did state 'Do not prompt an HCP in conversation by saying, for example, 'Have you seen the news about the fractures with canagliflozin?'.

An update was provided to the sales force on the amputation data for SGLT2is in a presentation dated March 2017 which informed the sales force of the likely changes to the SPCs for all SGLT2is. The presentation detailed further studies including CANVAS-R wherein the incidence of lower limb amputations for canagliflozin v placebo was not statistically significant. It further stated that a higher incidence of amputation was not observed across 12 other completed Phase 3/4 clinical trials'.

It reproduced expected label updates for Forxiga and canagliflozin.

An email in June 2017 advised the sales force that the CANVAS results must not be proactively discussed with customers. An objection handler was issued in July 2017 which was only to be used reactively in response to questions relating to the risk of lower limb amputation for Forxiga vs canagliflozin. According to AstraZeneca the information included was based on the factual wording in the medicines' SPCs. The Panel noted that both the objection handler and the March 2017 presentation stated that 'to date there had been no increased risk seen in the clinical trial programme for Forxiga' and 'To date we are not aware of any imbalance in lower limb amputations in the Forxiga clinical trial program'. The Panel further noted the representative's line manager's interview statement that it was now known that it was not a class effect. The Panel queried whether this was entirely consistent with the Forxiga SPC which stated that it was unclear whether there was a class effect.

The Panel noted the line manager's statement that there was no instruction to lead on a discussion of the SPC changes. AstraZeneca clarified that in the line manager's previous statement 'Where there is high cana use I am comfortable that my team discuss the side effect profile proactively with HCPs, including the amputation data' he/she was referring to the amputation data in the Forxiga detail aid which was in relation to Forxiga only and made no reference to canagliflozin. The Panel considered that this was in contrast to AstraZeneca's submission that the representative confirmed that he/she intended to discuss the changes to the Forxiga SPC and the SGLT2i class, and would have expected canagliflozin to have been discussed in that context, albeit the representative did not think that it was being raised proactively as he/she had verbal permission to call on the complainant with any new Forxiga data. It was also inconsistent with AstraZeneca's submission that in response to questioning the representative's line manager stated that the representative when discussing the amputation data noted that there was data to indicate an increased risk with canagliflozin but that it was unknown whether this was a class effect for all SGLT2is.

The Panel noted its general concerns about the briefing material as outlined above but did not consider that there was evidence to show that on the balance of probabilities AstraZeneca had provided briefing that advocated, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. No breach of the Code was ruled.

The Panel noted its concerns and rulings above but did not consider that a ruling of a breach of Clause 2 was warranted and no breach of Clause 2 was ruled.

A senior practice nurse (lead diabetes nurse), complained about the conduct of a medical representative with AstraZeneca UK Limited. The representative was promoting Forxiga (dapagliflozin) which was indicated to improve glycaemic control in adults aged 18 years or over with type 2 diabetes, either as monotherapy or as add-on combination therapy.

COMPLAINT

The complainant stated that there had been several occasions over the last few weeks when the representative had come into surgery asking to see him/her. All these occasions had been self-presentations at reception with no forwarding or booked appointment. When the representative was advised that the complainant was in surgery seeing patients he/she became quite insistent that the complainant be contacted. The representative was advised to email the complainant directly. The complainant stated that on one occasion he/she had to go into reception in the middle of a minor surgery procedure with a GP to collect a consent form. The representative proceeded to try to talk to him/her in view and ear shot of other patients (after being told that the complainant was busy and needed in surgery) telling him/her that he/she should be changing all diabetic patients from canagliflozin (Invokana, marketed by Janssen) to Forxiga in view of recent surveys linking canagliflozin to increased lower limb amputation.

The representative continued to follow the complainant down the corridor telling him/her how bad canagliflozin was. The complainant stated that he/she was happy to see representatives who wanted to advise him/her about their products but he/she found the AstraZeneca representative to be very unprofessional in his/her approach, basically slagging off her rival company. The complainant reiterated that this was not in a closed environment but down a corridor.

The complainant had since spoken to the canagliflozin representative to gain clarification on this matter and had decided to no longer see the AstraZeneca representative as his/her attitude was very threatening and unprofessional.

When writing to AstraZeneca, the Authority asked it to respond in relation to the requirements of Clauses 7.2, 7.4, 8.1, 9.1, 15.2, 15.4, 15.9 and 2 of the Code.

RESPONSE

AstraZeneca submitted that it strove to ensure that all of its interactions with health professionals were courteous, appropriately informative and conducted within both the spirit and letter of the Code. AstraZeneca submitted that it was, therefore, extremely disappointed to have received this complaint and accordingly had undertaken an extensive investigation that had involved formal interviews with the representative, his/her line manager, a review of all relevant call notes and all relevant briefing material to sales representatives. On the basis of this testimony and evidence AstraZeneca had been unable to substantiate the complainant's allegations. AstraZeneca believed that the representative acted reasonably and in a professional manner consistent with AstraZeneca's instructions. However, the complainant had clearly

misconstrued the representative's intent and actions and AstraZeneca apologised for any irritation or offence that had been caused.

AstraZeneca submitted that as noted above, the representative in question had been interviewed in relation to this complaint. It appeared that he/she called on the named surgery approximately every 6-8 weeks. This was reflected in the customer relationship management (CRM) system records. The calls were usually to do one of the following: to speak with one of the doctors at the surgery, to speak to one of the nurses, ie the complainant; or to hold a lunchtime meeting. It appeared that both a named doctor and the complainant had given the representative consent to call upon them whenever there were new updates in relation to Forxiga. AstraZeneca submitted that although the representative was not notified of the complainant's name during the investigation of this complaint, the representative had raised the complainant's name spontaneously during his/her interview.

It was likely that the 'recent' call to which the complainant referred was an interaction that took place at the surgery in June 2017. As noted in the interview notes provided, the representative asked at reception whether the complainant was free to speak with him/her. Staff at reception informed the representative that they would see if the complainant was free. The representative did not recall being told that the nurse was in minor surgery.

The representative then met the complainant in the corridor; the representative assumed that the complainant had been notified of his/her presence by reception and that the complainant had decided to come to meet with him/her. The conversation that followed implied that this had indeed been the case. The complainant asked if there was anything new to discuss about Forxiga; the representative recalled that he/she said that he/she had some safety information on Forxiga and the SGLT2i class but that the word amputation was not used. This conversation took place in the corridor but the representative recalled checking that there was no one else within earshot. The complainant then told the representative to make an appointment with him/her to discuss this data but not to book the next free appointment as the complainant was meeting with the canagliflozin representative. The representative recalled that he/she said it was not her job to discuss canagliflozin and advised the complainant to take up any questions about canagliflozin with that representative.

The representative categorically denied following the nurse down the corridor in an attempt to continue the conversation. The representative recalled that the interaction was brief as the nurse was busy but that it was pleasant and professional.

Following this interaction, the representative tried to call on both the named doctor and the complainant at the surgery in July but was unable to speak with either of them. Although not consistent with the complainant's recollection of when this interaction took place according to the representative's testimony and call records, the representative had previously called on the complainant in April 2017, but the representative could not recall whether the amputation data vs canagliflozin was discussed or not at that meeting.

From the representative's testimony and call records, it appeared any interaction between the two was brief and no reference was made to amputation data at all. On the basis of this evidence, AstraZeneca did not consider that the representative made any misleading or unsubstantiated statements and so it denied a breach of Clauses 7.2 and 7.4. Canagliflozin was only referred to in order to inform the complainant that he/she should raise any questions about this medicine with the canagliflozin representative; no disparaging statements were made and AstraZeneca did not consider that this interaction constituted a breach of Clause 8.1.

When questioned how, in general, he/she might discuss this data, the representative noted in his/her interview that he/she always clarified that all SGLT2is had a warning on the respective summary of product characteristics (SPCs) in relation to the risk of amputations; canagliflozin had more clinical findings on the SPC but it was unknown whether this constituted a class effect. Given this, and the materials and briefings received by the sales force about the risk of amputation (AstraZeneca referred to the details below), AstraZeneca did not consider that any discussion the representative had had in relation to the data had been misleading, was incapable of substantiation or was disparaging to canagliflozin.

AstraZeneca had also spoken to the representative's line manager in relation to joint calls with the representative and his/her observation of the representative's conduct, both generally and in relation to his/her discussion of the amputation data. The representative's line manager had stated that he/she typically accompanied the representative on calls every 4-6 weeks, although he/she had never called on the surgery at issue with the representative. The representative's line manager had never witnessed the representative discussing clinical data in an area where the discussion could be overheard by patients or reception. The most recent occasion on which the representative's line manager accompanied the representative on calls was late July 2017; on that date they called at three separate surgeries and all the clinical conversations took place in surgery rooms with closed doors.

The representative's line manager had never witnessed the representative insist on seeing a health professional when he/she had been told that he/she was busy. When told this, the representative might ask reception to let the health professional know that he/she was there if the health professional wanted to speak with him/her, but he/she did not insist that this was done.
In response to questions around whether he/she had seen the representative discuss amputation data compared to canagliflozin, the representative's line manager stated that he/she had and that his/her recollection was consistent with that of the representative's as noted above ie he/she noted that

there was data to indicate an increased risk with canagliflozin but that it was unknown whether this was a class effect for all SGLT2is.

AstraZeneca noted that some of the representative's line manager testimony in relation to the strategy of his/her team when discussing the amputation data raised some concerns, in particular, that there might have been an informal briefing to his/her team that was not certified. AstraZeneca had been unable to complete further investigations on this new matter prior to its deadline for responding to the original matter. AstraZeneca would, of course, continue to investigate this and act accordingly should it discover further evidence confirming activities had taken place which were contrary to the Code, including submitting a voluntary admission to the Authority.

Following the interview with the representative's line manager, the representative was spoken to again to clarify whether he/she had in fact asked the complainant what the canagliflozin representative might have said to him/her about the amputation data. The representative had reiterated that he/she did not; the only reason canagliflozin was raised during the interaction in June was because the complainant stated that he/she was seeing the canagliflozin representative at her next appointment and the representative replied that the complainant should raise any questions about this medicine with the canagliflozin representative. The representative also confirmed, as in his/her testimony, that she did not raise the amputation data proactively; the complainant had requested that the representative provide him/her with updates in relation to Forxiga and this was why she intended to discuss the amputation data with him/her.

AstraZeneca submitted that the representative had maintained high standards in his/her discussion of the amputation data, consistent with the requirements of Clause 15.2 and AstraZeneca denied the allegation of a breach of this clause.

Although there was no record or recollection from the AstraZeneca representative in question of a discussion of the amputation data in June, AstraZeneca would like to assure the Panel that all company-developed briefing materials and instructions to the field force were appropriate. As background, it was important to clarify the position of the class of medicines sodium-glucose cotransporter-2 inhibitors (SGLT2i), of which AstraZeneca's Forxiga was one of three licensed such medicines (Forxiga, Invokana and Jardiance). In relation to the risk of lower-limb amputation, the SPC for Invokana (canagliflozin), in Section 4.2, Special warnings and precautions for use, stated:

> **'Lower limb amputations**
>
> In ongoing, long-term clinical studies of canagliflozin in type 2 diabetes patients with cardiovascular disease (CVD) or at high risk for CVD, an increase in cases of lower limb amputation (primarily of the toe) has been observed in patients treated with canagliflozin. As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown. However, as precautionary measures, consideration should be given to carefully monitoring patients with a higher risk for amputation events and counselling patients about the importance of routine preventative foot care and maintaining adequate hydration. Consideration may also be given to stopping treatment with canagliflozin in patients that develop events preceding amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.'

The same section of the SPCs for both Forxiga and Jardiance stated:

> **'Lower limb amputations**
>
> An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.'

Thus, there appeared to be an increased risk of lower limb amputation with canagliflozin that had not been observed with the other medicines in the SGLT2i class. It was not known whether this could indeed be a class effect and a more general precaution continued to appear on the SPCs for the other two medicines.

The sales force were first briefed about this in July 2016 (ref JBN: 996743.011DOP). This briefing was intended to enable the sales force to respond to any questions from health professionals about the emerging data in relation to canagliflozin and, *inter alia*, toe amputations. AstraZeneca referred the PMCPA to this document and stated that the information contained within it was very factual and was intended for reactive use only; the sales force were specifically instructed that they must not prompt a health professional to ask a question about this.

There was an update provided to the sales force on the amputation data for SGLT2is in a presentation in March 2017 (Scientific Leadership, GB-5826 and 7b, Potential Risk of Lower Limb Amputations with SGLT-2is – An Update, GB-5839), which also informed the sales force of the likely changes to the SPCs for all SGLT2is. The instruction to the sales force was to stay on track and focus on the key messages for promoting Forxiga.

The current material and the associated briefing for the diabetes sales force in relation to lower limb amputation vs canagliflozin was provided (SGLT2i Amputations Objection Handler, GB-7857 and Briefing Document Amputations Objection Handler, GB-7927, respectively). These were rolled out to the sales force in July 2017 and AstraZeneca referred the PMCPA to the briefing document and stated that as well as the email invitation to the roll-out (Update on CANVAS, GB-7169) and the presentation used for this roll out (Diabetes Dial-In July 2017, GB-7522), the

objection handler was to be used reactively only, in response to questions relating to the risk of lower limb amputation for Forxiga vs that for canagliflozin. The information included in the objection handler was very much based around the factual wording in the respective current SPCs for Forxiga and Invokana; there was no over-exaggeration or distortion of the situation and no disparaging language was used.

AstraZeneca considered that there was no company-generated briefing for the sales force in relation to this data that advocated, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code and considered that all such briefing was compliant with the requirements of Clause 15.9.

In relation to call frequency, AstraZeneca provided records of calls made on the nurse at the surgery for this year: some of the calls were at associated practices with which it appeared the nurse was also affiliated. Given that the nurse had requested that the representative call on him/her with updated information on Forxiga, AstraZeneca did not consider that there was any evidence that either the frequency or manner of these calls was likely to cause inconvenience. The representative had been questioned as to what he/she did when he/she called on a health professional and found that they were not available to speak with him/her; as could be seen in his/her interview notes, the representative would not insist on seeing that health professional, but would book another appointment for the future.

In addition, all AstraZeneca representatives were trained on the AstraZeneca HCP Interactions Guidance, which detailed, *inter alia*, the requirements of Clause 15.4. The representative acknowledged that he/she had read and understood the requirements of this document in June 2017. In addition, a Contact Planning Brief was rolled out to Regional Business Managers every 6 months; the one relevant to the first half of 2017 referred to the requirements of Clause 15.4. The representative's line manager noted in his/her interview that he/she trained his/her team, including the representative, on each revised version and stated that his/her team were aware that they must not 'pester' health professionals.

Given this, AstraZeneca submitted that the representative's calls on the nurse at the surgery were consistent with the requirements of Clause 15.4.

Given the information above, AstraZeneca did not consider that, as a company, it had failed to maintain high standards in briefing its representatives on the amputation risk with SGLT2is and it denied the allegation of a breach of Clause 9.1. The company had not brought the industry into disrepute and denied a breach of Clause 2.

In response to a request for further information, AstraZeneca submitted that the consent from the two health professionals received by the representative was verbal and consequently there was no written documentation other than calls being logged in the CRM system.

AstraZeneca submitted that the representative confirmed that he/she intended to discuss the changes to the Forxiga SPC and the SGLT2i class, and would have expected canagliflozin to have been discussed in that context.

AstraZeneca explained that at the time of its initial response the company had not been able to complete its investigation into comments by the representative's manager which suggested that an informal briefing might have occurred. Having further interviewed the representative's manager and his/her manager AstraZeneca had found no evidence that the representative's manager provided an informal briefing to his/her team. The representative's manager clarified that as part of a routine regional planning discussion, he/she and fellow managers agreed the importance of understanding the differences between the SPCs for the SGLT2i class. There were increasing reports of prevailing misperceptions that all of the side effects were consistent across the class. This was particularly relevant in the context of the amputation data for which there were clear differences in wording in the SPCs. This SPC information was shared with the team to equip them to respond to any questions that a health professional might have raised on the subject in the context of a promotional call. There was no instruction to lead on a discussion of the SPC changes. AstraZeneca submitted that in the line managers' comment in his/her previous statement:

> 'Where there is high cana use I am comfortable that my team discuss the side effect profile proactively with HCPs, including the amputation data.'

The manager clarified that he/she was referring to the amputation data in the Forxiga detail aid which was in relation to Forxiga only and made no reference to canagliflozin.

FURTHER INFORMATION FROM THE COMPLAINANT

The complainant confirmed that the representative's recollection of events was different to what actually happened. With regard to the 'chance meeting' in reception with the representative, the complainant stated that the representative WAS fully aware that the complainant was in minor surgery as he/she expressly told the representative at least twice and as such could not discuss anything with him/her at that time. According to the complainant the whole incident was witnessed by the receptionist who clearly remembered the representative saying canagliflozin was dangerous and patients should be switched to dapagliflozin. The complainant explained that he/she did try to explain to the representative that he/she was seeing the canagliflozin representative the following week and would clarify the situation but was in no position at that time to make any judgement. The complainant stated that he/she gave his/her apologies and continued down the corridor to accompany a GP in minor surgery

but the representative CONTINUED to follow him/her [again all witnessed by the receptionists who were prepared to write a statement if required]. The complainant stated that the receptionists would also confirm the representative's many frequent visits and that the representative could be quite persistent. Therefore, it was with regret that the complainant would no longer continue to have dealings with the representative in the future.

PANEL RULING

The Panel noted that the parties' accounts of the exchange between the complainant and the AstraZeneca representative differed. The Panel noted the difficulty in dealing with complaints based on one party's word against the other; it was often impossible in such circumstances to determine precisely what had happened. Paragraph 2.2 of the Constitution and Procedure stated that a complainant had the burden of proving their complaint on the balance of probabilities. The Panel noted, however, that a high degree of dissatisfaction was usually required before an individual health professional was moved to submit a formal complaint.

The Panel noted that the Code required representatives, *inter alia*, to maintain a high standard of ethical conduct in the discharge of their duties (Clause 15.2) and to ensure that the frequency, timing and duration of calls together with the manner in which they were made did not cause inconvenience. The wishes of individuals on whom representatives wish to call and the arrangements in force at any particular establishment, must be observed (Clause 15.4).

The Panel noted that according to the complainant his/her receptionist would confirm the representative's frequent visits and that he/she could be quite persistent. The complainant also described the representative's behaviour as very threatening and unprofessional. The Panel noted AstraZeneca's submission that the representative did not recall being told that the complainant was in minor surgery when he/she asked to see him/her in June and denied following the nurse down the corridor in an attempt to continue the conversation. The Panel noted that the complainant confirmed that the representative was fully aware that he/she was in minor surgery and did follow him/her down the corridor which he/she stated was witnessed by receptionists. According to the unsigned statement of the representative's line manager he/she had never witnessed the representative insist on seeing a health professional if told that he/she was busy.

The Panel noted that whilst the representative's statement made it clear that the representative would not enter into a discussion in a public area and his/her line manager confirmed that he/she had never seen the representative do this, both the representative and complainant agreed that the conversation took place in the corridor. According to AstraZeneca the representative recalled checking that there was no one else within earshot. The representative's statement did not refer to checking but stated he/she 'believed there was no one in the corridor or within earshot'. The representative's statement explained that the patient waiting room was not along that corridor and that reception was behind a glass/wooden wall in its own separate room. This was at odds with the complainant's account, that the representative proceeded to try to talk to him/her in view and ear shot of other patients and was witnessed by the receptionists. The company document HCP Interactions Guidance dated 7/3/2017 stated that 1:1 calls may not be held where members of the public could overhear. Such guidance was also reflected in a Forxiga briefing document for the Amputation Objection Handler (GB-7927). In relation to the allegation that the conversation at issue took place within earshot and in full view of patients the Panel noted that the parties' accounts differed. It was not possible to determine where the truth lay. The complainant bore the burden of proof and in this regard the Panel did not consider that the complainant had established a breach of the Code on this point as alleged. No breach of Clause 15.2 was ruled.

Similarly, in relation to the general allegation that the representative's behaviour was threatening and unprofessional the Panel considered that this had not been established by the complainant and no breach of Clause 15.2 was ruled on this point.

The Panel noted AstraZeneca's submission that the representative called on the named surgery approximately every 6-8 weeks to either hold a lunchtime meeting or to speak to the complainant or one of the doctors as reflected in the CRM system. In contrast the Panel noted that the representative's statement referred to making such calls every 4-8 weeks. According to AstraZeneca the named doctor and complainant had given the representative verbal consent to call upon them whenever there were new updates in relation to Forxiga which is why the representative intended to discuss the amputation data with him/her and did not consider that he/she had raised it proactively. The Panel noted that the complainant made no particular comment in this regard but had described the representative's visits as self-presentations at reception with no forwarding or booked appointment. The Panel noted that AstraZeneca's HCP Interactions Guidance dated 7/3/2017 stated that a 'solicited contact may be recorded if during a prior interaction, the HCP or ORDM had 'given permission to call back at an agreed date and time or specific topic'. The Panel was also concerned that on such an important matter the relevant sentence, perhaps due to an omission or grammatical error did not make sense. In addition, it was unclear whether the Guidance covered an open-ended consent to call-back which applied until such consent was withdrawn or otherwise terminated. The Panel made no judgement on the acceptability of open-ended call backs and just considered the matter in relation to Clause 15.4. The Panel was concerned that the guidance did not refer to recording such permission. The Panel was concerned that AstraZeneca was relying on unrecorded verbal consent and the representative's recollection of the same to apparently categorise subsequent calls as solicited. The impression given to health professionals by these arrangements was important

bearing in mind the requirements of Clause 15.4 including that such visits should not cause inconvenience and that the wishes of individuals must be observed. The Panel considered that as a matter of good governance such consent should be recorded internally and in writing to the health professional so that all parties were clear about what had been agreed verbally. It was of particular note that the complainant described the representative's visits as self-presentations and raised concerns about their frequency.

The Panel noted that the HCP Interactions Guidance dated 7/3/2017 defined solicited contacts as set out above and stated that a solicited contact might be attendance at a group meeting including HCPs or ORDMs. The following page of the document describing AV/Rep Led meetings and stated that these occurred normally with more than one HCP and appeared to suggest that group calls were all solicited by definition. The Panel noted that the representative had recorded meetings with the complainant and a named doctor as a group call on more than one occasion and on one occasion the doctor had not attended, however, it was still recorded as such. The Panel queried whether AstraZeneca's definition of a solicited call or group call or permission to call back satisfied the requirement of a solicited call as referred to in the Code.

The Panel noted that according to the call notes summary provided by AstraZeneca the representative appeared to have called on the complainant four times between January and July. Two calls were described by AstraZeneca as group calls in an internal email dated 29 August summarising the calls at the surgery, however, AstraZeneca confirmed that only the complainant was present at one of these calls and the second group call did not actually take place. The Panel further noted that the same summary described a meeting with the complainant in January as a 1:1 call, however it appeared that the call report described the call type as group detail. It appeared that the representative called on the complainant three times at the named surgery within the six month period and all were recorded as 'solicited' calls. The Panel noted that the complainant's concerns were broader than calls and contacts and included attendances at reception.

Notwithstanding all of the points outlined above and noting the complainant's burden of proof the Panel considered that there was insufficient evidence to establish on the balance of probabilities whether the number of unsolicited calls on the complainant exceeded 3 on average. The Panel therefore ruled no breach of Clause 15.4. Nonetheless, the Panel noted that serious concerns remained about the company's governance in this area, including the poor guidance to representatives about permission from a health professional to call back and unclear guidance about, and poor recording of calls and contacts as set out above. In this regard the Panel considered that the company had failed to maintain high standards. A breach of Clause 9.1 was ruled. In addition, the Panel noted the poor governance shown by the representative with regards to call recording and the lack of detail therein meant that the representative had failed to maintain high standards and a breach of Clause 15.2 was ruled.

The Panel noted that there was no record of, or recollection from the representative in question of a discussion about the amputation data in June; the call record was blank and did not detail discussion. The Panel noted that according to the representative's interview notes a conversation was only logged in the CRM if product and key selling messages were mentioned and a dialogue ensued. If no dialogue ensued then the representative did not log the call. The call in June was logged in the CRM implying that a dialogue had occurred which was in contrast to the representative's recollection. The Panel noted that when questioned how, in general, he/she might discuss the amputation data, the representative noted that he/she always clarified that all SGLT2is had a warning on the respective summary of product characteristics (SPCs) in relation to the risk of amputations and that canagliflozin had more clinical findings on the SPC but it was unknown whether this constituted a class effect.

In relation to the conversation in question, the Panel noted that according to the representative's statement during the interaction the complainant asked if there was anything new to discuss about Forxiga; the representative recalled that he/she said that he/she had some safety information on Forxiga and the SGLT2i class but that the word amputation was not used. The Panel noted AstraZeneca's submission that according to the representative canagliflozin was only referred to in order to inform the complainant that he/she should raise any questions about this medicine with the canagliflozin representative. The Panel noted that the complainant and his/her receptionist remembered the representative saying canagliflozin was dangerous and patients should be switched to dapagliflozin.

The Panel considered that whilst it was likely that canaglifozin was discussed it was impossible to establish precisely what was said during the conversation and therefore it was not possible to determine on the balance of probabilities whether the representative had made misleading claims which were incapable of substantiation with regard to the amputation data for Forxiga or canagliflozin. No breach of Clauses 7.2 and 7.4 were ruled. The Panel did not consider that evidence had been provided by the complainant to show whether on the balance of probabilities the representative had disparaged canagliflozin as alleged and no breach of Clause 8.1 was ruled.

The Panel noted that Clause 15.9 required, *inter alia*, that briefing material must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The Panel noted the relevant warnings in Section 4.2 of the canagliflozin and Forxiga SPCs as set out in AstraZeneca's response.

In relation to the briefing material the Panel noted that the sales force was first briefed about the

increased risk of lower limb amputation with canagliflozin in July 2016 to enable the sales force to respond reactively to any questions from health professionals about the emerging data in relation to canagliflozin and, *inter alia*, toe amputations. The sales force was specifically instructed that they must not prompt a health professional to ask a question about this. The Panel noted that the briefing (Ref JBN: 996743.011 DOP July 2016) stated that the information could be discussed in response to a direct HCP enquiry or proactively with a HCP known to have a safety concern in relation to the SGLT-2 inhibitor class. The briefing did state 'Do not prompt an HCP in conversation by saying, for example, 'Have you seen the news about the fractures with canagliflozin?'.

An update (GB-5839) was provided to the sales force on the amputation data for SGLT2is in a presentation dated March 2017 which informed the sales force of the likely changes to the SPCs for all SGLT2is. The presentation detailed further studies including CANVAS-R which enrolled a similar population of patients to the previous CANVAS study and wherein the incidence of lower limb amputations for canagliflozin v placebo was not statistically significant. It further stated that a higher incidence of amputation was not observed across 12 other completed Phase 3/4 clinical trials'. It reproduced expected label updates for Forxiga and canagliflozin.

An email in June 2017 (GB-7169) advised the sales force that the CANVAS results must not be proactively discussed with customers. An objection handler (GB-7857) was issued in July 2017 which was only to be used reactively in response to questions relating to the risk of lower limb amputation for Forxiga vs that for canagliflozin. According to AstraZeneca the information included was based on the factual wording in the medicines' SPCs. The Panel noted that both the objection handler and the March 2017 presentation stated that 'to date there had been no increased risk seen in the clinical trial programme for Forxiga' and 'To date we are not aware of any imbalance in lower limb amputations in the Forxiga clinical trial program'. The Panel further noted the representative's line manager's interview statement that it was now known that it was not a class effect. The Panel queried whether this was entirely consistent with the Forxiga SPC which stated that it was unclear whether there was a class effect. The Panel noted the line manager's statement that there was no instruction to lead on a discussion of the SPC changes. AstraZeneca clarified that in the line manager's previous statement 'Where there is high cana use I am comfortable that my team discuss the side effect profile proactively with HCPs, including the amputation data' he/she was referring to the amputation data in the Forxiga detail aid which was in relation to Forxiga only and made no reference to canagliflozin. The Panel considered that this was in contrast to AstraZeneca's submission that the representative confirmed that he/she intended to discuss the changes to the Forxiga SPC and the SGLT2i class, and would have expected canagliflozin to have been discussed in that context, albeit the representative did not think that it was being raised proactively as he/she had verbal permission to call on the complainant with any new Forxiga data. It was also inconsistent with AstraZeneca's submission that in response to questioning the representative's line manager stated that the representative when discussing the amputation data noted that there was data to indicate an increased risk with canagliflozin but that it was unknown whether this was a class effect for all SGLT2is.

The Panel noted its general concerns about the briefing material as outlined above but did not consider that there was evidence to show that on the balance of probabilities AstraZeneca had provided briefing that advocated, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. No breach of Clause 15.9 was ruled.

The Panel noted its concerns and rulings above but did not consider that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such. In that regard, the Panel did not consider that the matter warranted such a ruling and so no breach of Clause 2 was ruled.

During the consideration of this case, the Panel considered that AstraZeneca would be well advised to review its process for permission to call back for the entire field force bearing in mind the letter and spirit of the Code, and its guidance on calls and contacts. In addition, the company should ensure that its representatives were entering calls and contacts accurately in its CRM system.

Complaint received **3 August 2017**

Case completed **26 January 2018**

CASE AUTH/2970/8/17

ANONYMOUS NON-CONTACTABLE v JANSSEN

Promotional email

An anonymous, non-contactable complainant submitted a complaint about the activities of a Janssen regional business manager (RBM). The complaint concerned the promotion of Invokana (canagliflozin) a sodium-glucose co-transport-2 (SGLT2) inhibitor. Invokana was indicated for the treatment of type 2 diabetes.

The complainant provided a copy of an email dated 22 June 2017 from the RBM to a GP which referred to a meeting the previous day.

Janssen explained that the GP also had a role for a GP federation, which represented a number of surgeries, including dispensing practices. Within this role, the GP led a review of dispensing deals across the federation.

The RBM had drafted a communication for the GP to comment on and ultimately send as well as a potential communication from a third party providing services for Janssen that Janssen was planning to send to the practices within the federation. The communication drafted for the GP to send referred to all SGLT2 inhibitors being recommended locally and that the federation had a preferred one, canagliflozin. As such, a preferential rate had been secured for the federated dispensing practices. A contact for clinical questions was included. This proposed communication stated that the third party service provider would be in touch to discuss the discount, relevant terms and conditions and the update of existing contracts and that as part of the diabetes programme Janssen had agreed a training programme to upskill diabetes knowledge and prescribing confidence in newer diabetes medicines. The proposed email from the third party service provider to individual practices referred to the communication from the named GP and the new [figure given] rebate for 'your practice'. It stated that this increased rebate was a result of the federation's decision to make Invokana the preferred SGLT2 product but was still in line with local guidance.

The RBM asked the GP whether the communication from the third party service provider could include the federation's logo. A table was to be included which listed each practice's current Invokana rebate which varied.

The complainant believed that the GP complained to Janssen about the email but was not sure it was being dealt with appropriately by Janssen. The complainant was also unsure that measures were being put in place in terms of training to stop the RBM sending such emails in the future.

The complainant was concerned that the wording in the email suggested that canagliflozin was the SGLT2 inhibitor preferred by the local prescribing and clinical effectiveness forum. This was inaccurate as it was jointly recommended within the class. There was also a suggestion of adding the federation logo to the third party's email communication to these surgeries in an attempt to add weight to the company's communications. The complainant queried whether a pharmaceutical company should try to influence the NHS in such a way. There was also a potential confidentiality breach given the sharing of the current discounts received by the GP surgeries without consent.

The detailed response from Janssen is given below.

The Panel noted that the email in question had been sent to the GP in his role for the local federation and purported to reflect an agreement reached at a meeting held with the RBM in question about Janssen's rebate scheme for dispensing practices. The email sought the GP's comments on a draft communication from the GP to the federation practices about an agreed preferential rate for canagliflozin. The second part of the email referred to a proposed communication from the third party service provider to relevant practices and the RBM asked whether the latter communication could have the federation logo on and stated that it would include the individual practice agreed discounts which were listed in the email.

The Panel had no way of knowing precisely what was said at the meeting between the RBM and the GP and therefore whether this was accurately reflected in the email. It appeared that the GP had not responded to the RBM's email but had contacted Janssen. The Panel noted the company's submission that the purpose of the email in question was to seek alignment and agreement for the wording of the wider communication. The Panel also noted the company's submission that the GP had confirmed to Janssen that he/she had requested a clarification email be sent so that he/she could understand the deal sufficiently to be able to take it to the federation for review. The Panel noted that there was an important difference between providing draft text for a communication to federation members and an email clarifying the agreement reached. The Panel queried whether this was the source of the GP's concerns. The Panel also noted that Janssen later stated a different rationale for sending the email namely to confirm the details of a conversation prior to formalising and communicating a contractual relationship. The Panel noted that it could be argued that the email in question did not make this sufficiently clear and in providing draft text for external communications went beyond the stated rationale. The Panel also noted that any external communication to federation members would have been subject to the company's approval and certification process.

Whilst the Panel had concerns about the email in question, there was no implication that the complainant considered that the rebate scheme was offered in connection with the promotion of medicines contrary to the requirements for terms of trade and the relevant supplementary information or that it was otherwise an inducement. No breach of the Code was ruled.

The Panel noted the complainant's concern that the email in question suggested to several surgeries that canagliflozin was the named local clinical effectiveness and prescribing forums 'preferred' SGLT2i which was inaccurate as it was jointly recommended in the class. The Panel noted that the email had not been sent to 'several surgeries' as implied by the complainant. The Panel noted that the first part of the email which covered the text of a proposed communication to relevant practices within the federation stated 'As you are aware, all SGLT2is are recommended locally. We as a federation have a preferred one within the class with canagliflozin'. The second proposed communication from the third party service provider stated that the 'increased rebate is as a result of the Federation's decision to make Invokana the preferred SGLT2 product but still in line with local guidelines'. In the Panel's view the first part of the email made it sufficiently clear that that all SGLT2is were recommended locally. However, the Panel considered that the second part of the email could have been clearer about the position of canagliflozin within the local guidelines. The Panel noted Janssen's submission that the wording of the email was less than ideal. Nonetheless, the Panel noted that whilst the email described Invokana as the federation's preferred SGLT2i, neither part of the email described it as the named local clinical effectiveness and prescribing forums 'preferred' SGLT2i as alleged. The Panel therefore ruled no breach of the Code based on the very narrow allegation.

The Panel noted that it might not necessarily be unacceptable to use the federation's logo on a communication to the individual practices within the federation provided that it was done with prior permission and appropriate approval and otherwise complied with the Code. The email made it clear that the addition of the logo was raised as a question, and, in the Panel's view, it was therefore for the federation to give its consent or otherwise. No communication had been sent to practices within the federation and the issue of disguised promotional activity did not arise. No breach of the Code was ruled in that regard.

The Panel noted that the complainant's allegation concerned what measures were now being put in place to ensure that the RBM was trained on relevant matters henceforth. On the limited information before the Panel it appeared that the training issues were now being addressed and no breach of the Code was ruled based on the narrow allegation.

The Panel considered that it was not unreasonable for the RBM to assume that the GP would be aware of the deals in place at the individual practices. The Panel considered that the RBM had been let down by the company in this regard. Nonetheless, confidential information had been disclosed by the RBM. This was a serious matter. The RBM had not maintained a high standard of ethical conduct and a breach of the Code was ruled. The Panel considered that the failure of Janssen to train the RBM before he/she discussed issues around confidential data with health professionals and on how to handle such data in accordance with the Code was a significant omission. High standards had not been maintained. A breach was ruled.

The Panel noted the complainant alleged that Janssen was not dealing with the GPs complaint appropriately. The Panel noted that the GP had not responded to Janssen's communications in July 2017. The complainant had not established that the GPs concerns were not being considered appropriately by Janssen and no breach was ruled in this regard.

The Panel noted its comments and rulings above. Noting that the proposed communications set out in the email did not advance past the draft stage, the Panel did not consider that a ruling of a breach of Clause 2 was warranted.

An anonymous, non-contactable complainant submitted a complaint about the activities of a Janssen regional business manager (RBM). The complaint concerned the promotion of Invokana (canagliflozin) a sodium-glucose co-transport-2 (SGLT2) inhibitor. Invokana was indicated for the treatment of type 2 diabetes.

The complainant provided a copy of an email dated 22 June 2017 from the RBM, to a GP which referred to a meeting the previous day.

Janssen explained that the GP had a role for the local GP federation which represented a number of surgeries, including a number of dispensing practices. Within his federation role, the GP led a review of dispensing deals across the federation.

The RBM had drafted a communication for the GP to comment on and ultimately send as well as a potential communication from a third party providing services to Janssen that Janssen was planning to send to the practices within the federation. The communication drafted for the GP to send referred to all SGLT2 inhibitors being recommended locally and that the federation had a preferred one, canagliflozin. As such, a preferential rate had been secured for the federated dispensing practices. A contact for clinical questions was also included. This proposed communication stated that the third party service provider, which managed Janssen's dispensing contracts, would be in touch to discuss the discount, relevant terms and conditions and the update of existing contracts. As part of the diabetes programme Janssen had agreed a training programme to upskill diabetes knowledge and prescribing confidence in newer diabetes medicines. The proposed email from the third party service provider to individual practices referred to

the communication from the named GP and the new 25% rebate for 'your practice'. It stated that this increased rebate was a result of the federation's decision to make Invokana the preferred SGLT2 product but was still in line with local guidance.

The RBM asked the GP whether the communication from the third party service provider could include the federation's logo. A table was to be included which listed each practice's current Invokana rebate which varied. The proposed communication would include contact details for clinical questions and the training programme.

COMPLAINT

The complainant stated that he/she had been made aware of an email sent by a Janssen RBM to a named GP regarding discounted pricing which the complainant alleged was in breach of the Code.

The complainant believed that the GP complained to Janssen about the email but was not sure it was being dealt with appropriately by Janssen. The complainant was also unsure that measures were being put in place in terms of training to stop the individual concerned sending such emails in the future.

The complainant was concerned that the wording in the email suggested to several surgeries that canagliflozin was the SGLT2 inhibitor preferred by the local prescribing and clinical effectiveness forum. This was inaccurate as it was jointly recommended within the class.

There was also a suggestion of adding the federation logo to a third party's email communication to these surgeries in an attempt to add weight to the company's communications. The complainant queried whether a pharmaceutical company should try to influence the NHS in such a way. There was also a potential confidentiality breach. Confidential information had been shared of the current discounts received by the GP surgeries without the consent of the surgeries concerned or the third party service providers.

In writing to Janssen, the Authority asked it to bear in mind the requirements of Clauses 7.2, 7.4, 9.1, 12.1, 15.2, 16.1, 18.1 and 2 of the Code.

RESPONSE

Janssen acknowledged a breach of Clauses 9.1 and 15.2 of the Code. It denied any breach of the Code regarding Clauses 7.2, 7.4, 12.1, 16.1, 18.1 or 2.

Janssen confirmed it had received an email from the GP at issue on 3 July. Janssen submitted that this was being addressed prior to the arrival of the anonymous complaint sent to PMCPA on 8 August. The points raised by the GP in the email dated 3 July concerned different (albeit related) aspects of the email sent to him from the RBM on 22 June.

Janssen explained that it operated a simple rebate scheme, the manufacturing discount scheme (MDS), for dispensing doctors whereby organisational purchases above a certain volume qualified for an annual rebate back to the organisation. This was a standard purchasing deal with a healthcare organisation that did not construe a benefit to any individual. This type of arrangement with hospitals, retail pharmacies and dispensaries in GP practices had been in place across the industry for many decades (certainly since before 1993) and therefore fell outside the scope of the Code as defined by the supplementary information to Clause 18.1. Accordingly, Janssen denied breaches of Clause 18.1.

The GP in question (in his/her role for the local federation) met with the RBM in question and an account manager on 21 June to discuss the MDS for Invokana and the discounts that might be available for members of the federation. The intention was to negotiate a group discount, whereby the collective of dispensaries (within the federation) might secure a higher discount than might be achievable individually through higher overall future volume purchases.

Following the meeting the RBM wrote to the GP (22 June) to confirm their mutual understanding of the arrangements so that the offer could be made to the wider group. The GP had subsequently confirmed that he/she requested the clarification email be sent to ensure he/she understood the deal sufficiently to be able to take it to the federation for review. Unfortunately, the GP was concerned about the email specifically with regard to its content and tone, as it did not accurately reflect his/her understanding of the conversation and breached confidentiality.

Within the email, the RBM suggested, based on his/her understanding from the meeting, specific content that the GP might use to write to the federation members; and also content that the third party service provider might use as part of a co-ordinated communication. As per Janssen policy, the final communications would have been reviewed and certified by Janssen and distributed with prescribing information, etc, as a formal promotional communication. This intent was indicated in the opening paragraph:

> 'As promised, here is the communication for you to have a look at and also our potential communication we are planning to send the practices from ….'

On 3 July, the GP emailed Janssen to express his/her concerns regarding the RBM's email.

Janssen understood that the GP's primary concerns about the email were in relation to the accuracy of the comments attributed to him/her by the RBM and the confidentiality of the commercial information shared. Janssen believed that these concerns stemmed from a genuine misunderstanding by the RBM and as such had already apologised to the GP.

Janssen acknowledged that the RBM's email could have been written differently, the clear and indisputable purpose was to seek the GP's alignment and agreement for the wording of the

wider communication. In that context there was no intention to mislead; indeed the exact opposite was true. In case the two parties had a different interpretation of the commercial discussion, the GP was given the opportunity to correct any inconsistencies. Accordingly, Janssen concluded that the rationale for sending the email - confirming the details of a conversation prior to formalizing and communicating a contractual relationship – was appropriate; even though the specific content was less than ideal.

Janssen addressed the specific concerns.

Allegation: 'The email implies that Canagliflozin was the SGLT2i inhibitor preferred by the local prescribing and clinical effectiveness forum'

For clarity, the local prescribing and clinical effectiveness forum was a strategic advisory network with the responsibility of ensuring the cost-effective use of medicines and other healthcare interventions and their functional integration into local healthcare delivery. The local formulary guidance was available online for SGLT2 inhibitors.

Specifically the 22 June email from the RBM to the GP stated:

> 'As promised, here is the communication for you to have a look at and also our potential communication we are planning to send the practices from ….
>
> As you are aware, all SGLT2is are recommended locally. We as a federation have a preferred one within the class with canagliflozin. As such, we have secured a preferential rate for all our federated dispensing practices.'

Janssen stated that it would have been helpful if the second paragraph was presented in italics to clearly indicate this was the proposed text for the communication to the wider federation members. However, a considered reading of the email layout and structure did make this apparent.

Later in the email, attention turned to the potential for the deal to also be communicated by the third party service provider. Again, the GP was asked to comment on the proposed text for use by the agency. Again, there was no inference that the local prescribing and effectiveness forum preferred canagliflozin – in fact the use of the word 'but' made it clear that the preferential positioning of canagliflozin by the GP federation (as was understood by the RBM when he/she wrote the email) was different from the approach taken by the local prescribing and effectiveness forum.

> 'Following [the GP's] communication to you regarding Invokana we are calling on behalf of Janssen to set you up on a new 25% rebate for your practice. This increased rebate is as a result of the Federation's decision to make Invokana the preferred SGLT2 product but still in line with local guidance from the local prescribing and effectiveness forum.'

It was clear that nothing in the email claimed or purported to imply that canagliflozin was preferred by the local prescribing and effectiveness forum and was intended to check the understanding of the position of the federation prior to any formal, approved communication. Accordingly, Janssen denied breaches of Clauses 7.2 and 7.4.

For clarity, the third party service provider was a commercial service. It was a J&J and MHRA approved company which offered a specialist service for communicating commercial discounts (non-clinical activity) with dispensing practices. The third party service provider delivered a number of activities for Janssen including setting up MDS (manufacturer discount schemes) with agreed accounts to receive discounts via rebate through their nominated wholesaler based on purchases in line with the Janssen dispensing scheme and administering the Janssen dispensing account contracts.

Allegation: Disguised promotion

Janssen submitted that the specific reason for listing Clause 12.1 was not clear as this did not appear to be an allegation of the complaint. Janssen assumed this was either in relation to the email to the GP, or in relation to the potential communication from the GP to the federation members.

Since the purpose of the 22 June email to the GP was to check and clarify the agreement reached in their meeting, as requested by the GP, and to suggest the content of a proposed subsequent communication, Janssen did not regard the email to the GP as disguised promotion and accordingly denied breaches of Clause 12.1. Additionally, the heading and content of the email were clearly about 'dispensing' and clearly sought the GP's views on the proposed group communication; the content and intention of the RBM's email was not in any sense disguised promotion.

Allegation: The email implies that including the federation logo on a communication is inappropriate

The RBM sought permission to add the federation logo to the communication from the third party service provider. Janssen submitted it was not inappropriate to seek permission to use the federation logo in respect of a deal negotiated with its members in a communication to its members to indicate the federation's support for that deal. There was no suggestion that Janssen's involvement would be absent from the communication, which would have been approved and certified prior to dissemination according to Janssen policy.

Accordingly, Janssen denied any breach of Clause 12.1 regarding disguised promotion, especially since the form of the communication in question had not even been formally drafted, let alone submitted for approval or disseminated and was preliminary in nature, as the email indicated.

Allegation: The email implies that including the specific discounts of the surgeries in the federation was a confidentiality breach

Janssen stated this was one of the key points in the GP's email of 3 July to Janssen Diabetes.

Janssen noted that the RBM openly stated the discounts in place for each of the federation members in his/her email to the GP.

All Janssen employees, including the RBM were trained on a wide variety of policies as part of their business conduct training, including the need to respect data privacy principles.

Janssen had confidentiality agreements in place with each of the surgeries for whom a specific discount was listed. It would therefore be inappropriate for Janssen to share those discounts with other individual members of the federation. Further, while the RBM gave the impression that the whole table was to be included in the third party service provider communication, this had not been – and would never have been – approved during the certification of the formal communication; and no communication had actually occurred, other than to the official negotiator, the GP in question.

Further to its internal investigation Janssen confirmed that the RBM, mistakenly, believed he/she was negotiating with the GP on behalf of the federation and assumed that the GP, in his/her role for the federation, already knew the commercial arrangements in place with each practice. The GP had since confirmed that this assumption was incorrect. Accordingly, Janssen had apologised to the GP, and accepted it was not appropriate for him/her to see the individual practice discounts currently in place between those practices and Janssen.

Accordingly, Janssen acknowledged a breach of Clauses 9.1 and 15.2 because the RBM inappropriately shared commercially confidential information on behalf of Janssen with an unauthorised third party.

Allegation: That the GP's complaint was not being dealt with appropriately

Janssen stated that obviously, the PMCPA would understand that investigations into complaints were not something the company publicised internally or externally and therefore there was no reason for the anonymous complainant to be aware of either the complaint or any actions Janssen might have taken.

Janssen submitted that it operated to the highest possible standards and it took immediate action to investigate the GP's concerns.

Janssen submitted that the timetable of events and actions (details provided) clearly demonstrated that it had commenced internal investigations and referred the findings for human resources review before it received the communication from the PMCPA and within the timeframe agreed with the GP.

The complainant also alleged a lack of training had been 'put in place' to stop the individual concerned 'sending such emails in the future'. Should Janssen decide that specific training was necessary, it would be established in line with the company disciplinary procedures. Janssen stated that the PMCPA would understand why this would not be for public consumption and would not be brought to the attention of the anonymous complainant.

The RBM received regular Code training and was last trained in July 2016.

Accordingly, Janssen denied a breach of Clause 16.1.

Clause 2

While Janssen acknowledged that the content of the RBM's email to the GP resulted in the GP contacting the company, it acted rapidly to clarify the issues and to take positive steps to alleviate the concerns.

While the company acknowledged that the RBM's actions were not ideal, it did not believe that he/she acted with any malice or intention to mislead. No communications were sent to any health professional other than an appointed negotiator for a purchasing group. The email to the GP was sent with the specific intention of clarifying the details of the deal and seeking agreement on the text and nature of the communication of that deal to the purchasing group he was representing.

Accordingly, Janssen submitted that its actions or those of its employees did not bring the industry into disrepute and consequently denied any breach of Clause 2.

Janssen submitted that it had email permission from the GP recorded in its system.

Janssen submitted that both the account manager who had accompanied the RBM and the RBM had passed the ABPI Representatives Examination.

The training referred to in the email in question related to the standard, fully approved, meetings that Janssen account managers routinely offered. The exact format of the training 'programme' had not yet been formalized; an aspect that would have been confirmed and agreed prior to any formal communication.

Janssen confirmed that no representatives from Napp were either present at the meeting with the GP or were involved with the discussions. The reference to Napp was only in the context of the co-promotion agreement in place between Janssen and Napp for the promotion of Invokana. The GP was familiar with the co-promotion agreement and with the local Napp account manager, which was why they were mentioned in the email, however, Napp had no involvement in this particular discussion.

In conclusion, Janssen acknowledged a breach of Clause 9.1 and 15.2 of the Code but denied any breach of Clauses 2, 7.2, 7.4, 12.1, 16.1 or 18.1.

In response to a request for further information Janssen provided the complete training history for the RBM concerned. The company noted that he/she had been trained on 5 modules which all

Janssen employees completed as part of their core curriculum in relation to email and email communication and had additionally been trained on another two relevant modules specific to the RBM role.

Upon the resolution of this case Janssen would implement any additional training, pertaining to email, or otherwise, to address any gaps that were identified.

Janssen summarised the training history for the RBM in relation to emails and email communication and provided an outline of the relevant learning objectives (details provided). Janssen confirmed that all trainings were up-to-date and noted that in addition to these trainings the RBM concerned was also trained on the 2016 Code and had completed the ABPI Representatives Examination.

Janssen also summarised the training history for the RBM concerned related to business conduct and data privacy and provided an outline of the relevant learning objectives (details provided). Again Janssen confirmed that all training was up-to-date.

Janssen submitted that it currently did not train RBM's or account managers specifically on confidentiality agreements in place with dispensing surgeries. Janssen acknowledged that this was a gap. As such, Janssen confirmed that the RBM was not trained on the confidentiality agreements in place with the dispensing surgeries in question. After the resolution of this case Janssen stated that it would ensure that training on these would be incorporated into curriculum for relevant staff going forward.

Janssen reiterated that the RBM concerned only shared the information assuming that the GP, operating as director of finance for the local federation, already knew the commercial arrangements in place with each practice and as such it was an honest mistake.

Janssen noted that, as demonstrated by the numerous policies and trainings it had in place with regards to business conduct and privacy, despite identifying this specific gap, employees were comprehensively trained on the general principles of business conduct, privacy and email communication.

Janssen provided a copy of the local formulary with regard to the use of SGLT2 inhibitors.

The development of the formulary was overseen by the local prescribing and effectiveness forum working in conjunction with the drugs and therapeutics committee hence the reference in the case to the local prescribing and effectiveness forum formulary, however, these were one and the same.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure stated that anonymous complaints would be accepted, but that like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. The Panel noted that extreme dissatisfaction was usually required on the part of an individual before he or she was moved to complain. All complaints were judged on the evidence provided by the parties. The complainant could not be contacted for more information.

The Panel noted that the email in question had been sent to the GP in his role for the local federation and purported to reflect an agreement reached at a meeting with the RBM in question about Janssen's rebate scheme for dispensing practices within the federation. The email sought the GP's comments on a draft communication from the GP to relevant practices within the federation about an agreed preferential rate for canagliflozin. The relevant part of the email concluded with 'Let me know if this is ok?' The second part of the email referred to a proposed communication from the third party service provider to relevant practices within the federation and introduced the text stating 'we wanted to put something along the lines of:' The RBM asked whether the latter communication could have the federation logo on and stated that it would include the table of existing individual practice agreed discounts which was also reproduced in the email.

The Panel noted the status of the complainant above. The Panel had no way of knowing precisely what was said at the meeting between the RBM and the GP and therefore whether this was accurately reflected in the email. It was not possible to contact the complainant for further details. It appeared that the GP in question had not responded to the RBM's email but had contacted Janssen. The Panel noted the company's submission that the purpose of the email in question was to seek alignment and agreement for the wording of the wider communication. The Panel also noted the company's submission that the GP had confirmed to Janssen that he/she had requested a clarification email be sent to ensure that he understood the deal sufficiently to be able to take it to the federation for review. The Panel noted that there was an important difference between providing draft text for a communication to federation members and an email clarifying the agreement reached. The Panel queried whether this was the source of the GP's concerns. The Panel also noted that Janssen later stated a different rationale for sending the email namely to confirm the details of a conversation prior to formalising and communicating a contractual relationship. The Panel noted that it could be argued that the email in question did not make this sufficiently clear and in providing draft text for external communications went beyond the stated rationale. The Panel also noted that any external communication to federation members would have been subject to the company's approval and certification process. The Panel considered that sending an email to confirm the terms of an agreement reached during such meetings about terms of trade and to seek comment on proposed communications was, in general terms, good practice.

The Panel noted that the case preparation manager had raised and the company had responded to the requirements of Clause 18.1 and its supplementary information, Terms of Trade which stated that such measures or trade practices which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 were excluded from the provisions of that clause. Whilst the Panel had concerns about the email in question, in its view the complainant did not raise a Clause 18.1 matter. There was no implication that the complainant considered that the rebate scheme was offered in connection with the promotion of medicines contrary to Clause 18.1 and the relevant supplementary information or that it was otherwise an inducement. No breach of Clause 18.1 was ruled.

The Panel noted the complainant's concern that the email in question suggested to several surgeries that canagliflozin was the [named local clinical effectiveness and prescribing forum] 'preferred' SGLT2i which was inaccurate as it was jointly recommended in the class. The Panel noted that the email had not been sent to 'several surgeries' as implied by the complainant. The Panel noted that the first part of the email which covered the text of a proposed communication to relevant practices within the federation stated 'As you are aware, all SGLT2is are recommended locally. We as a federation have a preferred one within the class with canagliflozin'. The second proposed communication from the third party service provider stated that the 'increased rebate is as a result of the Federation's decision to make Invokana the preferred SGLT2 product but still in line with local guidelines'. In the Panel's view the first part of the email made it sufficiently clear that that all SGLT2is were recommended locally. However, the Panel considered that the second part of the email could have been clearer about the position of canagliflozin within the local guidelines. The Panel noted Janssen's submission that the wording of the email was less than ideal. Nonetheless, the Panel noted that whilst the email described Invokana as the federation's preferred SGLT2i, neither part of the email described it as the [named local clinical effectiveness and prescribing forum] 'preferred' SGLT2i as alleged. The Panel therefore ruled no breach of Clauses 7.2 and 7.4 based on the very narrow allegation.

The complainant was concerned that the suggestion to add the federation logo to the communication from the third party service provider was an attempt by the company to add weight to the communication and influence the NHS. The Panel noted that Clause 12.1 stated that promotional material and activities must not be disguised. The Panel noted that it might not necessarily be unacceptable to use the federation's logo on a communication to the individual practices within the federation provided that it was done with prior permission and appropriate approval and otherwise complied with the Code. The Panel noted that the email in question made it clear that the addition of the logo was raised as a question, and in the Panel's view it was therefore for the federation to give its consent or otherwise. The Panel considered that it was not an unacceptable suggestion. In any event no communication had been sent to practices within the federation and the issue of disguised promotional activity did not arise. No breach of Clause 12.1 was ruled in that regard. The Panel noted that Clause 16.1 required that all relevant personnel including representatives and members of staff, and others retained by way of contract, concerned in any way with the preparation or approval of material or activities covered by the Code must be fully conversant with the Code and the relevant laws and regulations. The Panel noted Janssen's submission about its training program and that the individual had received regular Code training and was last trained in July 2016. The Panel noted Janssen's submission that it currently did not train RBM's or account managers specifically on confidentiality agreements in place with dispensing surgeries and acknowledged that this was a gap. The RBM in question had not been trained on the confidentiality agreements in place with the dispensing surgeries in question. The Panel further noted Janssen's submission that after the resolution of this case it would ensure that training on these would be incorporated into curriculum for relevant staff going forward and it would implement any additional training, pertaining to email, or otherwise, to address any gaps that were identified. The Panel noted that the complainant's allegation concerned what measures were now being put in place to ensure that the RBM was trained on relevant matters henceforth. On the limited information before the Panel it appeared that the training issues were now being addressed. The Panel therefore ruled no breach of Clause 16.1 based on the narrow allegation.

The Panel noted Janssen's explanation that the health professional at issue also had a role for the local federation, which represented a number of surgeries, including a number of dispensing practices. Within his/her federation role, the health professional led a review of dispensing deals across the federation.

Noting its comments above with regard to the RBM in question not being trained on the confidentiality agreements in place within the individual dispensing surgeries in question, the Panel considered that it was not unreasonable for the RBM to assume that the GP in his/her role as described above would be aware of the deals in place at the individual practices. The Panel considered that the RBM had been let down by the company in this regard. Nonetheless, the confidential information pertaining to a number of practices, excluding that of the GP, had been disclosed by the RBM. This was a serious matter. The Panel considered that disclosing such information did not comply with the requirements of the Code and a high standard of ethical conduct had not been adhered to as required by Clause 15.2 and a breach of that clause was ruled. The Panel considered that the failure of Janssen to train the RBM before he/she discussed issues around confidential data with health professionals and on how to handle such data in accordance with the Code was a significant omission. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that the complainant had alleged that Janssen was not dealing with the GPs complaint appropriately. No further details were provided.

The Panel noted Janssen's submission on this point and that the GP had not responded to Janssen's communications in July 2017 to update him/her on the progress of its investigation. The complainant had not established that the GPs concerns were not being considered appropriately by Janssen and no breach of Clause 9.1 was ruled in this regard.

The Panel noted its comments and rulings above. Noting that the proposed communications set out in the email did not advance past the draft stage, the Panel did not consider that a ruling of a breach of Clause 2 was warranted in the particular circumstances of this case.

During its consideration of this case the Panel noted that the communication was a draft and had only been sent to the named health professional. It did not appear that the communication had been sent to any of the individual practices. However, the Panel queried the RBM's understanding of the Code if he/she considered such an arrangement to be appropriate under the Code.

The Panel requested that Janssen be advised of its concerns.

Complaint received **8 August 2017**

Case completed **1 February 2018**

CASE AUTH/2978/9/17

ANONYMOUS NON-CONTACTABLE CONSULTANT DERMATOLOGIST v JANSSEN

Promotion of Tremfya

An anonymous, non-contactable consultant dermatologist complained about a Janssen symposium entitled 'Emerging Treatments for Psoriasis: Unlocking the IL-23 Pathway'. The symposium was part of the British Association of Dermatologists' (BAD) annual meeting held in Liverpool, July 2017.

The flyer for the symposium referred to emerging treatments for psoriasis and that the meeting would provide an opportunity for focussing on the pivotal role of IL-23. The similarities and differences in the mechanism of action of therapies which targeted this cytokine and the latest data for guselkumab and other IL-23 targeting molecules would be presented. The flyer stated at the bottom, in small blue font, that guselkumab was not licensed in the UK.

The complainant provided a copy of the flyer for the 'so called' symposium which he/she had been given at the Janssen exhibition stand. The complainant stated that although the symposium was entitled 'Emerging Treatments for Psoriasis: Unlocking the IL-23 Pathway', it was obviously a presentation about guselkumab (Tremfya) as the weight of discussion and evidence presented related mainly to that product. The complainant was surprised to see prescribing information at the end of the presentation. At the time, guselkumab was not licensed anywhere in the world and although the meeting appeared to be a 'scientific' symposium, it appeared to actually be mainly about guselkumab. The complainant alleged that it was unacceptable to discuss a medicine which was not licensed in that way.

The detailed response from Janssen appears below.

The Panel noted that promotion was defined as any activity undertaken by a pharmaceutical company or with its authority which promoted the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines. The Panel noted that although the Code prohibited the promotion of a medicine prior to the grant of its marketing authorization, certain activities with regard to unlicensed medicines were permitted such as the legitimate exchange of medical and scientific information during the development of a medicine provided that this did not constitute promotion which was prohibited.

The legitimate exchange of scientific information during the development of a medicine should involve debate that enhanced the current state of knowledge. To avoid being seen as promotional, it should not be a one way flow of information.

The Panel noted that the symposium started at 18:15 and consisted of two presentations on 'Leveraging IL-23 in psoriasis' and 'What next for IL-23 inhibition?' (from 18:20 until 18:50). Ten minutes were then set aside for Q&A and discussion and the seminar finished at 19:00. The Panel queried whether the agenda allowed for 'the exchange of information' given the very limited time for discussion and input from the audience.

The Panel noted that the first presentation (20 minutes) had a title slide of 'Selective blockade of IL-23 in psoriasis – A novel treatment concept'. Half of the 34 slides looked at selective IL-23 inhibition; risankizumab clinical trials featured on one slide, clinical trial results for tildrakizumab were discussed on 5 slides and data from guselkumab trials were on 8 slides.

The second presentation was entitled 'What next for IL-23 inhibition?'; the certificate for the material, however, described the item as 'Slide deck for 10 minute presentation titled 'What next for guselkumab?'. Focussing on how it could change clinical practice, what it would mean for patients and what trials are … [the text then became unreadable]'. Of the 19 slides, 12 were specifically about guselkumab clinical trials. The Panel noted the original title for the presentation had been changed. It queried whether such a product-specific slide deck would have been written by the speaker.

The second presentation included prescribing information for Stelara which was referred to in the briefing notes as IL-12/23 so it appeared that there was a promotional element to the symposium.

The Panel noted that the purpose of the symposium set out in the briefing document for speakers did not mention the exchange of information and there was very limited time for such.

The evaluation form asked attendees to assess the session in terms of overall interest, fulfilment of learning objectives and to rate 'the relevance of the content i.e. could it change your clinical practice?'. The evaluation form also invited attendees to ask for 'further information on the topics discussed during this meeting'. In that regard, Janssen appeared to be soliciting questions about its unlicensed medicine.

It appeared that the Janssen booth included a commercial section and medical information staff would be present at certain times to provide assistance on a number of issues including off-label indications/uses, pipeline products and investigator initiated studies (IIS).

In the Panel's view, it was reasonable to assume that, on the balance of probabilities, many of the booth visitors would ask about guselkumab. The briefing materials prepared staff for such questions and medical information staff were there to answer such questions.

The Panel considered that the symposium in July 2017 focussed on Janssen's product which was authorized by the FDA on 13 July. Although the term 'investigational' was not defined, the Panel queried whether a product for which a marketing authorization was applied for in the US and received just over a week after the symposium and was going through the EMEA process for a marketing authorization could be considered to be an 'investigational molecule' or being 'in development'. In the Panel's view, health professionals were likely to view guselkumab as a pre-licence product.

The Panel did not consider that the arrangements for the symposium would lead to an exchange of information. The limited time for discussion together with the balance of information presented being about Janssen's new product which would be likely to receive a marketing authorization within a few months meant that the medicine had been promoted prior to the grant of its marketing authorisation. A breach of the Code was ruled.

The Panel ruled a breach as high standards had not been maintained. Promotion of an unlicensed medicine brought discredit upon and reduced confidence in the pharmaceutical industry so a breach of Clause 2 was also ruled.

On appeal by Janssen of all of the Panel's rulings of breaches of the Code, the Appeal Board noted that under the objectives' the briefing for the speakers and chairman made no mention that discussion and an exchange of scientific information were essential; the stated objectives implied that data was being presented.

The Appeal Board noted from the transcript of the meeting that there were only two questions from the audience despite encouragement from the chair. The Appeal Board considered this was surprising given the data and the potential impact of a different treatment approach. The Appeal Board considered that the company should have done much more to engage the audience and to stimulate debate to enable two-way discussion and an exchange of medical and scientific information.

The Appeal Board considered that there was very little evidence of any legitimate scientific exchange. The Appeal Board did not consider whether the medicine was still in development; this had not been raised by the complainant. The Appeal Board considered that the balance of information presented in the second presentation was about Janssen's new product which would be likely to receive a marketing authorization within a few months and that this in conjunction with the points mentioned above meant that the medicine had been promoted prior to the grant of its marketing authorisation. The Appeal Board upheld the Panel's ruling of a breaches of the Code including Clause 2. The appeals on all points were unsuccessful.

An anonymous, non-contactable consultant dermatologist complained about a Janssen symposium entitled 'Emerging Treatments for Psoriasis: Unlocking the IL-23 Pathway'. The symposium was part of the British Association of Dermatologists' (BAD) annual meeting held in Liverpool, 4-6 July 2017.

The flyer for the symposium referred to emerging treatments for psoriasis and that the meeting would provide an opportunity for focussing on the pivotal role of IL-23. The similarities and differences in the mechanism of action of therapies which targeted this cytokine and the latest data for guselkumab and other IL-23 targeting molecules would be presented. The flyer stated at the bottom, in small blue font, that guselkumab was not licensed in the UK.

COMPLAINT

The complainant provided a copy of the flyer (ref PHGB/MEDed/0517/0010c) for the 'so called' symposium which he/she had been given at the Janssen exhibition stand. The complainant stated that although the symposium was entitled 'Emerging Treatments for Psoriasis: Unlocking the IL-23 Pathway', it was obviously a presentation about guselkumab (Tremfya), as the weight of discussion and evidence presented related mainly to that product. The complainant was surprised to see information at the end of the presentation which looked like the sort of material he/she would normally see at the end of a sales representative's documents, describing guselkumab prescribing features, side effects etc. The complainant did not think that, at the time, guselkumab was licensed anywhere in the world and certainly not in the UK and although the meeting appeared to be a 'scientific' symposium, it appeared to actually be mainly about guselkumab. The complainant alleged that it was unacceptable to discuss a medicine which was not licensed in that way.

When writing to Janssen, the Authority asked it to consider the requirements of Clauses 2, 3.1, 9.1 and 12.1 in relation to the symposium.

RESPONSE

Janssen submitted that no materials on its exhibition stand were about guselkumab or the Janssen symposium. The symposium flyer was only available in the BAD delegate bags at the conference; it was not available on the stand. The flyer clearly acknowledged Janssen's involvement, as it stated: 'This session is organised and funded by Janssen and intended for healthcare professionals only'.

Janssen submitted that commercial and medical activities were kept entirely separate and the exhibition stand at the BAD meeting was a promotional stand for Stelara (ustekinumab). The sales force briefing document (copy provided) was

clear and explicit in its instruction that commercial and sales staff were only to provide on-label product information for Stelara.

With regard to the symposium itself Janssen considered that it had acted in keeping with both the letter and the spirit of the PMCPA guidance about Clause 3 in that the fostering of legitimate exchange of medical and scientific information during the development of a medicine was permissible.

Janssen submitted that it had acted in accordance with the guidance, with the symposium's intent and structure being to foster legitimate scientific exchange. The audience was self-selected by virtue of being attendees at the UK's leading dermatological congress and the symposium was an integral part of the official congress programme, confirmed by the BAD programme committee.

Janssen submitted that when the symposium was held, (and still currently), guselkumab was not licensed in the UK for any indication.

On 13 July 2017, guselkumab was approved in the US by the FDA for the treatment of adults with moderate to severe plaque psoriasis who were candidates for systemic therapy or photo therapy.

On 15 September 2017, the Committee for Medicinal Products for Human Use (CHMP) gave a positive opinion for guselkumab in the treatment of adults with moderate to severe plaque psoriasis who were candidates for systemic therapy and the Final Commission Decision from the European Medicines Agency (EMA) was expected on 20 November 2017. There were two other selective IL-23 inhibitors in development for plaque psoriasis; tildrakizumab (Merck Sharp & Dohme, Sun Pharma, Almirall) and rizankizumab (Boehringer, Abbvie).

When the symposium was held, two phase III trials had been published on the use of tildrakizumab in this indication whilst only phase II data had been published on risankizumab. The development programs for both molecules were ongoing and data from these formed an integral part of the symposium. Janssen could not comment on the regulatory timelines of the other products. Guselkumab was also in development for pustular psoriasis, palmoplantar pustulosis, and psoriatic arthritis.

The speaker briefing guides included both general guidance around the Code clauses to be adhered to and additionally, specific guidance on inclusion of detailed analysis of the data from the development programmes of the other IL-23 inhibitors.

The presentations were prepared by the speakers and did not include any brand colours or logos or the brand name for guselkumab. Analyses of all 3 available IL-23 molecules were included and there were no case-based discussions or testimonials of the use of guselkumab outside of the clinical trial setting.

Janssen asserted that this was a scientific symposium on the role of IL-23 targeting molecules including guselkumab, with data for the other molecules presented in a fair and balanced manner.

The development program for guselkumab was more advanced compared with the other two molecules, in terms of timelines, number of studies and indications under investigation. The available data reflected this fact and informed the balance of information presented at the symposium.

Janssen provided a list and copies of the symposium material to include briefing documents, presentations and evaluation form. The company also provided a list of company employees who attended the meeting.

Janssen submitted that the symposium met the requirements of scientific exchange and as such it denied a breach of Clauses 3.1 and 12.1. Consequently, Janssen also believed that high standards had been maintained and that therefore it had not brought discredit upon, or reduced confidence in, the pharmaceutical industry. Janssen thus denied breaches of Clauses 9.1 or 2.

With regard to the complainant's comments about information seen at the end of the presentation, the deck presented by one of the speakers included Stelara prescribing information at the end of it, not as suggested by the complainant, guselkumab prescribing information which was not yet available. The Stelara prescribing information was included because Stelara data were shown and informed part of the discussion and it was a currently Janssen marketed product.

Janssen noted that there was no advertising of the symposium by commercial or sales staff, the speakers were all independent health practitioners and the speaker briefings demonstrated Janssen's commitment to the fair and balanced portrayal of the available data.

Janssen also noted that it had commented on the weighting of the data presented which reflected the more advanced clinical development program for guselkumab compared with the other selective IL-23 blocking agents. The company believed that the symposium met the requirements of scientific exchange and the activities surrounding it were therefore not in breach of Clauses 3.1 and 12.1. Janssen therefore denied breaches of Clauses 9.1 or 2.

Janssen repeated that it had maintained a high standard in all activities relating to the symposium and it would not be seen to either discredit, or reduce confidence in the industry.

In conclusion, Janssen denied any breach of Clauses 2, 3.1, 9.1 and 12.1 in relation to the symposium.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure for the Prescription Medicines Code of Practice Authority stated that anonymous complaints would be accepted but that like all other complaints,

the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties.

The Panel noted that Clause 1.2 defined promotion as any activity undertaken by a pharmaceutical company or with its authority which promoted the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines. The Panel noted that although Clause 3 prohibited the promotion of a medicine prior to the grant of its marketing authorization, the Code permitted companies to undertake certain activities with regard to unlicensed medicines. The supplementary information to Clause 3 provided additional details including a statement that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that this did not constitute promotion which was prohibited by Clause 3 or any other clause. The PMCPA Guidance about Clause 3 further stated that companies must ensure that such activities constituted a genuine exchange of information and were not promotional. Documents must not have the appearance of promotional material. It should be borne in mind that it would be a breach of the Code if non-promotional information on products or indications that were not licensed was used for a promotional purpose.

The legitimate exchange of scientific information during the development of a medicine should involve debate that enhanced the current state of knowledge. To avoid being seen as promotional, it should not be a one way flow of information.

The Panel noted that the symposium started at 18:15 and consisted of two presentations on 'Leveraging IL-23 in psoriasis' and 'What next for IL-23 inhibition?' (from 18:20 until 18:50). Ten minutes were then set aside for Q&A and discussion and the seminar finished at 19:00. The Panel queried whether the agenda allowed for 'the exchange of information' given the very limited time for discussion and input from the audience.

The Panel noted that the first presentation (20 minutes) had a title slide of 'Selective blockade of IL-23 in psoriasis – A novel treatment concept'. Half of the 34 slides looked at selective IL-23 inhibition; risankizumab clinical trials featured on one slide, clinical trial results for tildrakizumab were discussed on 5 slides and data from guselkumab trials were on 8 slides.

The second presentation was entitled 'What next for IL-23 inhibition?'; the certificate for the material, however, described the item as 'Slide deck for 10 minute presentation titled 'What next for guselkumab?'. Focussing on how it could change clinical practice, what it would mean for patients and what trials are … [the text then became unreadable]'. Of the 19 slides, 12 were specifically about guselkumab clinical trials. The Panel noted the original title for the presentation had been changed. It queried whether such a product-specific slide deck would have been written by the speaker.

The Panel noted that the second presentation included prescribing information for Stelara which was referred to in the briefing notes as IL-12/23 so it appeared that there was a promotional element to the symposium.

The purpose of the symposium was set out in the briefing document for speakers as:

'This is an educational symposium, and the objectives for attendees are:

- To revisit the structure and role of IL-23, including differentiating between the p40 and p19 subunits, and how these can be targeted independently by psoriasis treatments.
- To develop an understanding of guselkumab and other IL-23 molecules clinical trial data.
- To relate understanding of the clinical trial data to the future of your clinical practice and patient outcomes.'

The Panel noted that there was no mention of the exchange of information and there was very limited time for such.

The evaluation form asked attendees to assess the session in terms of overall interest and fulfilment of learning objectives. Attendees were also asked to rate 'the relevance of the content i.e. could it change your clinical practice?'. The evaluation form also invited attendees to ask for 'further information on the topics discussed during this meeting'. In that regard, Janssen appeared to be soliciting questions about its unlicensed medicine.

It appeared from the Janssen staff briefing notes that the Janssen booth included a commercial section and that medical information staff would be present at certain times to provide assistance on a number of issues including off-label indications/uses, pipeline products and IIS.

In the Panel's view, it was reasonable to assume that, on the balance of probabilities, many of the booth visitors would ask about guselkumab. The briefing materials prepared staff for such questions and medical information staff were available to answer such questions.

The Panel considered that the symposium in July 2017 focussed on Janssen's product which was authorized by the FDA on 13 July. Although the term 'investigational' was not defined, the Panel queried whether a product for which a marketing authorization was applied for in the US and received just over a week after the symposium and was going through the EMEA process for a marketing authorization could be considered to be an 'investigational molecule' or being 'in development'. In the Panel's view, health professionals were likely to view guselkumab as a pre-licence product.

The Panel did not consider that the arrangements for the symposium would lead to an exchange of information. The limited time for discussion together with the balance of information presented being about Janssen's new product which would be likely

to receive a marketing authorization within a few months meant that the medicine had been promoted

prior to the grant of its marketing authorisation. A breach of Clause 3.1 was ruled.

The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. Promotion of an unlicensed medicine brought discredit upon and reduced confidence in the pharmaceutical industry so a breach of Clause 2 was also ruled.

APPEAL BY JANSSEN

Janssen prided itself on being an ethical company and it did not agree with the Panel's rulings of breaches of Clause 2, 3.1 and 9.1 which it appealed.

Background

Janssen stated that the 97th Annual Meeting of the BAD that took place in Liverpool from 4-6 July 2017 was the largest dermatology meeting in the UK with over 1000 delegates attending a mixture of plenary sessions, keynote lecturers, special interest group sessions, hot topics and focus sessions, where scientific discussion and debate routinely took place, including at those sessions sponsored by pharmaceutical companies.

Janssen submitted that its activities at the congress included a Stelara only promotional stand in the main exhibition hall and the company-sponsored symposium in question.

In the spirit of transparency, Janssen pointed out that it had also held a hot topics session, covering registry data entitled 'Long-term management of psoriasis: applying learnings from registry data' and the slides were provided. The session was held within the exhibition hall, but separate to the stand and was an integral part of the congress program. This activity had not been subject to any complaint or alleged breach and was entirely unrelated to guselkumab or the symposium content.

Janssen submitted that its policy was to have clear separation between medical educational and commercial activities. Janssen reiterated this point to assert the fact that all activities pertaining to the symposium at the BAD congress were wholly owned and run by members of the UK Janssen Immunology Medical Affairs team, consisting of the medical education manager and the medical advisor working in collaboration with its retained medical communications agency. A brief description of these roles was provided.

Janssen submitted that both roles were entirely non-promotional in nature and reflected the fact the organisation of the symposium was in no way linked to commercial activities, such as the promotional stand at the congress. In line with Janssen's UK congress guidelines (ref TV-GDL-00753), which all Janssen employees at congress had to have completed prior to attendance, there were no Janssen sales personnel at the symposium and the symposium attendee list was not shared with them.

In addition, the symposium materials (invitations and slides) bore no resemblance to promotional materials, and this 45-minute symposium was the only Janssen organised activity at the BAD congress related to IL-23 or guselkumab. No follow-up activities were conducted with attendees.

Janssen noted that the Panel had queried whether the agenda allowed for 'the exchange of information' given the very limited time for discussion and input from the audience. The PMCPA's supplementary information with guidance on Clause 3 and specifically, wording directing companies to avoid being seen as disseminating data to expand the use of their products by ensuring that such activity must not be a 'one way flow of information'.

Janssen submitted that when the science, as it related to a new pathway or molecular target was new to the scientific community a certain amount of time needed to be devoted to the foundational knowledge, in order to facilitate a more informed debate. Janssen's assertion was that this was the balance it had sought to strike as it developed the content for the symposium. Whilst the Panel had examined the timings of the presentations, Janssen was not in agreement with the assessment of the proportion of time spent on the various elements of the symposium which would have afforded a true legitimate exchange.

Janssen submitted that it had examined audio recordings and raw transcripts of the symposium (provided) and when one excluded the welcome from the chair, house-keeping notes and speaker disclosures, twenty five percent (25%) of the rest of the symposium was devoted to questions and answers, which was an adequate proportion given the points discussed above.

Janssen submitted that there was no PMCPA guidance on the appropriate proportion of discussion time within such meetings, but stated that the amount of time at this meeting was aligned with Janssen policy of having at least 20% of the time being devoted to discussion. In order to facilitate this active discussion, questions could either be handed into the speakers by a card or asked directly from the floor. The discussion part of the symposium opened with the chair inviting questions from the audience with the words: 'We do have time for some questions. It would be nice if we could make this as interactive as possible'. The symposium only finished when all questions had been answered.

With regard to the Panel's note that 'the purpose of the symposium was set out in the briefing document …', Janssen submitted that this was an educational symposium, and the objectives for attendees were:

- To revisit the structure and role of IL-23, including differentiating between the p40 and p19 subunits, and how these could be targeted independently by psoriasis treatments.
- To develop an understanding of guselkumab and other IL-23 molecules clinical trial data.
- To relate understanding of the clinical trial data to the future of their clinical practice and patient outcomes.

Janssen confirmed that this was the first and only IL-23 symposium that it had held in the UK and that given this, reiterated the point that a certain amount of time needed to be spent on foundational knowledge of the pathophysiological elements of the IL-23 specific pathway to foster a more informed discussion. Janssen submitted that the breakdown of the symposium was as follows:

> Selective blockade of IL-23 in psoriasis – A novel treatment concept
> General psoriasis information ie pathogenesis, comorbidities etc (includes IL-17 inhibition information) – 19.67%
> IL-23 in general – 33.47%
> Guselkumab – 19.82%
> Risankizumab – 6.90%
> Tildrakizumab – 10.27%
>
> What next for IL-23 Inhibition?
> General psoriasis information ie pathogenesis, comorbidities etc – 0%
> IL-23 in general – 35.77%
> Guselkumab – 55.87%
> Risankizumab – 0%
> Tildrakizumab – 0%.

Janssen submitted that the balance of the data presented at the symposium was reflective of the disclosures in the public domain at the time of planning the symposium. A search of clinicaltrials.gov revealed that of the 18 studies evaluating IL-23 inhibitors in psoriasis, 8 were guselkumab trials, representing just under half of the combined investigational agents in this field. A thorough literature review was performed on selective IL-23 inhibitor development program (provided). The review was conducted by Janssen's medical communications agency and performed first in the week commencing 5 June 2017 and repeated in the week commencing 26 June (ie the week prior to the BAD congress) ensured that no new disclosures had been made in the intervening period. This document clearly demonstrated the greater number of guselkumab disclosures, owing to its more advanced development program and therefore reflected the balance of the data presented at the symposium.

Janssen pointed out that the late addition of recently published data (on risankizumab), which necessitated further rounds of review, also demonstrated its commitment to presenting a fair and balanced representation of the publicly up to date available data.

In response to the Panel's assessment of the second presenter's presentation, again, Janssen submitted that these were reflective of the ongoing program for the IL-23 inhibitors of which guselkumab was most advanced. These included further investigational indications such as psoriatic arthritis, inflammatory bowel disease and the possibility of disease modification with IL-23 inhibition. The data shown in relation to this were, from early phase trials, investigative in nature and in no way meant to promote the medicine for current clinical use. Rather, the aim was to inform the audience on the direction that clinical research on the IL-23 pathway in general was heading beyond only the psoriasis indication.

The symposium was 45 minutes attended by approximately 70 delegates, who were by definition, a self-selected audience and as previously stated, were invited to the symposium only through a flyer in the delegate bags. No invitations were made from the stand. Furthermore, there were no other Janssen activities including materials, posters or literature pertaining to IL-23 or guselkumab at the BAD meeting.

ith regard to the Panel's comment that '… the certificate for the material, however, described the item as "Slide deck for 10 minute presentation titled 'What next for guselkumab?"', Janssen submitted that the change of the original title from 'What next for IL-23 inhibition?' to 'What next for guselkumab?' was due to an unfortunate error by Janssen's agency which uploaded the job summary. As could be seen from Zinc from the first round of review, the document was always titled 'What next for IL 23 inhibition?'. Janssen referred to the briefing guide to the speaker as stated below and confirmed that no materials distributed to either speakers or delegates contained the title 'What next for guselkumab?.

Janssen noted that the Panel had queried 'whether such a product-specific slide deck would have been written by the speaker'. Janssen submitted that both speakers were eminent in their fields and as could be seen from their disclosures, conducted consultancy and research activities for numerous companies, including direct competitors in this therapy area. Specifically, the first presenter had been involved as an investigator in the development of all three IL-23 inhibitors, acted as a consultant in this field for several different pharmaceutical companies and had served as consultant and/or paid speaker for and/or participated in clinical trials. Details were provided.

Janssen submitted that its speaker briefings were also clear in its direction to its speakers: 'This meeting is non-promotional and aims to facilitate the exchange of scientific and medical information. We ask that speakers give a fair and balanced interpretation and analysis of data'. Janssen provided the email trail between its agency and the speakers requesting their slides to demonstrate that the slides were entirely the work of the speakers.

Janssen noted the Panel's comments about the evaluation form where attendees were also asked to rate 'the relevance of the content i.e. could it change your clinical practice?' and also invited to ask for 'further information on the topics discussed during this meeting'. In that regard, the Panel considered Janssen appeared to be soliciting questions about its unlicensed medicine. Janssen submitted that the evaluation form used was its standard template evaluation form, utilised at all medical educational events, completion of which was not compulsory. The primary use of the form was to collect feedback that allowed for continued improvement in the Janssen medical education programme. As previously stated, the symposium included topics covering the pathophysiology of psoriasis based on

the most current science. In particular, the newer IL-17 molecules, as well as discussions around co-morbidities such as uveitis and depression. Awareness of these might rightly have led clinicians to consider their practice and as such Janssen submitted that the section within the evaluation form about enquiring 'could it change your clinical practice' was appropriate in this setting. There was no inference that this was referring to prescribing habits and contrary to the Panel's suggestion neither was there any intention to solicit questions about Janssen's unlicensed medicine.

Rather, Janssen submitted that owing to fact that the symposium was short, Janssen chose to include in the form a section where the self-selected audience could ask any further scientific questions of its medical department should they not have had the opportunity in the symposium. This was to facilitate continued scientific exchange and any responses given would have been from the medical information team in response to the specific question asked. It also stipulated that the persons' email address/ phone number provided for the request would only be used for this purpose and no other follow up or promotional activity. Additionally, Janssen submitted that due to the fact the promotional stand at the BAD was a Stelara-only one and had no medical section/attendance, this was also included to ensure people did not seek out the promotional stand if they had any outstanding questions relating to the symposium. On examination of the evaluation forms Janssen identified a single request for information on IL-23.

Janssen submitted that its medical information department had reviewed all the guselkumab and IL-23 enquiries received over July 2017 and confirmed that no enquiries were logged during the BAD, and it had identified one delegate who attended the symposium and subsequently logged an enquiry via his account manager after the conference as follows:

> 'Dr X was at the BAD conference recently and he attended the guselkumab seminar. He is interested to understand more about this new molecule, especially around trials for 'disease modifying' capabilities. Please may I request an MSL visit? I explained as unlicensed I was unable to respond.'

Janssen submitted that the request had been processed through its medical information team.

Janssen noted that '… the Panel queried whether a product for which a marketing authorization was applied for in the US and received just over a week after the symposium and was going through the EMEA process for a marketing authorization could be considered to be an "investigational molecule" or being "in development". In the Panel's view, health professionals were likely to view guselkumab as a pre-licence product'. The Panel also noted that regulatory timelines for both the FDA and EMEA were close to the timing of the symposium and made the distinction between an investigational and pre-licence product. However, Janssen submitted that planning for the symposium commenced in March 2017 (email trail provided) and Janssen's internal working timelines for marketing authorisation from EMEA was in the first quarter of 2018. The EMEA timelines scenario planning (provided) demonstrated that Janssen's base case scenario for EC decision was 19 February 2018; eleven months ahead of when the planning began and seven months ahead of when the symposium was scheduled to occur. As it was, the EC decision arrived five to six months prior to when Janssen had anticipated and both at the time of planning and at the time the symposium occurred, Janssen could not have predicted this.

Janssen submitted that at the time this symposium was being planned and in the absence of prescriptive guidance on where the threshold between investigational and pre-licence product should lie, guselkumab could be considered an investigational product and was thus a legitimate candidate for a symposium at a learned congress where data were presented in a fair, balanced manner, reflective of the body of scientific disclosures in the public domain.

Janssen drew the Appeal Board's attention to the point made on the first presenter's first disclaimer slide to this effect, which stated 'This presentation contains information about products which are in development and are not licensed in the UK'.

Janssen noted that the Panel had noted that '… staff briefing notes that the Janssen booth included a commercial section and that medical information staff would be present at certain times to provide assistance on a number of issues including off-label indications …'. 'In the Panel's view, it was considered reasonable to assume that, on the balance of probabilities, many of the booth visitors would ask about guselkumab'. Janssen reiterated the clear separation between medical and commercial activities at the congress and it had also previously provided its briefing document to this end. Janssen again drew attention to the exact wording in the briefing, which stated that 'Medical Information (MI) Medical Education (who will be present at certain times) will provide assistance in the following situations upon request: – Off-label indications/ uses – Pipeline products – IIS – Additional in-depth information required – Adverse event (AE) reports – Product quality complaints (PQCs)'. Furthermore, there was no information about guselkumab or IL-23 at the booth ie no posters, papers, medical education materials, that any staff could have access to.

In addition, Janssen had a congress guideline which all staff were trained on which clearly delineated the role of medical and commercial at congresses (ref TVG-DL-00753 provided).

Janssen was, therefore, not in agreement with the Panel's view that there was, in any way, the intention to solicit off-licence questions about guselkumab. There were minor provisions made in the form of medical information request cards on the stand to capture any details of the requester and outline the questions that could then be followed up after the congress in a reactive manner. Janssen submitted that this was the provision of a responsible and legitimate medical information service. Contrary to the Panel's view regarding the balance of

probabilities, the number of guselkumab-related questions at the booth was zero.

With regard to the Panel's comments that the second presentation included prescribing information for Stelara … so it appeared there was a promotional element to the symposium', Janssen referred to previously stated rationale for inclusion of the Stelara prescribing information at the end of the presentations. The presentation included a trial which had Stelara as a comparator arm and although no promotional claims were made about Stelara, it submitted that provision of information such as contraindications, common and serious side effects and where to report adverse events for a licensed product would be of value to the audience. The decision to include the Stelara prescribing information at the symposium was so as not to drive delegates to the booth to seek prescribing information should they want it, and hence limit the traffic to the booth post the symposium. The use of the prescribing information was not intended to identify the symposium as being promotional, however, given historic cases, Janssen could see how this could be misconstrued by the Panel. Janssen's assertion was that the provision of prescribing information did not necessarily make an event promotional.

In conclusion, Janssen submitted that it had acted within the letter and the spirit of the Code. The limited amount of information shared about IL-23 inhibitors and guselkumab, which were all in development at the time of symposium had been demonstrated within the transcript of the symposium, as well as the opportunity for the audience members to participate in dialogue with the panel members for 25% of the time. Whilst guselkumab was being evaluated by the health authorities at the time of the symposium in July 2017, the licence had not yet been granted and therefore constituted a medicine in development. In fact, during the planning of the symposium the licence was not expected until Q1 2018, over 6 months from the time of the BAD meeting. No other activities related to IL-23 or guselkumab were conducted at the BAD by Janssen, and no materials were available. Usually the burden of proof sat with the complainant, however in this case it was an anonymous non-contactable one. Despite this, Janssen submitted that it had shown that this single symposium in the context of a learned society congress did not constitute pre-licence promotion, and hence denied breaches of Clauses 3.1, 9.1 and 2.

APPEAL BOARD RULING

The Appeal Board noted the supplementary information to Clause 3 stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under this or any other clause. The PMCPA Guidance about Clause 3 further stated that companies must ensure that such activities constituted a genuine exchange of information and were not promotional. Documents must not have the appearance of promotional material. It should be borne in mind that it would be a breach of the Code if non-promotional information on products or indications that were not licensed was used for a promotional purpose. The legitimate exchange of scientific information during the development of a medicine should involve debate that enhanced the current state of knowledge. To avoid being seen as promotional, it should not be a one way flow of information.

The Appeal Board noted that the symposium in question took place on 5 July 2017 and at that time although Janssen anticipated a CHMP opinion for guselkumab on 19 February 2018 it was in fact received on 15 September 2017. The marketing authorization was received in November 2017. Guselkumab was authorized by the FDA in the US on 13 July 2017.

With regard to the invitation flyer for the symposium, the Appeal Board considered that there was no evidence to show that this was available from the Janssen stand as alleged.

The Appeal Board noted that the symposium started at 18:15 and consisted of two presentations on 'Leveraging IL-23 in psoriasis' and 'What next for IL-23 inhibition?' (from 18:20 until 18:50). Ten minutes were then set aside for Q&A and discussion and the seminar finished at 19:00.

The Appeal Board noted that under the heading 'Meeting rationale and objectives' the briefing for the speakers and chairman made no mention that discussion and an exchange of scientific information were essential; the stated objectives implied that data was being presented. The general guidance for presentations stated that 'This meeting is non-promotional and aims to facilitate the exchange of scientific and medical information…' but did not make it clear that exchange of scientific information and discussion were critical.

The Appeal Board noted that Janssen provided guidance to the speakers about which topics should be discussed.

The Appeal Board noted that most of the available data for IL-23 inhibition related to guselkumab; there were two other selective IL-23 inhibitors in development for psoriasis; tildrakizumab and rizankizumab. There was no mention of tildrakizumab or rizankizumab data in the second presentation although this was included in the first presentation. The Appeal Board noted the trial data in the presentations which was discussed at the symposium; the transcript stated that these molecules presented a change in the treatment of psoriasis and that the chairman noted that '…it's important, obviously, for these companies to be first-to-market or have other differentiating data…'.

The Appeal Board noted Janssen's submission that the Zinc approval form (dated 4 July) for the second presentation was titled 'What next for guselkumab?' in error by its agency and that from the first round of the Zinc review the slide deck was always titled

'What's next for IL-23 inhibition?'. In that regard the Appeal Board noted that the Zinc approval dates were very close to the date of the symposium. The Appeal Board noted that of the 19 slides, 12 were specifically about guselkumab clinical trials. The Appeal Board noted from the Zinc approval form that the objective of the second presentation was to 'Develop an understanding of the guselkumab clinical trial data' and 'To relate understanding of the guselkumab clinical trial data to the future of your clinical practice and patient outcomes'. In that regard, the Appeal Board considered that the balance of the second presentation was specific to guselkumab.

The Appeal Board noted the information provided by Janssen regarding the time taken for the presentations and topics calculated from the transcript.

One of the symposium attendees had subsequently logged an enquiry via his/her Janssen account manager which had been referred to the medical information department. The account manager stated that 'Dr X was at the BAD conference recently and he attended the guselkumab seminar…'. It thus appeared that the perception of the symposium was that it was about guselkumab.

The Appeal Board considered that the inclusion of prescribing information for Jansen's product Stelara (which was licensed for the treatment of plaque psoriasis) on the second presentation added to the impression that the meeting was promotional.

The Appeal Board noted that the first (and main) presentation lasted for 20 minutes and was pre-recorded. The speaker was unavailable to answer questions at the meeting. The Appeal Board queried whether this format contributed to the low level of questions. After the presentations questions could either be handed into the speaker who was present or the chairman by a card, or asked directly from the floor.

The Appeal Board noted from the transcript of the meeting that there were only two questions from the audience despite encouragement from the chair. The Appeal Board considered this was surprising given the data and the potential impact of a different treatment approach. The Appeal Board considered that the company should have done much more to engage the audience and to stimulate debate to enable two-way discussion and an exchange of medical and scientific information. There were a number of simple practical ways of stimulating debate and yet these were absent.

The Appeal Board considered that there was very little evidence of any legitimate scientific exchange. The Appeal Board did not consider whether the medicine was still in development; this had not been raised by the complainant. The Appeal Board considered that the balance of information presented in the second presentation was about Janssen's new product which would be likely to receive a marketing authorization within a few months and that this in conjunction with the points mentioned above meant that the medicine had been promoted prior to the grant of its marketing authorisation. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.1. The appeal on this point was unsuccessful.

The Appeal Board considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of breach of Clause 9.1. Promotion of an unlicensed medicine brought discredit upon and reduced confidence in the pharmaceutical industry therefore the Appeal Board upheld the Panel's ruling of a breach of breach of Clause 2. The appeals on both points were unsuccessful.

Complaint received **25 September 2017**

Case completed **29 January 2018**

ANONYMOUS, NON-CONTACTABLE MEMBER OF THE PUBLIC v LEO

Alleged promotion of Kyntheum to the public

An anonymous, non-contactable complainant, who described themselves as a member of the public, complained about the promotion of Kyntheum (brodalumab) to the public by Leo Pharma. Kyntheum was indicated for the treatment of moderate to severe plaque psoriasis in adults who were candidates for systemic therapy.

The complainant stated that he/she went for a job interview at Leo for a role which would involve working on Kyntheum and the complainant was surprised by the amount of advertising for the product in the open waiting room. The complainant stated that he/she took a photograph of an advertisement which depicted a naked man and a number of claims. The indication was also included which the complainant did not think was licensed at the time of interview.

There was also a billboard upon which was stated 'The future is clear the future is Kyntheum'.

The complainant stated that he/she worked in the field and was not an expert on the Code but did not think a company could advertise to the public before the product had been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) or state 'well tolerated' when a number of patients in trials in the United States committed suicide.

The detailed response from Leo is given below.

The Panel noted Leo's submission that the materials referred to by the complainant were intended solely for the purpose of internal communications, as part of an internal campaign to engage staff in the launch of Kyntheum. Leo had submitted that the materials at issue were displayed within Leo's private, secure countryside-based offices within the staff coffee/ breakout area only. The Panel noted that Leo's offices were on the second floor and access to its offices was controlled; the only people who had access were Leo staff and visitors accompanied by a Leo staff member. The Panel noted Leo's submission that visitors would be shown to a room in the meetings area, away from the open-plan office and staff coffee area where the materials at issue were displayed.

The Panel considered that it was not necessarily unacceptable for a company to display product material within the confines of its offices, but such displays in areas routinely accessed by visitors, or even viewed by passers-by, needed to be appropriate. In the Panel's view, companies had to be aware of the impact and impression such material could have on visitors and the messages that might be conveyed. The Panel considered that if a visitor had seen the material at issue, they would be very aware that the company was shortly to launch a new product.

The Panel noted that the complainant had attended Leo's office to interview for a role working on Kyntheum. The Panel noted that the supplementary information stated that information about pharmaceutical companies provided to current or prospective employees might relate to both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. The Panel noted Leo's submission that the materials at issue were only on display after Kyntheum's marketing authorization had been received. In these circumstances, it was not unreasonable for a prospective employee when interviewing for a position which involved working with Kyntheum to see internal communications on the product. In these circumstances, the Panel considered that there was no evidence to support the complainant's allegation that Leo had promoted Kyntheum to the public prior to the grant of its market authorisation as alleged. No breaches of the Code were ruled including Clause 2.

The Panel noted the complainant's concern that Kyntheum was described in the material at issue as 'well-tolerated' when a number of patients in trials in the US had committed suicide. The Panel noted that Section 4.4, Special Warnings and Precautions for use, of the Kyntheum SPC,stated that suicidal ideation and behaviour, including completed suicide, had been reported in patients treated with Kyntheum. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour had not been established. The SPC advised that the risk and benefit of treatment with Kyntheum should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms. Patients, care givers and families should be advised of the need to be alert for such and if a patient suffered from new or worsening symptoms of depression and/or suicidal ideation or behaviour was identified it was recommended to discontinue treatment with Kyntheum. The Panel noted that suicidal ideation/ behaviour was not listed as an adverse event in Section 4.8 of the SPC. The Panel further noted Leo's submission that in the Kyntheum development programme as a whole across five different therapeutic indications, six cases of completed suicide were identified during 10,438 patient-years of follow-up exposure in 6,243 patients. The Panel noted that the study authors in Farahik *et al* 2016, a

review of phase III trials, stated that two completed suicides in AMAGINE-2 did not necessarily constitute a causal relationship especially given that patients with psoriasis were already at higher risk for depression, suicidal ideation, attempt and completed suicide.

The Panel noted the narrow nature of the allegation and that the complainant bore the burden of proof. The Panel did not consider that the complainant had established, on the balance of probabilities, that describing Kyntheum as well-tolerated was misleading or could not be substantiated due to the number of trial patients that had committed suicide and no breaches of the Code were ruled.

An anonymous, non-contactable complainant, who described themselves as a member of the public, complained about the promotion of Kyntheum (brodalumab) to the public by Leo Pharma. Kyntheum was indicated for the treatment of moderate to severe plaque psoriasis in adults who were candidates for systemic therapy.

COMPLAINT

The complainant stated that he/she went for a job interview at Leo's head office. The role would involve working on Kyntheum and the complainant was surprised by the amount of advertising for the product in the open waiting room. The complainant stated that he/she took a photograph of an advertisement which depicted a naked man and included the following claims:

> 'Confidence starts with clearance
>
> What does PASI 100 mean to Simon?
>
> Kyntheum targets the IL-17 pathway in a novel way, being the only biologic treatment for moderate to severe psoriasis that selectively targets the IL-17 receptor subunit A
>
> Patients achieving Pasi 100 are less likely to experience impairment to their health related quality of life than those with residual disease
>
> Kyntheum is superior to ustekinumab at achieving Pasi 100 at 12 weeks
> 44% vs 22% (Amagine 2) 37% vs 19% (amagine 3)
>
> Kyntheum has a simple induction schedule and is well tolerated.'

The complainant stated that the advertisement also included the indication which he/she did not think was licensed at the time of the interview.

There was also a billboard upon which was stated 'The future is clear the future is Kyntheum'.

The complainant stated that he/she worked in the field and was not an expert on the Code but did not think a company could advertise to the public before the product had been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) or state 'well tolerated' when a number of patients in the trials in the United States committed suicide.

When writing to Leo, the Authority asked it to consider the requirements of Clauses, 2, 3, 9.1, and 26.1 in relation to the alleged promotion of an unlicensed product to the public, and Clauses 7.2 and 7.4 in relation to the claim 'well tolerated'.

RESPONSE

Leo submitted that it took its responsibilities for Code compliance very seriously and was committed to adhering to the Code and all applicable regulations in all its business activities. It was therefore disappointing that a prospective employee had complained anonymously to the PMCPA about information they had seen on Kyntheum when attending for an interview.

Leo strongly refuted the complainant's allegations. The materials viewed by the prospective employee were intended for internal employees only and were displayed so that they would become familiar with a product launch campaign. Leo submitted that displaying the product information to internal employees was a genuinely non-promotional activity and complied with the Code.

Leo explained that access to its offices was controlled and no visitor could enter the premises unattended as documented in the company's Site Security policy. In this specific instance, the complainant attended the Leo office as a prospective employee for a Kyntheum role and not as a member of the public. In that regard, it would not be inappropriate for that prospective employee to have access to internal product related materials relevant to his/her role. Leo denied a breach of Clause 26.1.

Leo submitted that based on email records and discussions with the cross-functional team, internal communication activities in relation to the materials in question were initiated after Kyntheum received its marketing authorization. Leo noted that there was a 'Kyntheum countdown clock' in the staff coffee area as part of the pre-launch internal activities. The complainant had not stated when he/she attended the Leo office. However, regardless of the date of attendance, given the materials at issue were on display after the grant of the marketing authorization, there had been no breach of Clause 3.

The claim that Kyntheum was 'well tolerated' was factual, balanced, in line with the marketing authorization and supported by clinical evidence. Leo noted that 'generally well tolerated' was included in certified materials that were pre-vetted by the MHRA and thus it denied breaches of Clauses 7.2 and 7.4.

Leo stated that it followed that there were no breaches of Clauses 9.1 and 2.

With regard to the allegation that it had promoted Kyntheum to the public, Leo reiterated that the materials at issue were displayed within the private, secure offices of Leo within the staff coffee/breakout area only. Leo did not consider that that area was 'an open waiting room' and it was not intended or designed for visitors. There was a small waiting area adjacent to the coffee area but Leo had no record of

Kyntheum materials being displayed in this space. Leo stated that it could not address the complainant's allegation on this point without the photograph taken but added that members of the public had never had unrestricted access to the secure Leo offices. It would be physically impossible for them to see the materials in the offices.

Leo explained that its offices were on the second floor of a building in the countryside with no form of unrestricted public access. The building housed different companies (including Leo) with a common reception/waiting area on the ground floor. Post, packages and the like were dropped off at reception and visitors would report to the reception staff at this initial entry point into the building. Any visitor with a legitimate pre-arranged business purpose within the Leo office was announced by telephone to their Leo contact. Visitors were then collected from reception by Leo staff and were accompanied to a specific area within the Leo offices on the second floor.

Leo noted that entry to its office was only possible through two doors, both of which required staff security passes to access. The offices were laid out such that the formal meeting rooms were grouped together at one end of the second floor with their own coffee/refreshment area. Most visitors would be shown to a room in the meetings area, away from the open plan office and staff coffee area which were not designed or intended primarily for the use of visitors. Therefore, there had been no promotion to the public and Leo denied a breach of Clause 26.1.

Leo submitted that the marketing authorization for Kyntheum was granted on 17 July 2017 and, according to email records and discussion with the cross-functional team, the internal communications activities relating to the materials in question were initiated on 25 July. Leo thus denied a breach of Clause 3.

Furthermore, the materials referred to by the complainant had never been intended for promotion to the public, as alleged. All materials on display were intended solely for the purpose of internal communications, as part of an internal Leo campaign to engage staff throughout the organisation in the forthcoming launch of Kyntheum.

Leo stated that it had maintained high standards as the materials at issue were submitted for technical review and certification, for internal display to office staff. Information stating 'for internal use only, not for distribution' was included on all pieces. The materials were part of an internal communications campaign; they and were not excessive in number and contained different information to fully reflect a complex new product.

Kyntheum was the first biologic medicine launched by Leo and so it was even more relevant that all employees had a reasonable technical understanding of this new complex medicine as part of building the company's capabilities and expertise. The purpose of the materials was to ensure staff understood, were engaged and educated in the work being undertaken by a cross-functional team in preparation for the Kyntheum launch. That ensured that all staff, regardless of function, recognised the need to prioritise support for the launch.

Leo submitted that the manner of internal communication was common and routine practice in the pharmaceutical industry. It was legitimate to provide business information to current employees which might relate to existing medicines and those not yet marketed. The material on display had never been exhibited to the public.

Leo noted that the complainant described him/herself both as a member of the public and as a prospective Leo employee for a Kyntheum related role. It was therefore clear that his/her visit to Leo's offices was for a defined purpose. Leo did not consider it unacceptable for a prospective employee to have access to a normal day in the life of Leo at its offices, including any internal displays at the time, in particular, those relevant to his/her prospective role. Leo submitted that was in line with Clause 26.2.

The material in question was neither intended nor deliberately shared with any member of the public.

In summary, Leo reiterated that the material at issue was displayed in a private and secure office and directed at Leo employees for the legitimate purpose of internal engagement and familiarisation with a product launch campaign. All the information in question was displayed after the UK marketing authorization had been granted and so for that reason, and the others stated above, Leo denied a breach of Clause 3.

The material at issue had never been visible to the general public and, as stated above, there were multiple safety checks to control access to Leo's offices. The complainant attended the Leo office as a prospective employee and thus he/she did not meet the definition of a general member of the public. For that reason and all the others stated above, the company did not accept a breach of Clause 26.1.

Signatory oversight was maintained over the content and audience for the material at issue, which were marked 'For Internal Use Only'. Leo standards had been sufficiently high with clear controls and policies over visitor access, as described to prevent such an occurrence as alleged. In this regard and for the detailed reasons set out above, Leo denied breaches of Clauses 9.1 and 2.

In relation to the claim that Kyntheum was 'well tolerated' and the occurrence of suicides in the clinical trials, Leo submitted that the claims included in the materials at issue were substantiated by extensive clinical trial data in the summary of product characteristics (SPC) and were not misleading. The claim 'well tolerated' was intended to convey that the adverse event profile of Kyntheum was acceptable for routine clinical use in indicated patients.
The efficacy and safety of Kyntheum was assessed in 4,373 adult plaque psoriasis patients across three multi-national, randomised, double-blind, phase 3, placebo-controlled clinical trials (AMAGINE-1,

AMAGINE-2, and AMAGINE-3 (Lebwohl *et al* 2015 and Papp *et al* 2016). AMAGINE-2 and AMAGINE-3 were also active comparator (ustekinumab)-controlled (Lebwohl *et al* 2015). All three trials included a 12-week placebo-controlled induction phase, a double-blind duration of 52 weeks, and an open-label long-term extension. The week 12 PASI 100 response rates were significantly higher with 210mg of brodalumab than with ustekinumab (44% vs 22% [AMAGINE-2] and 37% vs 19% [AMAGINE-3], P<0.001) (Lebwohl *et al* 2015).

In the AMAGINE-2 and 3 studies, 97% of patients completed the 12-week induction schedule which was comparable to the adherence rates of placebo (97.1%, 95.6%) (Lebwohl *et al* 2015).

A recent published systematic review and meta-analysis of the safety and efficacy of Kyntheum stated that there was 'an acceptable safety profile and a robust efficacy in the treatment of moderate-to-severe plaque psoriasis' (Attia *et al* 2017). Another review demonstrated that the pooled proportion of patients who experienced adverse events at 12 weeks in all three studies was 57.6% among patients taking Kyntheum 210mg and 51.0% among patients on placebo (Farahnik *et al* 2016).

The most commonly reported adverse reactions in all Kyntheum treated patients were arthralgia (4.6%), headache (4.3%), fatigue (2.6%), diarrhoea (2.2%) and oropharyngeal pain (2.1%) (SPC).

Leo stated that suicidal ideation and behaviour (SIB) was not a listed adverse event in the SPC. The SPC stated 'suicidal ideation and behaviour, including completed suicide, have been reported in patients treated with Kyntheum. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour has not been established'. Leo stated that psoriasis had profound psychosocial implications and suicidal ideation had been reported in as many as 17.3% of patients (Lebwohl *et al* 2017). Moreover, treatment with Kyntheum improved anxiety and depression scores significantly from baseline in 73% and 67% of patients with moderate to severe psoriasis respectively (Papp *et al*). A higher patient satisfaction and quality of life was observed with Kyntheum compared with placebo. As determined by DLQI [Dermatology Life Quality Index] response rate, 56-61% of patients receiving Kyntheum achieved a DLQI of 0 or 1 indicating that psoriasis no longer impacted their lives at week 12 compared with 5-7% of patients receiving placebo (Lebwohl *et al* 2017).

In the Kyntheum development programme as a whole across 5 different therapeutic indications, six cases of completed suicide were identified, during 10,438 patient-years of follow-up exposure in 6,243 patients (FDA briefing document and Valeant sponsor's briefing document 2016). Of the six completed suicides, four were in the psoriasis program (during 9161.8 patient-years of follow-up exposure, one of which was later adjudicated as an indeterminate case) and one each in the psoriatic arthritis and rheumatoid arthritis programs (FDA briefing document and Valeant sponsor's briefing document 2016). The rate of completed suicides in the psoriasis program for Kyntheum (0.04 in 100 patient-years) was comparable with the rate reported from clinical trials for apremilast (0.052-0.062), secukinumab (0.034) and across all psoriasis trials (0.028) (Valeant sponsor's briefing document 2016).

Leo considered that Kyntheum had demonstrated good efficacy and a clinically acceptable safety profile and so it denied a breach of Clauses 7.2 and 7.4.

Leo reiterated that the material at issue was reviewed and certified and it submitted that its standards had been sufficiently high in this regard and for the detailed reasons set out above, denied a breach of Clauses 9.1 and 2.

Leo provided details of the materials on display and referred to by the complainant which included a Kyntheum Stand (ref MAT-10201) and launch poster (ref MAT-10447).

Summary

Leo stated that it had demonstrated that it took its responsibilities for compliance with the Code very seriously and always remained committed to adhering to the Code and all applicable regulations in its business activities.

The activity in question was entirely for internal purposes with a view to educate and engage employees in the launch of a new medicine. This was a legitimate business activity and common place in the pharmaceutical industry.

The materials in question were on display after the marketing authorization had been granted and thus the company did not accept a breach of Clause 3. The entire activity was undertaken within a private and secure area of Leo's offices with no intent to promote to the public. The materials at issue were displayed in the staff coffee area. The complainant described him/herself as a prospective employee for a role working on Kyntheum. In the course of his/her interview related interactions with Leo it was not inappropriate for him/her to have had access to internal materials. Leo submitted that it had no evidence to suggest that a member of the public had been exposed to this information in its offices. Leo thus did not accept there had been a breach of Clause 26.1.

Based on clinical trial evidence, Leo considered that the claim that Kyntheum was 'well tolerated' was factually correct, not misleading and based on robust scientific evidence as outlined above. The company thus did not accept that there had been a breach of Clause 7.2 and 7.4.

Maintaining high standards and compliance with the Code and all applicable regulations was of utmost importance to Leo. Signatory oversight and copy approval process were applied to the material at issue in order to ensure their content and audience were appropriate. The company did not accept there

had been breaches of Clauses 9.1 and 2 in regard to this entirely legitimate internal business activity.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure stated that anonymous complaints would be accepted but that, like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant could not be contacted for more information.

The Panel noted Leo's submission that the materials referred to by the complainant were intended solely for the purpose of internal communications, as part of an internal campaign to engage staff throughout the organisation in the forthcoming launch of Kyntheum. Leo had submitted that the materials at issue were displayed within Leo's private, secure countryside-based offices within the staff coffee/breakout area only. The Panel noted that Leo's offices were on the second floor and access to its offices was controlled; the only people who had access were Leo staff and visitors accompanied by a Leo staff member. The Panel noted Leo's submission that visitors would be shown to a room in the meetings area, away from the open-plan office and staff coffee area where the materials at issue were displayed.

The Panel considered that it was not necessarily unacceptable for a company to display product material within the confines of its offices, but such displays in areas routinely accessed by visitors, or even viewed by passers-by, needed to be appropriate. In the Panel's view, companies had to be aware of the impact and impression such material could have on visitors and the messages that might be conveyed. The Panel considered that if a visitor had seen the material at issue, they would be very aware that the company was shortly to launch a new product.

The Panel noted that the complainant had attended Leo's office to interview for a role working on Kyntheum. The Panel noted that the supplementary information to Clause 26.2 stated that information about pharmaceutical companies provided to current or prospective employees might relate to both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. The Panel noted Leo's submission that the marketing authorization for Kyntheum was granted on 17 July 2017 and, according to email records and discussion with the cross-functional team, the internal communication activities relating to the materials in question were initiated on 25 July; the materials at issue were therefore only on display after Kyntheum's marketing authorization had been received. In these circumstances, it was not unreasonable for a prospective employee when interviewing for a position which involved working with Kyntheum to see internal communications on the product. In these circumstances, the Panel considered that there was no evidence to support the complainant's allegation that Leo had promoted Kyntheum to the public prior to the grant of its market authorisation as alleged. No breach of Clauses 3.1, 26.1, 9.1 and 2 were ruled.

The Panel noted its comments above with regard to Clause 26.2 that information provided to current or prospective employees must be factual and presented in a balanced way. The Panel noted the complainant's concern that Kyntheum was described in the material at issue as 'well-tolerated' when a number of patients in trials in the US had committed suicide. The Panel noted that Section 4.4, Special Warnings and Precautions for use of the Kyntheum SPC, stated that suicidal ideation and behaviour, including completed suicide, had been reported in patients treated with Kyntheum. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour had not been established. The SPC advised that the risk and benefit of treatment with Kyntheum should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms. Patients, care givers and families should be advised of the need to be alert for such and if a patient suffered from new or worsening symptoms of depression and/or suicidal ideation or behaviour was identified it was recommended to discontinue treatment with Kyntheum. The Panel noted that suicidal ideation/behaviour was not listed as an adverse event in Section 4.8 of the SPC. The Panel further noted Leo's submission that in the Kyntheum development programme as a whole across five different therapeutic indications, six cases of completed suicide were identified during 10,438 patient-years of follow-up exposure in 6,243 patients. The Panel noted that the study authors in Farahik *et al* 2016, a review of phase III trials, stated that two completed suicides in AMAGINE-2 did not necessarily constitute a causal relationship especially given that patients with psoriasis were already at higher risk for depression, suicidal ideation, attempt and completed suicide.

The Panel noted the narrow nature of the allegation and that the complainant bore the burden of proof. The Panel did not consider that the complainant had established, on the balance of probabilities, that describing Kyntheum as well-tolerated was misleading or could not be substantiated due to the number of trial patients that had committed suicide and no breach of Clauses 7.2 and 7.4 were ruled.

During its consideration of this case the Panel noted that one of the items at issue (ref MAT-10201) included an apparently naked man who was sitting on an underground train seat between other passengers and holding an A3 newspaper which covered his upper thigh to his mid-chest. The supplementary information to Clause 9.1 stated that the use of naked or partially naked people for the purpose of attracting attention to the material or the use of sexual imagery for that purpose was unacceptable. The Panel did not consider that the imagery was sexual. It was of course not unacceptable to show bare skin when advertising

medicines for prescribing so long as the image was relevant and complied with the Code, including Clause 9.1. The quality and appearance of a patient's skin was relevant to the product. However the Panel considered that it was the subject's nakedness in a social setting which had the primary and immediate visual impact and was designed to draw attention to the material. The Panel queried whether the visual complied with the supplementary information to Clause 9.1 and requested that Leo's attention be drawn to this matter.

Complaint received **3 October 2017**

Case completed **8 February 2018**

CASE AUTH/2988/10/17

EMPLOYEE v OTSUKA

Use of LinkedIn to promote medicines

An anonymous, contactable complainant who described themselves as an employee of Otsuka Pharmaceuticals (UK), complained about a medical science liaison (MSL) employee's use of LinkedIn.

The complainant referred to the unethical activity and attitude of the MSL employee. The complainant stated that for the last six months, the employee had promoted unlicensed medicines. The complainant provided examples including in relation to Equelle (s-equol and soy isoflavones).

The complainant noted that the individual had over 300 followers on LinkedIn nearly all of whom were UK based.

The complainant alleged that a LinkedIn message, posted by the employee in May 2017 promoted tolvaptan, a prescription only medicine to the public and included a link which sent the reader to an article containing favourable data for tolvaptan (Jinarc) on a website called '4 traders'.

The complainant alleged that the senior member of staff with oversight of MSLs should not have posted promotional material to members of the public.

The complainant submitted that the posting of tolvaptan data raised two issues. Firstly, that posting favourable study results from Phase 3 data of a licensed prescription only medicine was in breach of the Code and secondly, the linked clinical study stated that 'trial enrolees were adults aged 18 to 65 with ADPKD-induced chronic kidney disease between late stage 2 to early stage 4'. In that regard, the complainant noted that two matters arose from the Jinarc summary of product characteristics (SPC) which related to the serious situation of promoting the unlicensed use and indication to members of the public.

Firstly, that the SPC stated that 'the safety and effectiveness of tolvaptan in ADPKD patients aged over 50 years has not yet been established' and secondly, the study included patients that were at the enhanced stage of CKD 4. Otsuka was thus promoting an unlicensed medicine to the public. The indication was limited to use in adults with chronic kidney disease stages 1 to 3.

In addition, the complainant submitted that the employee promoted brexpiprazole on LinkedIn by sending readers to an article which noted that the medicine had been accepted for review by the European Medicines Agency (EMA) for use in adults with schizophrenia. The article informed the reader that the medicine was licensed in a number of countries (US, Canada, under different named brands) and that if approved, the brand name in the EU would be Rxulti. The complainant alleged that this pre-licence advertising clearly breached the Code.

Finally, the complainant noted that the employee advertised Equelle, a non-hormonal supplement that purported to manage menopause symptoms, on LinkedIn. The article promoted to both patients and health professionals and stated 'Equelle is the product of fermentation of whole, non-GMO soy germ using a patented and proprietary process by the Otsuka Pharmaceutical Co., Ltd. The process results in the conversion of the daidzein to S-equol. Equelle tablets, created under current Good Manufacturing Practices, are clear coated and free of gluten, dairy, magnesium stearate and talc. Suggested patient use is two Equelle tablets daily, one tablet taken in the morning and one tablet at night, which provide the standardized dose of 10 mg of S-equol. Clinicians interested in ordering Equelle were invited to do so …' and contact details were provided.

The complainant alleged that the employee had brought the industry into disrepute in breach of Clause 2.

The detailed response from Otsuka is given below.

The Panel noted that the complaint concerned postings made by an employee on his/her personal LinkedIn account which Otsuka stated were made without its knowledge or approval.

The Panel noted that the individual in question had over 300 followers and at least some of these were members of the public. The Panel noted the company's submission that none of the articles had been provided to the employee by Otsuka. The employee had sourced the material and proactively shared it. The Panel noted however that this implied that the source material for the postings were entirely independent of Otsuka and that was not so. It appeared to the Panel that the tolvaptan and brexpiprazole articles reproduced Otsuka global press releases. Nonetheless, there was no evidence before the Panel that the company had encouraged their dissemination or that the UK company had any role in their creation. The Panel noted that the LinkedIn postings by a company employee each highlighted positive and newsworthy material about the company's products and thus the LinkedIn postings came within the scope of the Code.

In relation to the posting headed 'Otsuka: Announces Results of Phase 3 Data on Tolvaptan Under Development for ADPKD in US', linked to an article which bore the same title published on a financial website the Panel noted that the article bore the post script 'Otsuka Holdings Co Ltd published this content on 22 May 2017 and is

solely responsible for the information contained therein'. The article appeared to be a reproduction of an Otsuka global press release. The article discussed positive study results. The Panel noted Otsuka's submission that there was a significant possibility that some of the followers were not health professionals. The Panel considered that the proactive dissemination of the article to the employee's followers on LinkedIn constituted promotion of a prescription only medicine to the public. A breach of the Code was ruled as acknowledged by Otsuka.

The Panel noted Section 4.2 of the Jinarc SPC stated that the safety and effectiveness of tolvaptan in ADPKD patients over 50 years has not been established and that it was indicated for use in adults with ADPKD patients with CKD stage 1 to 3 at initiation of treatment. The Panel noted that study patients referred to in the article were 18 to 65 years of age with ADPKD- induced chronic kidney disease between late stage 2 to early stage 4. The Panel noted the promotional use of the article and considered that the article was inconsistent with the SPC on each of these points and a breach of the Code was ruled. The Panel considered that for the same reason the article was misleading and in breach of the Code.

The Panel considered that the promotional dissemination of the article by posting a link to it was such that the certification requirements were triggered as accepted by Otsuka. The LinkedIn posting including the article had not been certified and a breach of the Code was ruled. Similarly, the required prescribing information was not provided and a breach of the Code was ruled.

The Panel considered that the proactive dissemination of positive study results by an employee to all his/her LinkedIn followers was clearly promotional and did not consider that it was in any way a disguised promotional act. No breach of the Code was ruled.

The Panel considered there was no evidence that Otsuka had arranged or paid for the article to be published on the independent financial website such that the article was similar to sponsored material. The complainant had not established that a declaration of sponsorship ought to be on the original article and no 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 ruled no breach of the Code as the complainant had not raised a matter which related to meetings, hospitality and associated sponsorship. In relation to the complainants' allegation that the activities breached the definition of promotion. It was not capable of being breached *per se*. The Panel ruled no breach of the Code.

The Panel noted that the LinkedIn post was done by an individual employee using their own account and without the knowledge or authority of Otsuka. The Panel considered that Otsuka had been badly let down by its employee. Nonetheless, the Panel did not consider that this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use. The company had the requisite policies in place and the employee had been trained. No breach of Clause 2 was ruled.

The Panel noted that the employee had also posted a link to an article published on an external financial website headed 'H Lundbeck A/S: Lundbeck and Otsuka's brexpiprazole for adult patients with schizophrenia accepted for review by the EMA'. The Panel noted that the article referred to the fact that the EMA was expected to complete its review in the second quarter of 2018, and that it was already approved in the US and Canada. The article referred briefly to positive clinical data. The Panel noted its comments above about the conduct of the employee and Otsuka's responsibilities. The Panel considered that the proactive dissemination of the article to the employee's followers on LinkedIn constituted promotion of a prescription only medicine to the public. A breach of the Code was ruled. The Panel noted that brexpiprazole had been promoted prior to the grant of its licence and a breach of the Code was ruled. The Panel considered that the complaint on this point did not raise a matter, which related to meetings, hospitality and associated sponsorship, no breach of the Code was ruled.

The complainant also raised concerns about a link posted by the employee to an article published on a news wire headed 'NEW to the United States: Equelle, a non hormonal supplement clinically shown to help ease menopause symptoms' which discussed the availability of the product in the US and clinical data. The Panel noted Otsuka's submission that Equelle was not a prescription only medicine and therefore ruled no breach of the Code.

An anonymous, contactable complainant who described themselves as an employee of Otsuka Pharmaceuticals (UK) Ltd, complained about a named medical science liaison (MSL) employee's use of LinkedIn.

COMPLAINT

The complainant referred to the unethical activity and attitude of the MSL employee in question and the Authority's guidance on digital communications. The complainant stated that for the last six months, the employee in question had continued to promote medicines marketed by Otsuka Pharmaceuticals but unlicensed in the UK. The complainant was unable to prove the verbal messaging and instructions the employee had given to others in communicating this unlicensed information but provided three examples with evidence, of the employee's thinly veiled promotional activity to the public, in breach of the letter and spirit of the Code. The complainant particularly identified his/her example below in relation to Equelle (s-equol and soy isoflavones) as an action against the spirit of the Code.

The complainant noted that the employee currently had over 300 followers on LinkedIn nearly all of whom were UK based.

The first example provided by the complainant was a LinkedIn message, posted by the employee in May 2017. The post promoted tolvaptan (Jinarc), a prescription only medicine to the public and included a link which sent the reader to an article containing favourable data for tolvaptan on a financial website.

The complainant noted that in his/her LinkedIn profile, the employee stated that he/she undertook the day-to-day strategic and operational oversight of a team of people across various therapeutic areas and was responsible for, *inter alia*, the medical strategy planning by identifying key areas of focus and ensuring that this focus was undertaken in an efficient, strategic and highly scientific and compliant manner. The employee also claimed accountability for continuous development as well as training, leading, coaching and managing the team in collaboration with medical leadership. The complainant alleged that the senior member of staff in charge of actual operational oversight of MSLs should have been aware of the correctness of not posting promotional positive data to members of the public via LinkedIn.

The complainant stated that the posting of tolvaptan data raised two issues. Firstly, that posting favourable study results from Phase 3 data of a licensed prescription only medicine was in breach of the Code and secondly, the linked clinical study stated that 'trial enrolees were adults aged 18 to 65 with ADPKD-induced chronic kidney disease between late stage 2 to early stage 4'. In that regard, the complainant noted that two matters arose from the Jinarc (tolvaptan) summary of product characteristics (SPC) which related to the serious situation of promoting the unlicensed use and indication to members of the public.

The complainant's first concern was that the SPC stated that 'the safety and effectiveness of tolvaptan in ADPKD patients aged over 50 years has not yet been established' and secondly that the SPC stated that the product was for use in CKD 1 to 3 only whereas the study included patients that were at the enhanced stage of CKD 4. Otsuka was thus promoting an unlicensed medicine to the public. The indication was limited to use in adults with chronic kidney disease stages 1 to 3.

The complainant alleged breaches of Clauses 1.2, 2, 3, 4, 7, 9.1, 9.10, 12, 14, 22 and 26 of the Code.

In addition to the above, the complainant set out what he/she described as less detailed examples of breaches of the letter and spirit of the Code below. The complainant submitted that the employee promoted brexpiprazole on LinkedIn by sending readers to an article which noted that the medicine had been accepted for review by the European Medicines Agency (EMA) for use in adults with schizophrenia. The article informed the reader that the medicine was licensed in a number of countries (US, Canada, under different named brands) and that if the EMA approved the licence the brand name in the EU would be Rxulti. The complainant alleged that this pre-licence advertising by the employee clearly breached Clauses 3, 22 and 26 of the Code.

Finally, the complainant noted that in October the employee advertised Equelle on LinkedIn, a non-hormonal supplement that purported to manage menopause symptoms. The article posted on LinkedIn promoted to both patients and health professionals; the article stated 'Equelle is the product of fermentation of whole, non-GMO soy germ using a patented and proprietary process by the Otsuka Pharmaceutical Co., Ltd. The process results in the conversion of the daidzein to S-equol. Equelle tablets, created under current Good Manufacturing Practices, are clear coated and free of gluten, dairy, magnesium stearate and talc. Suggested patient use is two Equelle tablets daily, one tablet taken in the morning and one tablet at night, which provide the standardized dose of 10 mg of S-equol. Clinicians interested in ordering Equelle were invited to do so via [a named website]'.

The complainant stated that he/she had also shown another Otsuka (Japan) piece which the employee highlighted to Otsuka UK staff.

The complainant alleged that the employee's blatant promotion to patients and clinicians was against the spirit of the Code. The complainant noted that the employee referred, in LinkedIn, to having passed the ABPI Medical Representatives Examination. The complainant alleged that the employee boasted about his/her knowledge of the Code but that he/she had clearly shown no respect for it and had brought the industry into disrepute in breach of Clause 2.

RESPONSE

Otsuka stated that it expected the highest standards of ethical and professional behaviour, and compliance with the Code from all of its employees. It therefore took this complaint extremely seriously; it was disappointed that the complainant was a current employee given that the company promoted an open and transparent culture in which employees were encouraged to speak-up about compliance concerns either through internal channels or through an external speak-up facility. This was an area the company was committed to working on further in light of this complaint.

Otsuka submitted that following receipt of the complaint and appreciating the extremely serious nature of it, the morning after the complaint was received:

- the highlighted posts were removed from the personal LinkedIn account
- assurances were obtained from the employee that there were no other such posts on any other social media platforms
- other actions were taken pursuant to Otsuka's policies
- Otsuka's social media policies were re-circulated to all UK employees with online retraining for all to be undertaken by 16 November. That training would include a test that required a 100% pass rate with scenarios such as posting company information on social media

In addition to the above:

- a company meeting was conducted on 15 November to retrain staff on the social media policy and to highlight the external speak-up facility
- there would be face-to-face training in December where staff would be further retrained on the Otsuka social media policies as well as the PMCPA guidance on digital communications. This training would also highlight the external speak-up facility and employees would be encouraged to use this facility if they were concerned about compliance within the organisation
- Code training materials would also be updated to include a specific section on social media.

Otsuka submitted that it was committed to ensuring compliance with both the spirit and letter of the Code. The company had a comprehensive set of policies and standard operating procedures (SOPs) which reflected the requirements of the Code and all employees were promptly trained on the policies relevant to their role and responsibilities when first employed by Otsuka and at regular intervals thereafter. Social media was recognised as an area that needed specific attention in order to ensure compliance and all UK employees were trained on a specific European policy.

Otsuka noted that the employee in question joined the company in early 2017; he/she currently had a small number of direct reports. The employee was up-to-date on all training including the Code, business ethics and compliance, social media and the policy relating specifically to his/her role. Details of the training courses undertaken by the employee were provided.

Otsuka provided copies of its Group Global Policy for Use of Social Media (version 4) and European Policy EU-POL-ALL-004 'Social Media Policy' (version 3) and the associated test. The test required a good understanding of the principles behind ensuring compliance when using social media. Otsuka noted that the employee completed training on the most recent version of this policy in September 2017 and had passed the associated mandatory test. Section 3.2 'General Principles Regarding Producing and Sharing Information Online' of the European policy clearly stated 'Region Europe employees must not comment on or post information via personal social media channels that relate or refer to medicines or devices provided by Otsuka'. It also stated 'All social media activities initiated by Region Europe employees via professional social media channels must not link or refer to any pharmaceutical product or medical device, pre- or post-launch'.

Otsuka also provided a European policy document relevant to the employee's role which clearly stated that 'Discussions and activities must be conducted in the spirit of contributing to the practice of medicine, maintaining trusted peer-to-peer relationships and enhancing patient best care. They must therefore be non-promotional in content and tone nor seek to promote the administration, consumption, prescription, purchase, recommendation, sale, supply or use of Otsuka medicines ...'. Section 3.5.4 stated that relevant staff were prohibited from engaging in off-label discussions with health professionals except in response to unsolicited requests in one-to-one situations or in discussions relating to investigator sponsored studies.

With regard to the materials posted by the employee, Otsuka noted that they had all been taken from external websites. Otsuka submitted that Equelle was not a prescription only medicine. With the Equelle posting there was a further screen shot from the Otsuka Japan website. However, none of the material was provided to the employee by Otsuka. The materials had been sourced externally by him/her and proactively shared on his/her LinkedIn profile in clear contravention of Otsuka's social media policies.

Otsuka stated that as part of ongoing internal investigation, the employee had categorically confirmed that she did not give any instructions to his/her team about the materials which were the subject of this complaint.

There was no certificate approving the materials as these had not been provided to the employee by Otsuka.

Otsuka stated that as noted above, it had clear guidance and training about the use of social media. The activities in question were not conducted on the instructions of Otsuka; the materials posted by the employee on his/her LinkedIn profile had not been provided by Otsuka. The employee's activities clearly contravened the relevant Otsuka policies as well as the Otsuka Group Global Code of Business Ethics.

In relation to the specific clauses cited in the complaint, Otsuka acknowledged:

Clause 1.2: The activities of the employee unintentionally, but, in effect, promoted three Otsuka products to his/her LinkedIn followers; it was possible that many of these were not health professionals.

Clause 3: Two of the LinkedIn posts in question mentioned either an unlicensed medicine (brexpiprazole) or highlighted data not in accordance with the EU marketing authorisation (Jinarc (tolvaptan)).

Clause 4: Prescribing information was not provided for what was in effect, although unintended, promotional material. There was also no adverse event statement included with the material.

Clause 7: As set out above, the employee's activities unintentionally but, in effect, promoted three Otsuka products to his/her LinkedIn followers. There was the possibility that many of these were not health professionals. Otsuka acknowledged that the LinkedIn posts did not meet the quality standards of Clause 7.

Clause 9.1: The employee's activities clearly failed to maintain high standards.

Clause 26: These activities were unintended as, but in effect, promoted prescription only medicines to the employee's LinkedIn followers. There was a significant possibility that some of these followers were not health professionals, therefore there was a significant chance that prescription only medicines were advertised to the public.

Otsuka noted, however, that in respect of each of the above clauses, whilst the individual was an Otsuka employee, his/her activities in question were not initiated, sanctioned or authorised by the company; indeed, they were in direct contravention of Otsuka's SOPs and policies. As soon as these activities were highlighted, the posts were removed from LinkedIn, assurances were received that no other such posts existed, other action was taken and the social media policies were recirculated to all Otsuka employees. A company meeting had been held to retrain staff on the social media policy and to highlight the external speak-up facility. All employees would also be further retrained on the Otsuka social media policies as well as the PMCPA guidance on digital communications at a face-to-face meeting in December. This training would reiterate the external speak-up facility and employees would be encouraged to use this facility if they had compliance concerns within the organisation. Code training materials would also be updated to include a specific section on social media.

Clause 9.10: Otsuka did not consider that there had been any breach of Clause 9.10 (Declaration of Sponsorship). These activities were not conducted at the request of Otsuka.

Clause 12: As set out above, the employee's activities were not conducted at the request of Otsuka and were in direct contravention of company policies and SOPs. The employee shared data about Otsuka's products from external websites without realising that this, in effect, promoted those products. However, Otsuka considered that this material, whilst in effect promotional, was not disguised.

Clause 14: Whilst Otsuka acknowledged that the employee's activities had, in effect, promoted three of the company's products, the majority of the materials posted were from external websites and all were shared on the employee's own LinkedIn profile without the authority or knowledge of Otsuka and indeed, in direct contravention of company policies and SOPs. As such, this material was not, and would not be, certified by and on behalf of Otsuka.

Clause 22: Otsuka noted that Clause 22 concerned 'Meetings, Hospitality and Sponsorship'. As there was no meeting, hospitality or sponsorship in connection with this complaint, the company did not consider that Clause 22 was relevant.

Clause 2: Otsuka recognized that a breach of Clause 2 required particular censure, ie when activities or materials associated with promotion brought discredit upon, or reduced confidence in, the pharmaceutical industry. However, the company hoped that in light of the circumstances of this complaint, as summarised below, the Panel would conclude that there had not been a breach of Clause 2.

Conclusion

Otsuka acknowledged that the employee's activities, and the materials posted by him/her on LinkedIn had breached a number of clauses of the Code and included, in effect, promotion of an unlicensed medicine or indication, and to members of the public, which were significant breaches of the Code.

However, Otsuka again noted that it took ethics and compliance extremely seriously and had put in place comprehensive and robust policies and SOPs upon which all employees were regularly trained.

In this instance, despite comprehensive training, including a test with a similar scenario to this instance, a single employee, who was relatively new to Otsuka, had acted independently in a way that was in breach of both the Code and Otsuka's own policies and SOPs by three times sharing material from external websites with his/her followers on LinkedIn. These issues were not initiated, sanctioned or authorised by Otsuka.

Once notified of this complaint, Otsuka acted swiftly to ensure that the materials in question were immediately removed from LinkedIn and obtained assurances that they were not available on any other social media sites. Other action had been taken. Otsuka had also reissued its social media policies to all employees with all employees having already undertaken further training on the policies at a company meeting in November 2017. Face-to-face training would also be conducted in December 2017 on social media policies and the PMCPA guidance on digital communications. Employees would also be reminded about the external speak-up facility in case of compliance concerns. Code training would also be updated to include a specific section on social media.

Otsuka noted that while it acknowledged that the employee's activities were in breach of the Code which it deeply regretted, this was without the authorisation of Otsuka. Otsuka had taken, and continued to take, all reasonable measures to ensure that employees were appropriately trained in the use and management of social media to prevent such instances occurring and had acted quickly to remove the materials and take appropriate measures once it had been notified of the complaint.

Otsuka stated that it had alerted all Otsuka employees to the fact that it had received a complaint about the use of social media. The company had mandated that all employees promptly confirm in writing that none of their personal social media accounts contained posts about Otsuka products.

Otsuka submitted that it was not possible for it or any other pharmaceutical company to actively and comprehensively monitor its employees'

social media accounts. The training that Otsuka provided on compliance with the Code and the Otsuka social media policy was extensive and set out very clear guidance around acceptable use of personal social media accounts. This complaint concerned one employee who, despite being made aware of the requirements of Otsuka's policies and being trained on them, contravened clear and strict internal policies and various clauses of the Code. This was being dealt with appropriately through an internal investigation. The immediate re-training of all Otsuka UK employees was part of a series of steps that would be taken to avoid this happening again in the future. This would be reinforced by a face-to-face meeting in December 2017 for all Otsuka Pharmaceuticals UK Ltd employees where there would be comprehensive training on social media, the Code, PMCPA guidance on digital communications and the Otsuka policy and SOPs.

PANEL RULING

The Panel noted that the complaint concerned postings made by an employee on his/her personal LinkedIn account which Otsuka stated were made without its knowledge or approval.

The Panel noted that LinkedIn was different to some other social media platforms in that it was a business and employment-orientated network and was primarily although not exclusively associated with an individual's professional heritage and current employment and interests. In the pharmaceutical industry the Panel noted that an individual's followers on LinkedIn might, albeit not exclusively, be directly or indirectly associated with the healthcare industry. In the Panel's view it was of course not unacceptable for company employees to use personal LinkedIn accounts. The Code would not automatically apply to postings on a personal account however such postings might potentially be covered by the Code and the company be found responsible for postings by an employee. Whether the Code applied to such a posting should be decided on a case by case basis taking into account all of the circumstances including the nature of the material disseminated, any product references, the company's role if any in relation to the creation or availability of the material posted, whether such posting was directed, encouraged or otherwise acquiesced to by the company. The status and role of the employee might also be relevant.

The Panel noted that Clause 26.1 prohibited the promotion of prescription only medicines to the public. Clause 26.2 permitted information about prescription only medicines to be supplied directly or indirectly to the public but such information must be factual and presented in a balanced way. The quality standards in Clause 7 also applied to information provided to the public.

The Panel noted that in particular junior employees were often keen to link to senior employees and thus all employees should be mindful of the impression given about the acceptability of matters posted. In the Panel's view companies should give unambiguous guidance to help ensure that such forums were not used by employees in a way that was potentially within the scope of and inconsistent with the Code, particularly Clause 26.
The Panel noted that the employee in question had over 300 LinkedIn followers. Otsuka accepted that at least some of these were members of the public. The Panel noted the company's submission that none of the articles had been provided to the employee by Otsuka and all had been taken by the employee in question from external websites. The employee had sourced the material and proactively shared it. The Panel noted, however, that this implied that the source material for the postings were entirely independent of Otsuka and that was not so. It appeared to the Panel that the tolvaptan and brexpiprazole articles reproduced Otsuka global press releases. Nonetheless, there was no evidence before the Panel that the company had encouraged their dissemination or that the UK company had any role in their creation. The Panel noted that the LinkedIn postings by a company employee each highlighted positive and newsworthy material about the company's products and thus the LinkedIn postings came within the scope of the Code.

In relation to the posting headed 'Otsuka: Announces Results of Phase 3 Data on Tolvaptan Under Development for ADPKD in US', linked to an article which bore the same title published on a financial website the Panel noted that the article bore the post script 'Otsuka Holdings Co Ltd published this content on 22 May 2017 and is solely responsible for the information contained therein'. The article appeared to be a reproduction of an Otsuka global press release. The article discussed positive study results. The Panel noted Otsuka's submission that there was a significant possibility that some of the followers were not health professionals. The Panel considered that the proactive dissemination of the article to the employee's followers on LinkedIn constituted promotion of a prescription only medicine to the public. A breach of Clause 26.1 was ruled as acknowledged by Otsuka.

The Panel noted Section 4.2 of the Jinarc SPC stated that the safety and effectiveness of tolvaptan in ADPKD patients over 50 years has not been established and that it was indicated for use in adults with ADPKD patients with CKD stage 1 to 3 at initiation of treatment. The Panel noted that study patients referred to in the article were 18 to 65 years of age with ADPKD- induced chronic kidney disease between late stage 2 to early stage 4. The Panel noted the promotional use of the article and considered that the article was inconsistent with the product's licence on each of these points and a breach of Clause 3.2 was ruled. The Panel considered that for the same reason the article was misleading and in breach of Clause 7.2.

The Panel noted that the article had not been certified. The Panel did not know whether the use of the original press release which appeared to have been issued by the global company came within the scope of the UK Code. It was not the subject of complaint. The Panel considered that the promotional dissemination of the article by posting a link to it was such that the certification requirements

were triggered as accepted by Otsuka. The LinkedIn posting including the article had not been certified in accordance with Clause 14.1 and a breach of that Clause was ruled. Similarly, the required prescribing information was not provided and a breach of Clause 4.1 was ruled.

In relation to Clause 12.1 the Panel considered that the proactive dissemination of positive study results by a company employee beyond the company to all his/her LinkedIn followers was clearly promotional and did not consider that it was in any way a disguised promotional act. No breach of Clause 12.1 was ruled.

The Panel noted that the complainant had not set out why the LinkedIn post including the article was in breach of Clause 9.10. The Panel considered that it was clear that the link to the article had been posted by an Otsuka employee. Whilst the article apparently reproduced a global press release that Otsuka global was responsible for there was no evidence that Otsuka had arranged or paid for the article to be published on the independent financial website such that the article was similar to sponsored material. Nonetheless, the Panel had decided that the company was responsible for the employee's decision to disseminate the article on LinkedIn. The complainant bore the burden of proof. The complainant had not established that a declaration of sponsorship ought to be on the original article and no breach of Clause 9.10 was ruled.

The Panel noted its rulings above of breaches of the Code and considered that high standards had not been maintained; a breach of Clause 9.1 was ruled.

The Panel ruled that there was no breach of Clause 22 which related to meetings, hospitality and associated sponsorship. In relation to the complainants' allegation that the activities breached Clause 1.2 the Panel noted that Clause 1.2 was a statement of principle and set out the definition of promotion. It was not capable of being breached *per se*. The Panel ruled no breach of Clause 1.2 as it considered that it was not applicable; no breach of that Clause was ruled.

The Panel noted that the LinkedIn post was done by an individual employee using their own account and without the knowledge or authority of Otsuka. The Panel considered that company employees ought to be cautious when using social media in areas which impinged on their professional role or the commercial interests of their company. As stated above companies should give clear and unambiguous guidance in this regard. The Panel noted that the Otsuka Group Global Policy for Use of Social Medial stated that in using social media, Otsuka Group companies and their employees were required to observe local laws, regulations, code and the like. The policy applied to social media activities, regardless of whether such activities were done for personal reasons or on behalf of the company, during work time or personal time and whether inside or outside of the workplace. The Panel noted that the Europe Social Media Policy stated that employees must not comment on or post information via personal social media channels that relate or refer to medicines or devices provided by Otsuka. The policy also stated that employees who engaged with Otsuka-related social media activities via personal social media accounts should only do so if, *inter alia*, the content did not mention or refer to medicines or products. The employee had completed training on this Policy (version 2) in February 2017 and (version 3) in September 2017, on each occasion passing the associated mandatory test. The company thus had a policy in place that should have prevented the employee from posting such material on LinkedIn. The complainant had stated that the posting in question was made in May 2017. The Panel noted that the employee in question had joined the company earlier that year. The Panel further noted that the Medical Science Liaison Policy also stated that MSLs were prohibited from engaging in off-label discussions with health professionals except in response to unsolicited requests and in discussions related to investigator initiated studies. The Panel considered that Otsuka had been badly let down by its employee. Nonetheless, the Panel did not consider that this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use. The Company had the requisite policies in place and the employee had been trained. No breach of Clause 2 was ruled.

The Panel noted that the employee had also posted a link to an article published on an external financial website headed 'H Lundbeck A/S: Lundbeck and Otsuka's brexpiprazole for adult patients with schizophrenia accepted for review by the EMA' and alleged breaches of Clauses 3, 22 and 26. The Panel noted that the article referred to the fact that the EMA was expected to complete its review in the second quarter of 2018, and that it was already approved in the US and Canada. The article referred briefly to positive clinical data. The Panel noted its comments above about Clause 26, the conduct of the employee and Otsuka's responsibilities. The Panel considered that the proactive dissemination of the article to the employee's followers (over 300) on LinkedIn constituted promotion of a prescription only medicine to the public. A breach of Clause 26.1 was ruled. The Panel noted that brexpiprazole had been promoted prior to the grant of its licence and a breach of Clause 3.1 was ruled. The Panel considered that the complaint on this point did not raise a Clause 22 matter, which related to meetings, hospitality and associated sponsorship, no breach of that Clause was ruled.

The complainant also raised concerns about a link posted by the employee to an article published on a news wire headed 'NEW to the United States: Equelle, a non hormonal supplement clinically shown to help ease menopause symptoms' which discussed the availability of the product in the US and clinical data. At the end, after ordering details, and information about another company, information about Otsuka was provided and readers invited to visit its global website. The Panel noted that unlike the previous matters the complainant had not cited clauses of the Code specific to this link. The complainant did state that his/her concerns about promoting a prescription only medicine to the

public applied to all three matters and referred to the spirit of the Code in relation to Equelle. The Panel noted Otsuka's submission that Equelle was not a prescription only medicine and therefore ruled no breach of Clause 26.1.

The complainant also provided a copy of a page from Otsuka's global Japanese website about Equelle. The Panel noted that this page did not appear to have been posted on LinkedIn but noted the complainant's allegation that the employee had highlighted it to UK staff. The Panel noted that the complainant bore the burden of proof and had not provided any evidence to show that this had occurred or explained why such activity would be in breach of the Code. Otsuka had not responded to this point. The Panel made no ruling as it did not consider that it had a valid complaint in this regard.

Complaint received **31 October 2017**

Case completed **31 January 2018**

ANONYMOUS NON-CONTACTABLE v PFIZER AND BRISTOL-MYERS SQUIBB

Meeting arrangements

An anonymous, non-contactable complainant referred to two evening meetings held by Pfizer and Bristol-Myers Squibb Pharmaceuticals at a named restaurant in April and October 2017.

The complainant was concerned that the educational meetings were not held in a private room; only a thin curtain separated the health professionals from the diners in the restaurant and so members of the public could hear the content of the talk. The complainant understood this was in breach of the Code.

The complainant explained that several times during the course of both evenings, a member of the Pfizer team asked members of the public in the restaurant to be quiet as their conversations were becoming too loud and raucous and could be heard over the speaker.

The complainant added that several GPs stated that the only reason for attending the meeting was for the food and unlimited supply of drinks.

The complainant stated that he/she valued the education provided by pharmaceutical companies but felt that on these two occasions the companies had let themselves down.

The detailed response from the companies are given below.

The Panel noted that the entrance to the private dining area was described as a heavy curtain. The floorplan provided showed that the main dining area was approximately 8 metres away. It appeared, although it was not entirely clear, that the bar / service point opposite the entrance to the private dining room was not a standalone social area but rather the point from which waiters would collect food and drink. The Panel was concerned that it appeared that members of the public would have to walk past the curtain to use the toilet facilities. It noted Pfizer's submission that the speaker was situated at the far end of the room and did not use any audio projection system and that there was background music in the dining area. It also noted that at the October meeting only, Pfizer requested that restaurant staff speaking loudly outside the private meeting room reduce their noise. Background noise from this meeting was referred to in a delegate's feedback form. This was contrary to the complainant's assertion that a similar request at each meeting was made to members of the public. At the very least it was clear that an unacceptable level of external noise had been heard albeit for a limited period in the private meeting room. The Panel noted that it had not been provided with feedback forms for the April meeting. However noting the burden of proof the Panel did not consider that the complainant had established on the balance of probabilities that members of the public had heard the presentation. The Panel therefore considered that prescription only medicines had not been promoted to the public and ruled no breach of the Code.

The Panel noted that in relation to the April meeting a drink was offered on arrival and a second drink was permitted alongside the main course. On each occasion the companies submitted that the majority of delegates chose a soft drink. The Panel did not have an itemised copy of the bill but noted the company's submission that the overall cost of food and drink at the meeting was around £1200, excluding the service charge and the cost per head was £36.11 which included £11.11 per head spent on drinks including coffees. The Panel noted the status of the complainant described above and considered that the complainant had not established that the level of hospitality was unacceptable as alleged. No breach was ruled.

In relation to the October meeting the Panel noted that the arrangements were similar. Again the Panel did not have an itemised copy of the bill. The overall cost of food and drink was £575, a cost of £38.33 per head including £8.90 per head on drinks excluding coffees. The Panel similarly considered that the complainant had not established that the level of hospitality was unacceptable as alleged. No breach was ruled.

Noting its rulings above the Panel considered that there was no evidence that high standards had not been maintained nor that Clause 2 had been breached and no breaches of the Code were ruled included Clause 2.

An anonymous, non-contactable complainant referred to two evening meetings held by Pfizer Limited and Bristol-Myers Squibb Pharmaceuticals Limited at a named restaurant in April and October 2017.

COMPLAINT

The complainant stated that he/she was concerned that the educational meetings were not held in a private room; only a thin curtain separated the health professionals from the diners in the restaurant and so members of the public could hear the content of the talk. The complainant understood this was in breach of the Code.

The complainant explained that several times during the course of both evenings, a member of the Pfizer team asked members of the public in the restaurant to be quiet as their conversations were becoming too loud and raucous and could be heard over the speaker.

The complainant added that several GPs stated that the only reason for attending the meeting was for the food and unlimited supply of drinks.

The complainant stated that he/she was not aware of all the employees present but he/she named three who were at the meeting.

The complainant stated that he/she valued the education provided by pharmaceutical companies but felt that on these two occasions the companies had let themselves down.

When writing to Pfizer and Bristol-Myers Squibb, the Authority asked them to consider the requirements of Clauses 2, 9.1, 22.1 and 26.1.

RESPONSE

Bristol-Myers Squibb stated that the second meeting held in October was held on a different date to that stated by the complainant. Pfizer responded to the substantive complaint on behalf of both companies and submitted that it organised the meetings on behalf of the Bristol-Myers Squibb/Pfizer Alliance. Employees of both companies attended the meeting in April but only Pfizer employees attended the one in October.

Pfizer explained that the restaurant at issue, the venue for both meetings, was on a dual carriageway between two large towns, giving easy access for meeting attendees from both areas. There was ample free parking for attendees and a private meeting room to accommodate up to 70.

The private meeting room was in a distinctly separate part of the restaurant and at a distance from the main public dining area (a floor plan was provided). The private meeting room was separated from the restaurant entrance and bar/service area by a solid wall and a heavy duty curtain which was closed all the time during the course of the speaker presentations. The curtain was only opened to allow food to be brought into the meeting room. The speakers delivered their presentations, without any audio projection system, from a position in the meeting room which was furthest from the curtain.

There was background music in the public dining area throughout the duration of the meeting. The venue arrangements were such that it was not possible for the expert speaker presentations and discussions to be heard by those in the public dining area.

Pfizer stated that at neither meeting did it or Bristol-Myers Squibb ask those in the public dining area to be quiet. The distance between the public dining area and the meeting room was such that noise made by the other diners would not disturb those in the meeting room. At the October meeting Pfizer politely requested that the restaurant staff supporting the meeting reduce their noise, as they were talking loudly directly outside the meeting room.

Pfizer submitted that the meeting room arrangements described above provided appropriate and sufficient separation from the main public dining area to ensure that prescription only medicines were not advertised to the public.

In April 2017, GPs, practice nurses and a small number of aligned secondary care specialists working in the area were invited by the local Pfizer sales team to attend a promotional speaker meeting, 'Atrial Fibrillation: Stroke and How to Prevent it – Stroke Prevention in NVAF [nonvalvular atrial fibrillation] Case Studies'. A promotionally certified educational presentation of 78 slides was presented by a local expert who went on to lead an interactive discussion on two relevant case studies which was also supported by a promotionally certified slide deck.

Twenty six health professionals attended the meeting together with two staff each from Pfizer and Bristol-Myers Squibb and the guest speaker; 31 attendees in all. The attendees arrived at the restaurant between 6.45pm and 7.30pm and were offered a drink on arrival. As the venue was only accessible by car, the majority of attendees ordered a soft drink. The first course of a 2 course set menu was served before the start of the presentation with the main course being served, after completion of the presentation, case studies and question and answer session. Jugs of water were available on the table throughout the meal and a second drink from the bar was offered when the main course was served; the majority again selected a non-alcoholic drink. The restaurant bill was settled at 9.34pm and attendees left the restaurant between 9.45pm and 10pm.

Pfizer stated that the overall cost of food and drink provided at the April meeting was £1119.36 to which a ten percent service charge was added due to the large number of meeing attendees. This represented a cost per head of £36.11, excluding the service charge, and hospitality was appropriate and secondary to the education provided.

In October 2017, GPs, practice nurses and a small number of aligned secondary care specialists working in the area were invited by the local Pfizer sales team to attend a promotional speaker meeting. 'Modern Management in Primary Care: A Case Study of Non-Valvular Atrial Fibrillation'. A promotionally certified presentation of 84 slides was presented by a recognised local expert. 12 health professionals attended the meeting together with two of Pfizer's staff and the guest speaker ie 15 in all.

Invited health professionals arrived at the restaurant between 7pm and 7.30pm and the meeting and the meal followed the same format as in April. Again the majority of attendees selected a non-alcoholic drink. Attendees had all left the restaurant by 10pm

and the restaurant bill was settled at 10.20pm. The overall cost of food and drink was £575 ie £38.33 per head. Pfizer submitted that this level of hospitality was appropriate and secondary to the education provided.

Pfizer submitted that the restaurant's location and facilities provided an appropriate venue in which to host the two meetings. The hospitality provided was reasonable and secondary to the significant, high quality educational content delivered by the expert speakers. The costs involved did not exceed the level which attendees would adopt if paying for themselves. The arrangements for both meetings were therefore consistent with the requirements of Clause 22.1.

In conclusion Pfizer stated:

- The proposed arrangements for the meetings, including the venue and hospitality, were checked against the Code and approved in-house ahead of commencing planning of the meeting.
- The meetings were legitimate educational events, delivered by recognised experts with fully certified content.
- The actual costs of the hospitality provided at the meetings were reasonable and did not exceed the level which attendees would adopt if paying for themselves. The hospitality was secondary to the educational agenda and fell well below the Code limit.
- The meeting room arrangements provided appropriate and sufficient separation from the main public dining area to ensure that prescription only medicines were not advertised to the public.

Pfizer submitted that high standards were maintained throughout the planning and delivery of these promotional speaker meetings and the activities and materials associated with these meetings had not brought discredit upon, or reduced confidence in, the industry.

In response to a request for further information Pfizer provided a photograph of the restaurant bill and credit card receipt for the meeting held in April. Pfizer submitted that the photograph confirmed that the total bill of £1231.30 was settled by credit card at 9.34pm. Pfizer noted that an enclosure provided with its previous response detailed that the two course set menu cost £25 per head with drinks costing £11.11 per head. A 10% service charge was added to the bill due to the large number of attendees.

Pfizer also provided a photograph of the restaurant bill and credit card receipt for the meeting held in October. Pfizer submitted that the photograph confirmed that the total bill of £575 was settled by credit card at 10:22pm. Pfizer noted that an enclosure provided with its previous response detailed that the two course set menu cost £25 per head with an additional spend of £2.40 per head for vegetarian starter dishes. Drinks cost £8.90 per head and coffees £2.90. [After the completion of this case Pfizer advised that the cost of coffee worked out at £2.00 per head. The Authority noted that Pfizer had previously submitted the cost of coffee was £2.90 and in a subsequent response described the cost of tea and coffee as £2.50.] No service charge was added to this bill due to the lower number of meeting attendees.

Pfizer confirmed no payments associated with the two meetings were made using the representative's cash floats.

In response to a further request for information Pfizer provided copies of the speaker meeting form for the meetings. The form was completed by the Pfizer employee who planned the meeting and by completing the form confirmed that the details provided were accurate and the line manager signed the form to confirm that he/she believed the meeting arrangements to be appropriate and compliant with the Code and company SOPs. The speaker meeting form must be completed and approved before any meeting plans could be progressed.

Pfizer provided a copy of a document which provided specific details and guidance on hospitality at Pfizer organised meetings and sponsored third party meetings. The policy allowed one alcoholic drink, such as a glass of wine or beer, to be provided to accompany a meal at the evening meeting. Pfizer colleagues received regular training on its policies and processes associated with meetings and hospitality.

Pfizer explained that the staff at the restaurant had extensive experience hosting pharmaceutical company meetings and were very familiar with the restrictions on hospitality that applied to the industry. Many of the companies that used the restaurant, like Pfizer, had a one alcoholic drink per attendee policy and the restaurant staff were used to working to that limit. Pfizer employees responsible for organising the meetings confirmed that on both occasions they briefed the restaurant staff on management of drinks during the meetings prior to the attendees arriving. Restaurant staff were instructed to serve drinks by the glass and not to serve spirits or bottles of wine and not to serve meeting attendees at the bar. On arrival each delegate was approached by a member of the restaurant staff and a drink order taken, a second drink order was taken approximately two hours later at the end of the speaker presentations. Jugs of water were available on the table throughout both meetings and coffee and tea was offered at the end of the meals.

Pfizer submitted that a detailed breakdown of the drinks consumed was not available however the two Pfizer employees that were at both meetings confirmed that there was no inappropriate alcohol consumption. The restaurant was not accessible by foot and therefore the majority of attendees drove to the meetings. A small number of beers were ordered as a first drink at both meetings with the remaining drinks ordered being soft drinks such as orange juice mixed with lemonade and Lassi (a traditional Indian yoghurt drink). No wine was served at either meeting. The relevant sections of the restaurant drinks menu were provided and the restaurant confirmed that a soft drink such as orange or pineapple juice mixed with lemonade was charged at £4.00 and a glass of Lassi £3.95. Details of the prices of the types of drinks that were consumed

at both meetings were provided including tea and coffee at £2.50.

Pfizer identified an average cost per head for drinks of £11.11 at the April meeting. Pfizer confirmed, based on the prices detailed in the table above and discussions with the Pfizer employees at the meeting, that the attendees either had two soft drinks and a coffee or in some cases a large beer, a soft drink and a coffee. The speaker and Pfizer employees had additional soft drinks ahead of the meeting starting.

At the meeting in October, £134.00 was spent on drinks (excluding coffees). This represented an average cost of £8.90 per head. The Pfizer employees recalled five large and one small beer being ordered on arrival with all other drinks ordered being soft drinks. Pfizer submitted that again, based on the prices detailed above and discussions with the Pfizer employees at the meeting it confirmed that attendees had either one beer and a soft drink or two soft drinks. As with the meeting in April, the speaker and Pfizer colleagues had additional soft drinks during the evening.

The restaurant provided a different meeting host for each of the meetings and Pfizer believed that the lack of differentiation between the food and drinks bill for the April meeting reflected the different approach of the meeting host supporting that particular meeting.

Pfizer submitted that through its discussions with the employees responsible for organising the meetings and its reconciliation of the restaurant drinks prices with the final bill, Pfizer could find absolutely no evidence of unlimited or an inappropriate supply of alcoholic drinks.

Pfizer submitted that whilst it was not able to demonstrate exactly what each individual attendee drank at the meetings it found no evidence to suggest that inappropriate amounts of alcohol were consumed at either meeting. Pfizer reiterated that both meetings had significant high quality educational content, delivered by two respected experts in the field. Pfizer strongly refuted the suggestion that some GPs were only at the meeting for the food and unlimited supply of drinks. The complaint letter suggested that the complainant was an attendee at both meetings; however the meeting attendee lists indicated that only two health professionals attended both meetings and Pfizer submitted that it had no reason to believe that either of these attendees were unhappy with any of the arrangements for the meetings giving them cause to complain. Anonymous feedback was collected from all 12 health professional attendees at the 11 October meeting and the collated comments which were provided indicated that the attendees found the meeting to be highly educational and well organised. If an attendee had felt that any of the arrangements were inappropriate they had an opportunity to provide that feedback directly to Pfizer. The feedback provided by the attendees did not support the allegation that the 'only reason for attending the meeting was for the food and unlimited supply of drinks'.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure for the Prescription Medicines Code of Practice Authority stated that anonymous complaints would be accepted but that like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant could not be contacted for more information.

Clause 26.1 prohibited the promotion of prescription only medicines to the public. The Panel noted the complainant's allegation that at each meeting members of the public could hear the presentation. The Panel noted that the floorplan showed that to access the meeting room one had to walk to the end of the entrance corridor, past a waiting area. The entrance to the private dining area was over 3 metres from what was described as the bar/service area. To the right of the entrance to the private dining area was the toilet facility. The private dining area was separated from the entrance and waiting areas by a solid wall. The entrance to the private dining area was described as a heavy curtain. The floorplan provided showed that the main dining area was approximately 8 metres away. It appeared, although it was not entirely clear, that the bar/service point opposite the entrance to the private dining room was not a standalone social area but rather the point from which waiters would collect food and drink. The Panel considered that it was not necessarily unacceptable for an entry to a private dining area to be a heavy curtain as described, however the arrangements had to comply with the Code. In the particular circumstances of this case the Panel was concerned that it appeared that members of the public would have to walk past the curtain to use the toilet facilities. It noted Pfizer's submission that the speaker was situated at the far end of the room and did not use any audio projection system and that there was background music in the dining area. It also noted the company's submission that at the October meeting only, Pfizer politely requested that restaurant staff speaking loudly outside the private meeting room reduced their noise. Background noise from this meeting was referred to in a delegate's feedback form. This was contrary to the complainant's assertion that a similar request at each meeting was made to members of the public. At the very least it was clear that an unacceptable level of external noise had been heard albeit for a limited period in the private meeting room. The Panel noted that it had not been provided with feedback forms for the April meeting. However noting the burden of proof the Panel did not consider that the complainant had established on the balance of probabilities that members of the public had heard the presentation. The Panel therefore considered that prescription only medicines had not been promoted to the public and ruled no breach of Clause 26.1.

In relation to the hospitality the Panel noted that Clause 22.1 provided that hospitality must be strictly limited to the main purpose of the event and secondary to the purpose of the meeting ie subsistence only. The level of subsistence must be appropriate and not out of proportion to the occasion. The costs involved must not exceed that level which participants would normally adopt when paying for themselves. The cost of the meal, including drinks must not exceed £75 per person excluding vat and gratuities.

The Panel noted that in relation to the April meeting a drink was offered on arrival and a second drink was permitted alongside the main course. On each occasion the companies submitted that the majority of delegates chose a soft drink. The presentation, case studies and Q & A session took place before the main course and after the starter. The Panel did not have an itemised copy of the bill/ receipt but noted the company's submission that the overall cost of food and drink at the meeting was £1119.36, excluding the service charge and the cost per head was £36.11 which included £11.11 per head spent on drinks including coffees. In this regard the Panel noted that the cost of individual drinks might be described as high, noting for example that the venue charged £4.00 for a non-alcoholic soft drink with a mixer such as orange and lemonade. The Panel noted the status of the complainant described above and considered that the complainant had not established that the level of hospitality was unacceptable as alleged. No breach of Clause 22.1 was ruled.

In relation to the October meeting the Panel noted that the arrangements were similar. All attendees had left the restaurant by 10 pm. Again the Panel did not have an itemised copy of the bill. The overall cost of food and drink was £575, a cost of £38.33 per head including £8.90 per head on drinks including coffees [At the completion of the case Pfizer pointed out an error by the Panel as £8.90 excluded the cost of coffees]. The Panel similarly considered that the complainant had not established that the level of hospitality was unacceptable as alleged. No breach of Clause 22.1 was ruled.

Noting its rulings above the Panel considered that there was no evidence that high standards had not been maintained. No breach of Clause 9.1 was ruled. Similarly the Panel considered that there was no evidence that Clause 2 had been breached and no breach of that Clause was ruled accordingly.

During its consideration of this case the Panel noted that the companies were unable to provide itemised evidence about alcohol consumption and considered that companies would be well-advised to request that relevant details were itemised on bills etc.

Complaint received **13 November 2017**

Case completed **17 January 2018**

COMPLAINANT v NAPP

Asthma review service

A complaint was received about the activities of Napp Pharmaceuticals in relation to its asthma review service.

Napp's product Flutiform (fluticasone and formoterol) was indicated in the regular treatment of asthma where use of combination product (an inhaled corticosteroid (ICS) and a long-acting beta 2 agonist (LABA)) was appropriate.

The complainant was concerned about the conflict of interest in the offering of pharmacists for asthma/ diabetes reviews for quality outcome framework (QOF). The complainant alleged that he/she had heard from a number of customers that companies such as Napp doing this favoured its products and put patients on these without taking into consideration the preferences of the nurses or patients. In one particular case, a nurse noted that the Napp pharmacist had moved the majority of her patients on to Flutiform and the patients were not happy.

The detailed response from Napp appears below.

The Panel noted that therapy review services were permitted and their acceptability as far as the Code was concerned depended on a number of factors including the arrangements, how and to whom the service was offered.

The Panel noted Napp's submission that whilst it funded the pharmacist-led service, the choice of therapy remained the decision of the GP, and offering of the service was not conditional on the prescribing of any Napp product.

The Panel noted that there were a number of ICS/ LABA combinations on the market. The Panel had some concerns about how the services were offered and whether all the features of the services amounted to a clinical assessment of patients. With regard to the complainant's view that a 'Napp pharmacist' had moved the majority of patients to Napp's product Flutiform without taking into consideration the preferences of the nurses or patients, the Panel noted that it was not necessarily a breach of the Code not to take into account the nurses or patients preferences if the GP or other prescriber considered otherwise. The Panel noted that the complainant bore the burden of proof and had provided no evidence to support his/her allegation. The Panel therefore ruled no breaches of the Code based on the narrow allegation including Clause 2.

A complaint was received about views of asthma patients referring to the activities of Napp Pharmaceuticals Limited.

Napp's product Flutiform (fluticasone and formoterol) was indicated in the regular treatment of asthma where the use of combination product (an inhaled corticosteroid (ICS) and a long-acting beta 2 agonist (LABA)) was appropriate.

COMPLAINT

The complainant stated that he/she wanted to raise concerns for the conflict of interest going on currently in the pharmaceutical industry – specifically in the offering of pharmacists in practice to aid with asthma/diabetes reviews for quality outcome framework (QOF). Whilst this used to be a practice happily provided by the pharmaceutical industry, the complainant alleged it now presented a significant conflict of interest with the companies putting patients on to their products. The complainant stated he/she had heard from a number of customers that companies such as Napp doing this favoured Napp products and put patients on these, and did not take in to consideration the preferences of the nurses or patients. In one particular case, a nurse noted that the Napp pharmacist had moved the majority of her patients on to Flutiform and the patients were not happy.

The complainant queried how this practice was allowed in the industry? If all were being held accountable for their actions, surely this was a conflict of interest?

In writing to Napp attention was drawn to the requirements of Clauses 2, 9.1, and 19.2 of the Code.

RESPONSE

Napp submitted that it took the Code very seriously and conducted its business in a responsible, ethical and professional manner at all times. Napp submitted that its pharmacist led asthma therapy review service was entirely consistent with Clause 19 of the Code. The reviews were not switch services and importantly it had received two previous complaints about the conduct of the therapy review services, neither of which were upheld by the Panel – Case AUTH/2808/12/15 and Case AUTH/2956/5/17.

Napp contracted three third-party providers of therapy review services and details were provided. The reason why Napp had two pharmacist-led services and a nurse-led service was as a result of health professional feedback that some GP practices preferred a therapy review to be undertaken by nurses whilst others preferred this to be led by a pharmacist. The Napp asthma therapy review services were both designed, organised and conducted in the same way, differing only by the use of either pharmacists or nurses to deliver the service.

Napp absolutely refuted that its therapy review services constituted a medicine switch as it was not conducting the reviews to put patients on Napp products as suggested by the complainant. The majority of the patient reviews did not result in a new medicine being prescribed. Instead the patient had a structured review, including the following:

- asthma assessment
- taught optimal asthma inhaler technique
- clinical examination, or their existing inhaler dose optimised
- compliance/education on non-adherence
- stop existing medicine
- lifestyle advice (triggers etc).

Clause 19 medical and educational goods and services (MEGS) clearly explained that a therapeutic review 'is a legitimate activity for a pharmaceutical company to support and/or assist'. Thus, the complainant was incorrect that this was a 'conflict of interest'. Napp was not involved in the reviews either directly or indirectly and did not stipulate that its product should be recommended. The briefing documents for the service providers stated:

> 'pharmacists will only implement therapeutic review services and will not:
>
> - Recommend a specific pharmaceutical product
> - Write prescriptions
> - Recommend or take any action that does not comply with the practice treatment protocol.'

Napp submitted that whilst it funded the service, therapy choice arising from the patient clinical review process remained the decision of the GP, and offering of the service was not conditional on the prescribing of any Napp product.

The comprehensive reviews were not primarily conducted for QOF. Rather they were primarily to enhance patient care and benefit the NHS. The reviews ensured that patients were receiving optimal treatment, both non-medicinal and/or medicinal. This was made clear in the certified protocols, briefing documents and training materials.

With regard to the complainant's view that 'I have heard from a number of my customers that companies such as Napp doing this favour Napp products and put patients on these, and do not take in to consideration the nurses preference or the patients', Napp submitted that the complainant was correct that several pharmaceutical companies provided asthma therapy review services to the NHS. The pharmacists were employed by Napp's providers, so were not 'Napp pharmacists'. The complainant did not make it clear who specifically were his/her 'customers', were they GP practices, doctors, nurses or other? A therapy review service could not favour any medicine (ie a Napp product) and the prescribing decision remained clearly with the patient's prescriber, which was usually a GP, or could be a qualified nurse-prescriber. The protocol documents made this clear, and were aligned to Clause 19. The protocol stated '… pharmacists do not suggest and will not implement switch services which simply change a patient from one medication to another without a full clinical assessment'.

Napp submitted that the service model (details provided) clearly indicated that all decisions and signatures were made by the lead GP:

The introduction to the service stated:

> 'The clinician responsible for the care of his/her patients retains full control over the entire process. NAPP supports this non-promotional service in full accordance with the ABPI Code of Practice for the Pharmaceutical Industry. The arrangements for a therapy review must enhance patient care, or benefit the NHS and maintain patient care.
>
> Whilst the service is funded and organised on behalf of Napp Pharmaceuticals Limited, therapy choice arising from the patient review process remains the choice and sole decision of the lead GP, and offering of the service will not be conditional on the prescribing of any Napp products or services.'

The service model for the second service provider (details provided) highlighted that the GP decided on any patient interventions:

The introduction to the service stated:

> '… pharmacists will only engage in the provision of services which enhance patient care or benefit the NHS and maintain patient care. Whilst the service is funded and organised on behalf of Napp Pharmaceuticals, therapy choice arising from the patient review process remains the choice and sole decision of the GP, and offering of the service will not be conditional on the prescribing of any Napp products or services.'

Therefore, Napp submitted it was clear that a 'Napp pharmacist' (they were employees of Napp's third party providers, and not Napp) could not make a prescribing decision (as clearly stated in the therapy review protocols) and so could not, as the complainant suggested, move the 'majority of her patients on to flutiform'. The 'one particular case' was not supported by any evidence as part of the allegation and Napp was unable to comment further unless more detail was provided. This practice was clearly not allowed in the pharmaceutical industry as it would be against Clause 19, and by association would not maintain high standards (Clause 9.1), and ultimately bring the industry into disrepute (Clause 2). Napp again refuted that it had conducted a switch programme disguised as a therapy review service.

Napp had received confirmation from both providers that they had received no complaints from any practices or patients about a change to their medicine following an asthma therapy review.

Napp provided details of the pharmacist-led asthma therapy review services.

There were 11 certified documents (through ZINC) detailing the asthma therapy review service by one provider on behalf of Napp. There were 10 certified documents (through ZINC) detailing the asthma therapy review service by the other provider.

The pharmacist-led asthma therapy review services were offered to GP practices which were selected based upon clear criteria, (identical for both providers).

Practice selection criteria

In order to deliver the maximum patient and practice benefit the following practices may benefit most from the service:

1. Practices in high areas of asthma prevalence or where high levels of variation in care exist in comparison to other CCGs/practices within their own locality.
2. Practices lacking a trained respiratory nurse specialist.
3. Practices requiring additional resource to effectively review their asthma population.'

Napp submitted that as its therapy review service was not a switch programme, it did not therefore collect data on the 'proportion of patients at each practice who have been switched to flutiform/other Napp products'.

Details of when the service commenced and the number of practices were provided.

Napp did not monitor any uplift in sales in areas where the therapy review services had been conducted. Neither were representatives' bonuses based on this service to the NHS. The company did not include any planned or future asthma therapeutic reviews in the calculations used to determine the sales targets, did not incentivise staff based on these reviews and no individual sales person's target was affected by the asthma reviews. A respiratory senior scientific advisor oversaw the service as this was a non-promotional role within the Napp medical department and he/she had regular contact with the service provider, along with provision of a management report to discuss any operational issues. The report was discussed within Napp's medical and code compliance department which allowed the company to ensure that the service providers were offering the service in accordance to the provision of MEGS as set out in Clause 19.2.

The briefing document specified the dos and don'ts for account managers in terms of non-promotional vs promotional calls as represented by a flow diagram. The Q&A section of this document specified that once a therapeutic review was in progress in a practice, account managers were not allowed to discuss the asthma review service with any of the health professionals in that practice. It also detailed the requirements of the therapeutic review service in accordance with the Code.

Napp account business managers (ABMs) and healthcare development managers (HDMs) were the only people allowed to discuss the therapeutic review service in detail in a non-promotional call once a practice had expressed interest following the brief introduction.

The ABMS and HDMs were all trained face to face according to the detailed information in the training slides including a specific briefing document for the ABMs/HDMs which included:

> 'You may introduce the service by giving a brief description of the service during the promotional call but may not instigate a detailed description about the service at the same time as a call when products are being promoted, this should be done in a non-promotional call.
>
> **You should ensure the following is adhered to:**
>
> - Napp support of this review must **NOT** be dependent on the customer prescribing a Napp product. This must be neither the fact in practice nor the impression given either verbally or in any documents connected with the project, internal or external
> - The prescribing of specific products must **NOT** be linked to the service either in conversation, or in writing, with any customer
> - Detailed discussion about the service must **NOT** be initiated at the same time as a call at which products are promoted.'

In addition, following the comprehensive training, the ABMs/HDMs received a validation test before any introduction of this service to practices and they had to score 100%.

Napp submitted that the service providers' pharmacists were all trained in asthma management and associated national asthma guidelines. The pharmacists were given a comprehensive briefing document on the conduct of the asthma therapy reviews, including compliance and pharmacovigilance.

All pharmacists involved in the therapy review delivery were qualified, registered, members of the relevant governing body (the General Pharmaceutical Council (GPhC) for England, Scotland and Wales and the Pharmaceutical Society of Northern Ireland (PSNI) and as such bound by their own standards of conduct, ethics and performance. The standards helped to ensure patients using pharmacy services received safe and effective care.

In conclusion, Napp strongly refuted all allegations about the provision of a pharmacist-led asthma therapy review service as a 'conflict of interest'. It submitted that it had provided comprehensive evidence that it had robust and compliant processes and training to implement a genuine high quality non-promotional therapeutic review service via its third party suppliers. Two previous Napp cases had been scrutinised and no breaches of the Code were ruled in relation to the nurse-led (Case AUTH/2808/12/15) or pharmacist-led (Case AUTH/2956/5/17) services. Integral to this non-promotional service to the NHS, the company submitted it had continued to pay particular focus on Clauses 19.1 and 19.2. It had continued to

maintain high standards as per Clause 9.1, and this activity had not brought discredit upon, or reduced confidence in the pharmaceutical industry as per Clause 2.

PANEL RULING

The Panel noted Napp's submission that it had received two previous complaints about the conduct of its therapy review services and no breaches of the Code had been ruled. The Panel noted that it could only rule based on the evidence provided by both parties in relation to the specific allegations made. Each case was considered on its own merits. The previous complaints were about aspects of how the services were used or offered rather than the actual services.

Previous cases

The Panel's ruling in Case AUTH/2808/12/15 in relation to the ORCA therapy review service included that 'Whilst some concerns were outlined the Panel did not consider that the complainant in that case had proved his complaint on the balance of probabilities. The Panel did not consider that there was any evidence before it to demonstrate that the service as implemented was included in individual sales targets or was only offered where a switch was guaranteed as alleged. The Panel thus ruled no breach of Clauses 18.1 and 19.1. Subsequently no breach of Clauses 9.1 and 2 were also ruled'.

In Case AUTH/2956/5/17 the Panel noted there were differences since it considered Case AUTH/2808/12/15. The documents provided in Case AUTH/2956/5/17 were dated between September and December 2016. There was no indication whether the materials had simply been changed to reflect the new pharmacist-led service or other changes had been made. The Panel had to consider the service in relation to the allegations about the promotional materials which focussed on switching patients to Flutiform. The Panel noted Napp's submission that account managers, including the complainant, were only allowed to introduce the service briefly and in accordance with the briefing document. Napp had further submitted that the complainant received a live 1 hour, on-line WebEx training on the new pharmacist-led review service and process. This was a 'virtual' face-to-face training which included a Q&A session and a follow-up briefing document to further clarify the process which specified the dos and don'ts for account managers in terms of non-promotional vs promotional calls and to which was attached the service introduction document. Napp noted that the complainant acknowledged that he had read and understood the briefing document. The Q&A stated that once a therapeutic review was in progress in a practice, account managers were not allowed to discuss the asthma review service with any of the health professionals in that practice. The briefing included relevant requirements from the Code. The Panel noted Napp's submission that the complainant was not informed when these service nurses or pharmacists would be within his target surgeries because there were no therapy review services within his entire region during the time he was employed. The Panel further noted that the complainant was informed by his manager not to introduce the therapy review service and if he did so it was against instruction.

The Panel noted that a briefing document, the training slides for account managers and the material provided by the complainant set out what discussions could take place in a promotional call and a non-promotional call. The promotional call flow diagram covered two possible situations for customers which had agreed to switch, firstly where there was no request for assistance and secondly where assistance was requested. In both situations no therapeutic review would be offered. The flow diagram for the non-promotional call whereby the health professional had an interest in therapeutic review, the service introduction document was to be used and the practice referred to the ABM/HDM. The Panel did not consider the training materials were sufficiently clear given that the main promotional message for account managers was for a switch to take place. In addition, leavepieces promoting the switch were to be left at the end of the call. There was no flow diagram or other instructions in the training material for the situation when the service was briefly introduced during a promotional call. It was not clear from the briefing documents for account managers or ABMs/HDMs that if a practice had agreed to switch, the service could not be offered in that practice even in a subsequent non-promotional call by the account manager or an ABM/HDM. However, this did not necessarily mean that the therapy review service offered by Napp was linked to the promotion of Flutiform as alleged. The Panel noted its comments and rulings above and although concerned about the relationship between the promotional messages about switching and the service which provided resource to change patients' medication including to Napp's product Flutiform, it did not consider that the complainant had shown on the balance of probabilities that the arrangements failed to meet the requirements of Clause 19.2. The Panel therefore ruled no breach of Clause 19.2. The Panel did not consider that the complainant had provided evidence that in pursuit of sales, Napp's compliance and briefing on switches from the ABM were very lax as alleged. The Panel consequently ruled no breach of Clauses 9.1 and 2.

Case AUTH/2993/11/17

Turning to the present case, the Panel noted that the allegations were different to those considered in the previous two cases.

The Panel noted that under Clause 19 of the Code medical and educational goods and services which enhanced patient care or benefited the NHS and maintained patient care could be provided subject to the provisions of Clause 18.1. They must not be provided to individuals for their personal benefit. The supplementary information to Clause 19.1 gave further details. Pharmaceutical companies could promote a simple switch from one product to another but must not assist a health professional in implementing that switch. A therapeutic review which aimed to ensure that patients received optimal

treatment following a clinical assessment was a legitimate activity for a pharmaceutical company to support and/or assist. The result of such clinical assessments might require, among other things, possible changes of treatment including changes of dose or medicine or cessation of treatment. A genuine therapeutic review should include a comprehensive range of relevant treatment choices including non–medicinal choices, for the health professional and should not be limited to the medicines of the sponsoring pharmaceutical company. The decision to change or commence treatment must be made for each individual patient by the prescriber and every decision to change an individual patient's treatment must be documented with evidence that it was made on rational grounds.

The Panel noted Napp's submission that whilst it funded the pharmacist-led service, therapy choice arising from the patient clinical review process remained the decision of the GP, and offering of the service was not conditional on the prescribing of any Napp product. This was stated in the pharmacist briefing documents. The documents detailing the service also stated that 'pharmacists will only implement therapeutic review services and will not:

- Recommend a specific pharmaceutical product
- Write prescriptions
- Recommend or take any action that does not comply with the practice treatment protocol.'

The Panel noted that there were a number of ICS/LABA combinations on the market for the prescriber to choose from. The Panel had some concerns about how the services were offered and whether all the features of the services amounted to a clinical assessment of patients. With regard to the complainant's view that a 'Napp pharmacist' had moved the majority of patients to Napp's product Flutiform without taking into consideration the preferences of the nurses or patients, the Panel noted that it was not necessarily a breach of the Code not to take into account the nurses or patients preferences if the GP or other prescriber considered otherwise. The Panel noted that the complainant bore the burden of proof and provided no evidence to support his/her allegation that a 'Napp pharmacist' had moved the majority of patients to Napp's product without taking into consideration the preferences of the nurses or patients. The Panel therefore ruled no breach of Clause 19.2 based on the narrow allegation and consequently no breach of Clauses 9.1 and 2.

Complaint received **29 November 2017**

Case completed **31 January 2018**

CASE AUTH/3005/12/17

DIRECTOR v BIOGEN

Clinical trial disclosure (Tecfidera)

A study published online in Current Medical Research & Opinion (CMRO) on 8 December 2017 was entitled 'Clinical trial transparency update: an assessment of the disclosure of results of company-sponsored trials associated with new medicines approved in Europe in 2014'. The study authors were B R Deane, LiveWire Editorial Communications and Dr S Porkess, Interim Executive Director of Research Medical and Innovation at the Association of the British Pharmaceutical Industry (ABPI) and Director of Actaros Consultancy and the MedicoMarketing Partnership. Publication support for the study was funded by the ABPI.

The 2017 study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2016. It covered 32 new medicines (except vaccines) from 22 companies that were approved by the European Medicines Agency (EMA) in 2014. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in an EMA European Public Assessment Report (EPAR). The CMRO study did not include the specific data for each product. This was available in the supplemental information via a website link. Neither the study nor the supplemental information identified specific clinical trials. The CMRO study did not assess the content of disclosure against any specific requirements.

The Director decided that the study was such that she had received information from which it appeared that Biogen might have breached the Code and decided in accordance with Paragraph 5.1 of the Constitution and Procedure to take the matter up as a complaint.

The supplemental information gave details of disclosure of clinical trial results for each product irrespective of sponsor in the form of a table which gave details for the studies for Tecfidera (dimethyl fumarate).

The detailed response from Biogen is given below.

General detailed comments from the Panel are given below.

With regard to Tecfidera, the Panel noted the CMRO publication in that three evaluable trials had not been disclosed within the timeframe. The disclosure percentage at 12 months measured from the later of the first date of regulatory approval or trial completion date was 67%. The disclosure percentage at 31 July 2016 was 100%.

Tecfidera was first approved and available in March 2013.

The Panel considered that the Second 2012 Code and thus the Joint Position 2009 were relevant.

The Panel noted that the trials completed in October 2009, March 2012 and March 2010. The three trials should have been disclosed by March 2014. The Panel noted Biogen's submission that Biogen UK was sponsor of the three trials despite there being no UK investigators, sites or patients. The trials therefore fell within the scope of the UK Code. The results of the three trials had not been disclosed by March 2014. The Panel thus ruled a breach of the Code. The delay in disclosure meant that high standards had not been maintained and a breach of the Code was ruled.

As the data had now been publicly disclosed the Panel considered that there was no breach of Clause 2 and ruled accordingly.

A study published online in Current Medical Research & Opinion (CMRO) on 8 December 2017 was entitled 'Clinical trial transparency update: an assessment of the disclosure of results of company-sponsored trials associated with new medicines approved in Europe in 2014'. The study authors were B R Deane, LiveWire Editorial Communications and Dr S Porkess, Interim Executive Director of Research Medical and Innovation at the Association of the British Pharmaceutical Industry (ABPI) and Director of Actaros Consultancy Ltd and the MedicoMarketing Partnership. Publication support for the study was funded by the ABPI.

The study referred to the three previously reported studies which covered medicines approved in Europe in 2009, 2010 and 2011 (Rawal and Deane 2014), in 2012 (Rawal and Deane 2015) and in 2014 (Deane and Sivarajah 2016).

The 2017 study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2016. It covered 32 new medicines (except vaccines) from 22 companies that were approved by the European Medicines Agency (EMA) in 2014.

It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in an EMA European Public Assessment Report (EPAR). The CMRO study did not include the specific data for each product. This was available in the supplemental information via a website link. Neither the study nor the supplemental information identified specific clinical trials. The CMRO study did not assess the content of disclosure against any specific requirements.

The Director decided that the study was such that she had received information from which it appeared

that Biogen Idec Limited might have breached the Code and decided in accordance with Paragraph 5.1 of the Constitution and Procedure to take the matter up as a complaint.

COMPLAINT

The study assessed the proportion of trials for which results had been disclosed on a registry or in the scientific literature either within 12 months of the later of either first regulatory approval either by the EMA or by the US Food and Drug Administration (FDA) or trial completion, or by 31 July 2016 (end of survey). Of the completed trials associated with 32 new medicines licensed to 22 different companies in 2014, results of 93% (505/542) had been disclosed within 12 months and results of 96% (518/542) had been disclosed by 31 July 2016.

The supplemental information gave details of disclosure of clinical trial results for each product irrespective of sponsor. The data for Tecfidera (dimethyl fumarate) were as follows:

Phase	Total Complete by July 2016	Un-evaluable	Evaluable	Disclosed in 12-month timeframe	Disclosed Percentage at 12 months	Complete by 31 July 2016	Disclosed at 31 July 2016	Disclosure percentage at 31 July 2016
Phase I & II	5	1	4	1	25%	4	4	100%
Phase III	6	3	3	3	100%	3	3	100%
Phase IV	5	4	1	1	100%	1	1	100%
Other	5	2	1	1	100%	1	1	100%
Total	**19**	**10**	**9**	**6**	**67%**	**9**	**9**	**100%**

The explanation of terms given in the documentation was as follows:

Total complete by 31 July 2016	Total number of company sponsored trials identified which were completed by 31 July 2016
Unevaluable	Trials with completion date within the last 12 months or key dates missing – excluded from the analysis
Evaluable	Trials with all criteria present including dates, and hence the base number of trials which could be evaluated for the assessment
Disclosed in 12 month timeframe	Evaluable trials which were disclosed within the target 12 months [12 months measured from the later of: the first date of regulatory approval (in Europe or the US) or the trial completion date]
Disclosed percentage at 12 months	Proportion of evaluable trials which were disclosed within 12 months [12 months measured from the later of: the first date of regulatory approval (in Europe or the US) or the trial completion date]
Completed before 31 July 2016	Number of evaluable trials completed before 31 July 2016
Disclosed at 31 July 2016	Number of evaluable trials with results disclosed by 31 July 2016
Disclosure percentage at 31 July 2016	Proportion of evaluable trials which were disclosed by 31 July 2016

When writing to Biogen the Authority asked it to bear in mind the requirements of Clauses 2, 9.1 and 13.1 of the Code. The Authority noted that previous editions of the Code would be relevant and provided details.

RESPONSE

Biogen stated that the complaint related to the product Tecfidera and was based on the study (sponsored by the ABPI) published online in the Current Medical Research and Opinion (CMRO) dated 8 December 2017 in which Biogen was listed as one of the companies with medicines approved in Europe in 2014. The complaint was that of the completed clinical trials of 32 new medicines licensed to 22 different companies in 2014, results of 93% had been disclosed within 12 months and results of 96% had been disclosed by 31 July 2016.

Biogen stated that there were 19 company sponsored clinical trials carried out in relation to Tecfidera ranging from Phase I to IV. Of these, all but 3 (Phase I and II) trials were disclosed by March 2014. These 3 remaining trials were disclosed by March 2015. In was Biogen's understanding that it was cited as being the responsible company as it was the European Market Authorisation Holder. Tecfidera received market authorisation by the EMA in January 2014.

Biogen submitted it was committed to sharing information and publishing clinical trials. To this end, by January 2014 it established and started to

implement policies and procedures to comply with the PhRMA/IFPMA/EFPIA Principles for Responsible Clinical Trial Data Share and to comply with national regulatory systems.

By 2015, Biogen had further advanced its procedures encompassing the PhRMA/EFPIA/IFPMA/JPMA Joint Position Statements and local industry bodies including the ABPI, to ensure registration and publication of clinical trial results in a timely manner. Biogen's corporate website was enhanced to provide additional details to the public regarding its policy and the results of completed clinical trials. It appreciated that in setting up and implementing the systems in the USA and its affiliates in Europe, there might have been some delay in the publishing of the clinical trial results. However, all disclosures were completed by March 2015 and since then disclosure of clinical trial results had been streamlined.

The three Phase I and II studies were disclosed as follows:

a) The CHMP summary for Tecfidera was published on 22 March 2013, the EPAR public assessment report was published on 26 February 2014. All three of the clinical trials complied with the requirements of the 2009 Joint Position Statement for registration of the clinical trial within 21 days after the initiation of patient enrolment.
b) All clinical trial results were disclosed in accordance with the EU Article 11 of the Clinical Trial Directive 2001/20/EC, Article 57 of Regulation (EC) No 726/2004 and Article 41 of the Paediatric Regulation (EC) No 1901/2006.
c) All three of the clinical trials were not in scope of US Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (PL110-85).
d) Study ID: 109MS101. The clinical trial results were published in March 2015;
   - The Clinical Study Report (CSR) Synopsis was shared via Biogen.com's website in March 2015
   - Results were submitted to the EudraCT database in March 2016 (prior to the required date); however, the EU did not make the results of Phase I studies publicly available.

   e) Study ID: 109MS201. The clinical trial results were published in March 2015;
   - The CSR Synopsis was shared via Biogen.com's website in March 2015
   - Results were not required to be submitted to the EudraCT database
   - Although results were not required per US on ClinicalTrials.gov; Biogen posted results in May 2015.

f) Study ID: 109RA201. The clinical trial results were published in March 2015
   - The CSR Synopsis was shared via Biogen.com's website in March 2015
   - Results were submitted to the EudraCT database in March 2016 (prior to the required date) and are publicly available
   - Results were not required per US on Clinical Trials.gov.

In conclusion, Biogen submitted that these were evaluable studies and were Phase I and II studies. The results of the studies were positive, therefore there was no incentive to not publish. As stated above, the policies, procedures and systems within Biogen were fully implemented, all studies were published and since then had been disclosed within time. Whilst it was unfortunate that the results were not disclosed within the required timeframes, all results were made publicly available as of March 2015. Most importantly, Biogen did not believe that the delay in disclosure impacted patient safety or public health.

In response to a request for further information, Biogen submitted that Tecfidera was first approved and available in the US on 27 March 2013. Biogen submitted that the completion dates (LPO dates) were October 2009 for trial 109MS101, March 2012 for trial 109MS201, and March 2010 for trial 109RA201. Biogen submitted that both Biogen USA and Biogen UK were listed on all trial documents as the trial sponsor even for the trial that only ran in the US. There were no trial sites or investigators in the UK. Trial 109MS101 had a site in Germany, trial 109MS201 had US sites and trial 109RA201 had sites in Australia, Canada, Czech, India, Poland and Slovakia. No UK patients were enrolled in these three trials.

General comments from the Panel

The Panel noted that all the cases would be considered under the Constitution and Procedure in the 2016 Code as this was in operation when the CMRO study was published and the complaint proceedings commenced. The Panel noted that the study concluded that of the completed trials associated with 32 new medicines licensed to 22 different companies in 2014, results of 93% had been disclosed within 12 months and results of 96% had been disclosed by 31 July 2016.

The Panel noted that the CMRO publication in question was an extension of previously reported data from three studies. One study related to new medicines approved in Europe in 2009, 2010 and 2011 (Rawal and Deane 2014) which found that over three-quarters of all these trials were disclosed within 12 months and almost 90% were disclosed by the end of the study. That study was the subject of an external complaint which gave rise to 27 cases in 2013 and 2014. The second study (Rawal and Deane 2015) was not the subject of external complaint but was taken up under Paragraph 5.1 of the Constitution and Procedure in 2015 leading to 15 cases. The second study found that the results of 90% had been disclosed within 12 months and results of 92% had been disclosed by 31 July 2014. Most of these cases were not in breach of the Code because they were not within the scope of the Code as there was no UK involvement and therefore only limited details were published on the PMCPA website. The third study (Deane and Sivarajah 2016) was not the subject of external complaint but was taken up under Paragraph 5.1 of the Constitution and Procedure in 2016 leading to 17 cases. The third study found that the results of 90% had been disclosed within 12 months and results of 93% had been disclosed by 31 July 2015. Most of these cases were not in breach of the Code because they were not within the scope

of the Code as there was no UK involvement and therefore only limited details were published on the PMCPA website.

The PMCPA had published an item in the May 2017 Code of Practice Review and the decision tree was on the PMCPA website. The present case was not the subject of external complaint. The study itself formed the basis of the complaint.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a trial was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well-established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities came within the scope of the Code such as activities relating to UK health professionals or activities carried out in the UK.

Clause 13.1 of the 2016 and 2015 editions of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patient enrolment) and the results of completed trials for medicines licensed for use and commercially available in at least one country. Further information was to be found in the current Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the current Joint Position on the Publication of Clinical Trial Results in the Scientific Literature, both at www.ifpma.org.en/ethics/clinical-trials-disclosure.html. Companies must include on the home page of their website, information as to where details of their clinical trials could be found.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed in the study were members of IFPMA and/or EFPIA.
The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

> **'Clause 7.5 Data from Clinical Trials**
>
> Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

'Companies must disclose details of clinical trials.'
The relevant supplementary information stated:

'Clause 21.3 Details of Clinical Trials

This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (http://clinicaltrials.ifpma.org).

Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'

The relevant supplementary information stated:

'Clause 21.3 Details of Clinical Trials

This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at http://clinicaltrials.ifpma.org.

Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code came into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014. These requirements were to be found in Clause 13.1 of the 2015 Code. The relevant supplementary information had been amended in the 2015 Code to replace the year of the relevant joint positions with the word 'current', to add a reference to the medicine being licensed and 'commercially available' and to update the website address. The 2015 Code came into effect on 1 May 2015 for newly introduced requirements following a transition period from 1 January 2015 until 30 April 2015. Similarly the 2016 Code came into effect on 1 May 2016 for newly introduced requirements following a transition from 1 January 2016 to 30 April 2016. The study at issue was posted online on 8 December 2017.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free, publicly accessible, internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the matter for consideration related to the disclosure of clinical trial results. With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after

the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code, and thus which joint position applied, was complicated. It noted that the 2011 Code which, taking account of the transition period, came into operation on 1 May 2011, was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 30 April 2012 under the 2011 Code and 1 May 2012 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the joint position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014, 2015 and 2016 Codes). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

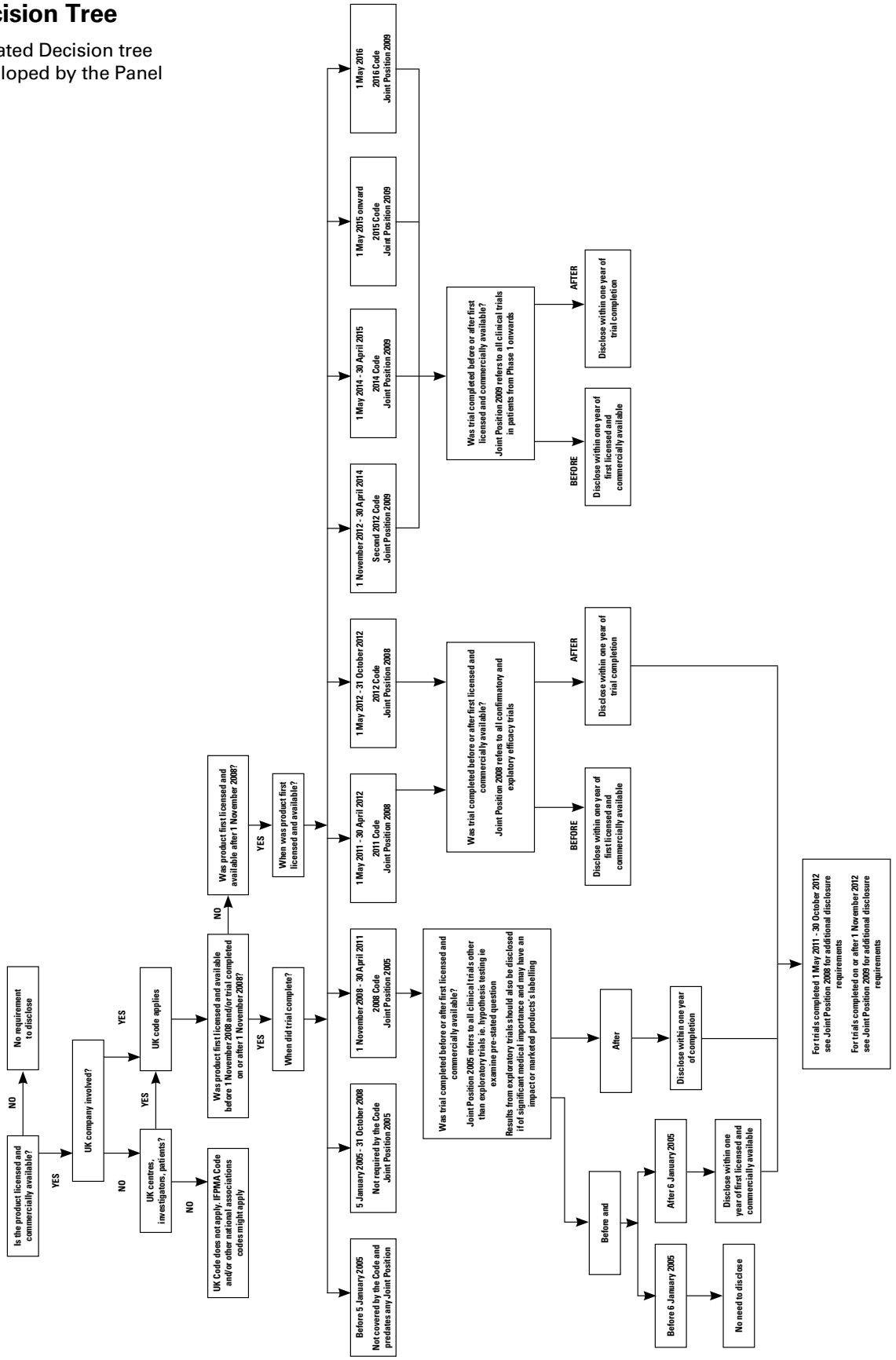
Noting that the CMRO study referred to licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than one year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the matter for consideration was whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights.

The Panel referred to the decision tree in the previous cases which had been updated in 2016 and published in case reports and on the PMCPA website in May 2017. An update (to the information about the 2015 and 2016 Codes) appears on the next page.

The Panel considered that companies would be well advised to ensure that all the clinical trial results were disclosed as required by the codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the CMRO publication at issue and thus the matter for consideration was only about whether or not trial results had been disclosed and the timeframe for such disclosure. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

Decision Tree

Updated Decision tree developed by the Panel



The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study related to products approved for marketing by the EMA in 2014 and searched for the data between 1 May and 31 July 2016. The study was published online on 8 December 2017. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the date the product was first licensed and commercially available anywhere in the world might pre-date EMA and/or the US approval.

PANEL RULING IN CASE AUTH/3005/12/17

The Panel noted the CMRO publication in that three evaluable trials had not been disclosed within the timeframe. The disclosure percentage at 12 months measured from the later of the first date of regulatory approval or trial completion date was 67%. The disclosure percentage at 31 July 2016 was 100%.

The Panel noted Biogen's submission that Tecfidera was first approved and available in the US on 27 March 2013. The Second 2012 Code and thus the Joint Position 2009 were relevant.

The Panel noted that one of the trials (109MS101) completed in October 2009, one (109MS201) in March 2012 and the other (109RA201) in March 2010. The Panel noted that on the information before it all three trials should have been disclosed by 27 March 2014. The Panel noted Biogen's submission that Biogen UK was sponsor of the three trials despite there being no UK investigators, sites or patients. The trials therefore fell within the scope of the UK Code. The Panel noted that the results of the three trials had not been disclosed by 27 March 2014. The Panel thus ruled a breach of Clause 13.1. The Panel noted Biogen's submission with regards to when the results of each trial were disclosed. The delay in disclosure meant that high standards had not been maintained and a breach of Clause 9.1 was ruled.

As the results had now been publicly disclosed the Panel considered that there was no breach of Clause 2 and ruled accordingly.

Complaint received **20 December 2017**

Case completed **13 March 2018**

CASE AUTH/3008/1/18

TEVA v PHARMASURE

Provision of a chocolate hamper

The Medicines and Healthcare products Regulatory Agency (MHRA) referred a complaint to the PMCPA that it had received from Teva UK about the provision of a chocolate hamper to a group of health professionals by a representative from Pharmasure.

Teva explained that, in December, its meeting for a clinical team at a named hospital, was briefly interrupted by a representative from Pharmasure droping off a substantial high street chocolate hamper. The gift to the team was on behalf of Pharmasure.

Teva alleged that the gift was inappropriate as it was not inexpensive or relevant to the practice of medicine or pharmacy.

The detailed response from Pharmasure is given below.

The Panel noted Pharmasure's submission that its representative had promoted both supplements and prescription only medicines (POMs) to the fertility unit up until November 2017. When the chocolate hamper was delivered he/she solely promoted medicines to the unit but none were discussed during the visit. The Panel disagreed with Pharmasure's submission that this meant that the chocolate hamper was not provided in connection with the promotion of any medicines.

The Panel considered that whilst promotional activity in relation to supplements was not within the scope of the Code, if a representative promoting supplements called on the same health professionals to promote medicines then the Code would apply.

The Panel noted that a representative whose role was to promote medicines had given a chocolate hamper to a group of health professionals. The Code prohibited the provision of items to health professionals save for very limited circumstances. The chocolate hamper did not fit within the exemptions set out in the Code.

The Panel noted Pharmasure's submission regarding the relevance of UK law as at the time the company was not covered by the Code.

The Panel could only rule in relation to the Code. The prohibitions in the Code regarding the provision of items to health professionals etc although more restrictive than UK law, were not inconsistent with those requirements which allowed items that were inexpensive and relevant to the practice of medicine or pharmacy. Given the requirements of UK law the Panel did not consider it was unreasonable to rule that the provision of the chocolate hamper was unacceptable and in breach of the Code.

The Panel noted Pharmasure's estimation that representatives who promoted medicines had given chocolate hampers to up to 15 fertility units. Extra care and guidance was required when representatives promoted medicines and something not covered by the Code such as supplements. The Panel considered that the provision of the chocolate hamper by the representative who promoted medicines meant that Pharmasure had not maintained high standards. A further breach of the Code was ruled. The Panel considered that whilst it could be argued that the representative had not maintained a high standard and had failed to comply with the Code, this was due to the company's arrangements and in that regard the matter was covered by its ruling above. No further breach was ruled.

The Panel noted its ruling above regarding the provision of the hamper and considered that the arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was concerned about the arrangements, however it noted that when the chocolate hampers were given the company was not on the list of non-member companies that had agreed to comply with the Code and accept the jurisdiction of the PMCPA. In the exceptional circumstances of this case, and on balance, the Panel decided not to report Pharmasure to the Code of Practice Appeal Board.

The Medicines and Healthcare products Regulatory Agency (MHRA) referred a complaint to the PMCPA that it had received from Teva UK Ltd about the provision of a chocolate hamper to a group of health professionals by a representative from Pharmasure. The MHRA forwarded the complaint to the Authority and the Authority invited Pharmasure to join the non-members' list and to respond to the complaint which it duly did.

COMPLAINT

Teva explained that on 14 December, two of its staff conducted a lunchtime presentation to a clinical team at a named private hospital. Teva provided details of those who had attended; they were all nurses, health professionals or clinical scientists. The meeting was briefly interrupted by the unscheduled arrival of a named representative from Pharmasure. The Pharmasure representative had visited only to drop off a substantial high street chocolate hamper for the team, which was handed over to the fertility centre manager. The gift was clearly not given in any personal capacity but on behalf of Pharmasure as it contained a compliments slip from the company.

Teva considered that the gift was inappropriate as it was not inexpensive or relevant to the practice of medicine or pharmacy.

When writing to Pharmasure to advise it of the complaint, the Authority asked it to bear in mind the requirements of Clauses 2, 9.1, 15.2 and 18.1 of the Code.

RESPONSE

In mitigation, Pharmasure firstly submitted that the majority of its promotional activity was in relation to supplements which fell outside the jurisdiction of the Code and where there was no equivalent constraint as to the giving of gifts. The chocolate hampers were intended for customers of these supplement products. Pharmasure explained that it took on a dedicated team of supplements sales people in January/February 2017. The company's medical representatives also sold Inofolic and subsequently Condensyl (both supplements) until November 2017, when they focussed solely on prescription only medicines (POMs).

Secondly, Pharmasure noted that each hamper cost £37.50 (inc VAT) and would have comprised little more than a festive treat for each member of a team of 10. However, the company accepted that the gift was not relevant to the practice of medicine and might not have been an appropriate expression of Christmas spirit.

Pharmasure stated that the representative had visited the hospital in question to follow up on a nurse ultrasound training discussion with one of the nurses and to organise a meeting with the team at the unit. He/she also took the opportunity to drop off the chocolate hamper for the team; it was intended to be shared between the 10 or so personnel at the unit as a Christmas treat. No other items were provided. The box contained a printed Pharmasure compliments slip, upon which was written 'Merry Christmas'.

Pharmasure stated that it purchased 74 hampers which were intended for employees, suppliers and the supplements sales team. Between 4 and 6 hampers were given to each sales person which erroneously included the medical representatives. Pharmasure estimated that its medical representatives gave hampers to up to 15 fertility units.

Pharmasure submitted that it was embarrassed by the incident and it took the procedural implications of it seriously. The company acknowledged the breach and that on the prescription side of the business there was not an adequate control system in relation to these gifts.

Pharmasure stated that it had begun a full review and overhaul of its promotional processes which it would complete within 3 months; it would not engage in further promotional activity during that period. The company undertook to establish a sound compliance approval system for promotional activity linked to its medicines in order to avoid breaches of the Code in future.

In response to a request for further information Pharmasure submitted that its POM sales representatives had sold supplements to fertility units for several years as well as promoting POMs. As Pharmasure's business was focussed on fertility treatment it was difficult for its sales team to always avoid promoting supplements in units where they might also promote POMs.

Pharmasure submitted that in November 2017 it formally asked its POM representatives to cease promoting supplements, leaving that responsibility to it supplements sales team. The reality, however, was that there had to be a transition period where the POM sales team continued to respond to queries and follow-ups for supplements until the supplements team were established in these units.

Pharmasure accepted that the representative at issue was officially a POM representative when the chocolate hamper was given. However, Pharmasure submitted that when the chocolate hamper was delivered, no products were discussed and the representative had promoted supplements to this unit during the previous year.

Pharmasure did not consider that the giving of the chocolate hamper brought discredit upon or reduced confidence in the pharmaceutical industry. None of the examples in the supplementary information relating to Clause 2 applied to this complaint, except possibly 'inducement to prescribe'. Pharmasure stated, however, that it was highly unlikely that a few bars of chocolate would induce a fertility unit to change its prescribing of high value, specialised gonadotrophin products and, for this reason, it did not believe the last example applied in this instance. Pharmasure denied a breach of Clause 2.

Pharmasure agreed that high standards must be maintained at all times and when it reviewed the supplementary information to Clause 9.1 it considered that it had not promoted POMs in a way that was unsuitable or in bad taste and it denied a breach of that clause.

Pharmasure submitted that its representatives were trained to maintain high ethical standards; they acted with integrity, honesty and provided accurate, balanced information. The fact that the representative in question had recently officially changed responsibility from promoting supplements and POMs to promoting POMs only contributed to confusion on the day. In that respect, Pharmasure submitted that it might be considered that the provision of a gift, albeit modest, did not comply with the relevant requirements of the Code. Pharmasure noted that there was no supplementary information to Clause 15.2.

Pharmasure submitted that the chocolates were not provided in connection with the promotion of any medicines. The unit in question had been previously visited by the representative at issue many times in connection with supplements and the very recent change to his/her responsibility to promoting only POMs did not negate his/her history with the unit.

Pharmasure submitted that there was no reference to any product on the chocolates or given alongside the chocolates. None of the supplementary information to Clause 18.1 appeared to apply to small gifts of chocolates.

Pharmasure confirmed that the representative at issue was a POM representative and that he/she had promoted two supplements as well as three POMs to the particular unit in this case during 2017.

With regard to the other units that received the chocolate hamper, Pharmasure submitted that the same confusion applied but all units concerned were units where supplements had been consistently promoted and that there was no promotion of any products when the chocolate hampers were given.

Pharmasure submitted that it was a small company focussed on a specialist niche; in order to be able to efficiently access potential customers throughout the UK it had recently trained its supplements team to be able to sell POMs and its POMs representatives were again also selling supplements.

PANEL RULING

The Panel noted that Paragraph 5.3 of the Constitution and Procedure stated that a complaint from a pharmaceutical company would be accepted only if the Director is satisfied that the company concerned has previously informed the company alleged to have breached the Code that it proposed to make a formal complaint and offered inter-company dialogue at a senior level in an attempt to resolve the matter, but that this offer was refused or dialogue proved unsuccessful.

The Panel considered that whilst inter-company dialogue had not occurred in this particular case, the case preparation manager had accepted the complaint as it had been received via the MHRA. Teva had originally submitted the complaint to the MHRA as Pharmasure was not on the list of non-member companies that agreed to abide by the Code and accept the jurisdiction of the PMCPA. On being notified of the complaint, Pharmasure had agreed to join the list.

The Panel noted that Clause 18.1 of the Code required that no gift, pecuniary advantage or benefit might be supplied, offered or promised to members of the health professions or to other relevant decision makers in connection with the promotion of medicines or as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine subject to the provision of Clauses 18.2 and 18.3. Clause 18.2 permitted patient support items and Clause 18.3 permitted the provision of inexpensive notebooks, pens and pencils for use at certain meetings.

The Panel noted Pharmasure's submission that the representative at issue had promoted both supplements and POMs to the fertility unit up until November 2017. When the chocolate hamper was delivered he/she solely promoted medicines to the unit but none were discussed during the visit. The Panel disagreed with Pharmasure's submission that this meant that the chocolate hamper was not provided in connection with the promotion of any medicines.

The Panel further noted that the Code covered the promotion of medicines (Clause 1.3). Whilst promotional activity in relation to supplements was not within the scope of the Code, if a representative promoting supplements called on the same health professionals to promote medicines then the Code would apply.

The Panel noted that a representative whose role was to promote medicines had given a chocolate hamper to a group of health professionals. The Code prohibited the provision of items to health professionals save for very limited circumstances. The chocolate hamper did not fit within the exemptions set out in the Code.

The Panel noted Pharmasure's submission regarding the relevance of UK law as at the time the company was not covered by the Code.

The Panel could only rule in relation to the Code. The prohibitions in the Code regarding the provision of items to health professionals etc although more restrictive than UK law, were not inconsistent with the requirements of UK law which allowed items which were inexpensive and relevant to the practice of medicine or pharmacy. Given the requirements of UK law the Panel did not consider it was unreasonable to rule that the provision of the chocolate hamper was unacceptable and in breach of Clause 18.1 of the Code.

The Panel noted Pharmasure's estimation that representatives who promoted medicines had given chocolate hampers to up to 15 fertility units. Extra care and guidance was required when representatives were promoting medicines and something not covered by the Code such as supplements. The Panel considered that the provision of the chocolate hamper by the representative who promoted medicines meant that Pharmasure had not maintained high standards. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 15.2. Whilst it could be argued that the representative had not maintained a high standard and had failed to comply with the Code, this was due to the company's arrangements. The Panel considered that the matter was covered by its ruling of a breach of Clause 9.1 and therefore ruled no breach of Clause 15.2.

The Panel disagreed with Pharmasure's submission that none of the examples in the supplementary information relating to Clause 2 applied to this complaint except possibly inducement to prescribe and it was highly unlikely that a few bars of chocolate would induce a fertility unit to change its prescribing habits. The Panel noted that the list of examples in the supplementary information to Clause 2 was not exhaustive. The Panel noted its ruling of Clause 18.1 above and considered that the arrangements brought discredit upon, and reduced

confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was concerned about the arrangements however it noted that at the time the chocolate hampers were given the company was not on the list of non-member companies that have agreed to comply with the Code and accept the jurisdiction of the PMCPA. In the exceptional circumstances of this case, and on balance, the Panel decided not to report Pharmasure to the Code of Practice Appeal Board for it to consider in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Panel noted that Pharmasure recently decided that all of its representatives would promote both supplements and medicines. The company needed to be certain that it instructed representatives carefully to ensure compliance with the Code.

Complaint received **4 January 2018**

Case completed **27 March 2018**

CASE AUTH/3011/1/18

GLAXOSMITHKLINE v ASTRAZENECA

Press release issued by AstraZeneca

GlaxoSmithKline complained about an AstraZeneca PLC press release dated 10 November 2017. The press release was entitled 'Benralizumab receives positive EU CHMP [Committee for Medicinal Products for Human Use] opinion for severe, uncontrolled eosinophilic asthma'. The press release referred to the European Medicines Agency (EMA) positive opinion which recommended the marketing authorization of benralizumab as an add-on maintenance treatment in adults with severe eosinophilic asthma inadequately controlled, despite high dose inhaled corticosteroids (ICS) plus long-acting beta-agonists (LABA). The press release was issued by AstraZeneca PLC, an ABPI member, on the www.astrazeneca.com website which clearly stated that 'This website was operated by AstraZeneca UK Limited'.

GlaxoSmithKline alleged that the data on the clinical endpoints presented in the press release (including annual asthma exacerbations rate [AAER], lung function [LF] and median reduction in daily oral corticosteroids [OCS] use and adverse events [AE]) based on clinical trials SIROCCO, CALIMA and ZONDA were unbalanced and misleading due to the omission of the full available evidence.

GlaxoSmithKline alleged that the statement 'Up to 51% reduction in the annual asthma exacerbations rate (AERR) versus placebo' did not give a balanced picture of benralizumab efficacy. It was data from only one of the two regulatory studies with the more favourable efficacy result. In the other regulatory study, there was a 28% reduction vs placebo.

GlaxoSmithKline alleged that the statement 'Rapid improvement in lung function (290mL increase in forced expiratory volume in one second (FEV1) from baseline at 4 weeks) after the first dose, providing an early indication of effectiveness' did not give a balanced picture of the onset of benralizumab efficacy in a placebo-controlled trial and was misleading as it was not corrected for the placebo response. An improvement in the placebo arm was relevant to this claim. Also, secondary endpoints in CALIMA and in SIROCCO showed respectively a 116ml and 159ml improvement vs placebo in FEV1 at the end of the studies. 'Rapid improvement' was alleged to be an all-encompassing claim without the context of whether this was sustained or how efficacy in this case related to effectiveness. GlaxoSmithKline alleged, therefore, this was exaggerated, misleading and unbalanced.

GlaxoSmithKline alleged that the statement '75% median reduction in daily OCS use and discontinuation of OCS use in 52% of eligible patients' was unbalanced and misleading for a number of reasons firstly the exacerbation reduction was presented as 'versus placebo' while FEV1 improvement and OCS reduction data were presented as 'from baseline'. The placebo arm had a 25% reduction, to give a true representation of OCS reduction, efficacy vs placebo data should be presented as a 'median reduction in daily OCS use of 50% versus placebo'.

GlaxoSmithKline was also concerned that the statement 'An overall adverse event profile similar to placebo' was misleading with respect to patient safety. Without any context of the adverse event profile, and any differences with placebo, it was inappropriate to present the safety profile of a new, black triangle medicine in this way. It raised false hopes and could result in inappropriate prescribing and mislead with respect to the safety of the product.

GlaxoSmithKline stated that indeed, any medicine related adverse events in CALIMA were 8% for placebo vs 13% in the benralizumab arm, 10 benralizumab patients (2%) and 4 (<1%) who received placebo discontinued treatment because of adverse events and 2 patients had an adverse event leading to death vs none in the placebo arm. A comparable trend could be observed in SIROCCO: 18 benralizumab patients (2%) and three (1%) who received placebo discontinued treatment because of adverse events. Although these might be low numbers it was not only a factually incorrect statement but also not acceptable to state they were similar to placebo without any detail or context.

GlaxoSmithKline stated that if key clinical data had not been omitted and the vs placebo data had been included, the conclusion on clinical efficacy and safety would have been different.

In addition, GlaxoSmithKline alleged that the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' was inappropriate as in particular 'speed of onset', 'convenience' and would 'make a real difference' were promotional and could not be substantiated by clinical trial data. GlaxoSmithKline stated that this also set unfounded hopes and misled the media into believing that all patients would have a response with no context of the response rate nor any clinical context regarding the speed of onset. In addition, GlaxoSmithKline alleged that to claim that benralizumab was convenient when it was administered by subcutaneous injection, every 4 weeks for 3 doses and then every 8 weeks, compared with inhalers or oral medication, was misleading.

In summary, GlaxoSmithKline alleged breaches of the Code as well as of the MHRA Blue Guide Section 6.6. To present clinical trial data in a misleading way and to issue a promotional press release did not maintain the high standards expected from a pharmaceutical company. In addition, the intent to promote in a misleading manner and the incorrect and misleading presentation of safety data had a potential impact on patient safety, and the failure to address GlaxoSmithKline's concerns, brought discredit upon, and reduced confidence in, the pharmaceutical industry, in breach of Clause 2.

The detailed response from AstraZeneca appears below.

The Panel noted that its role was to consider matters in relation to the Code and not the MHRA Blue Guide.

The Panel considered that the press release was subject to the Code. It then went on to consider the allegations made by GlaxoSmithKline.
The Panel noted that the summary of product characteristics (SPC) stated that Fasenra (benralizumab) was first authorised on 8 January 2018. The recommended dose of benralizumab was 30mg every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. Fasenra was intended for long-term treatment. A decision to continue the therapy should be made at least annually based on disease severity, level of exacerbation control and blood eosinophil counts. The SPC stated, under special warnings and precautions for use, that abrupt discontinuation of corticosteroids after initiation of Fasenra therapy was not recommended. Reduction in corticosteroid doses, if appropriate, should be gradual and performed under the supervision of a physician.

The Panel noted that the press release stated that patients in SIROCCO and CALIMA received standard of care medicine (including high dose inhaled corticosteroids and long acting beta 2 agonists) and were randomized to receive benralizumab 30mg every 4 weeks, 30mg every 4 weeks for the first 3 doses followed by 30mg every 8 weeks or placebo via a subcutaneous injection.

With regard to the claim 'Up to 51% reduction in the annual asthma exacerbations rate (AERR) versus placebo', the Panel noted this was from SIROCCO. CALIMA stated that annual exacerbation rates were approximately 28% lower than with placebo. The Panel considered that the use of the phrase 'up to 51%' was misleading as it did not reflect the range and information made available to the public had not been presented in a balanced way. Breaches of the Code were ruled.

With regard to the claim 'Rapid improvement in lung function (290mL increase in forced expiratory volume in FEV1 from baseline at 4 weeks) after the first dose, providing an early indication of effectiveness', the Panel noted that SIROCCO concluded that both benralizumab dosing regimens significantly improved pre-bronchodilator FEV1 in patients at week 48 compared with placebo. The difference between benralizumab 30mg every 8 weeks and placebo (in patients with baseline eosinophils ≥ 300 cells per mcl was 159ml (p = 0.0006). The Panel noted AstraZeneca's submission that the 290ml increase in FEV1 from baseline at week 4 data as stated in the press release came from SIROCCO. Data on file had been created which stated that at week 4 there was a 290ml increase in FEV1 for benralizumab and a 209ml increase for placebo (p=0.039) versus baseline. The estimated difference between benralizumab and placebo was 81ml.

CALIMA concluded that benralizumab significantly improved pre-bronchodilator FEV1. Improvements in pre-bronchodilator FEV1 were present within 4 weeks of treatment start and were maintained through the treatment period. At week 56 the difference between benralizumab 30mg every 8 weeks and placebo (in patients with baseline eosinophils ≥ 300 cells per mcl) was 116ml (p = 0.0102). The Panel noted that CALIMA stated that annual exacerbation rates, pre-bronchodilator FEV1 and total asthma scores were not affected by benralizumab for the subset of patients receiving medium-dosage inhaled corticosteroids plus LABA with blood eosinophils ≥ 300 cells per mcl at baseline.

The data on file for CALIMA at week 4 showed there was a 280ml increase in FEV1 for benralizumab 30mg every 8 weeks and 152ml for placebo (p=0.002) versus baseline. The estimated difference between benralizumab and placebo was 127ml.

The SIROCCO and CALIMA data on file stated that the analysis of these endpoints were not multiplicity protected and therefore p values were reported as nominal. Results were descriptive only.

The Panel noted that the ZONDA study (Nair *et al* (2017)) assessed the effects of benralizumab versus placebo on the reduction in oral glucocorticoid dose whilst maintaining asthma control in adults with severe asthma. ZONDA concluded that benralizumab showed significant clinically relevant benefits compared with placebo on oral glucocorticoid use and exacerbation rates. These effects occurred without a sustained effect on FEV1.

The Panel noted that the claim in the press release referred to a rapid improvement in lung function. It appeared to the Panel that if the improvements in FEV1 at 4 weeks in SIROCCO and CALIMA were seen as rapid improvement in lung function then there was evidence to support the change in both the treated and placebo groups. The Panel considered that it was misleading and exaggerated not to include the placebo data in the press release to ensure that the improvements from baseline were not confused with improvements compared with placebo. Information to the public had not been presented in a balanced way and breaches of the Code were ruled. The data was capable of substantiation so no breach was ruled in that regard.

With regard to the claim '75% median reduction in daily OCS use and discontinuation of OCS use in 52% of eligible patients', the Panel considered that

it was not clear that the reduction in daily OCS use difference was compared to baseline. The SPC gave the placebo reduction as 25%. The Panel considered that the data in the press release was not placed in context; the press release was misleading in this regard and information to the public had not been presented in a balanced way. Breaches of the Code were ruled.

With regard to the claim 'an overall adverse event profile similar to placebo', the Panel noted that the medicine was new and at the time of the press release it was not licensed in the UK. The intended audience would not necessarily be familiar with the incidence of adverse events with placebo. The claim referred to the addition of benralizumab rather than the overall incidence of adverse events when the medicine was used in addition to high-dose inhaled corticosteroids plus long acting beta agonists. The SPC stated that the most common adverse reactions during treatment were headache (8%) and pharyngitis (3%). Injection site reactions (eg pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with the recommended benralizumab dose compared with 1.9% in patients treated with placebo.

The Panel was concerned about the lack of context for the claim in the press release to an audience that were, in effect, members of the public. There was no further data in the press release about adverse events. The press release was misleading in this regard; it was not balanced. The Panel considered that the claim exaggerated the properties of the product and information to the public about the adverse event profile had not been presented in a balanced way. Breaches of the Code were ruled.

The Panel considered that as the press release was not specifically intended for patients taking the medicine, there was no need to include an inverted black equilateral triangle together with a statement about additional monitoring and reporting of side-effects. No breach was ruled.

With regard to GlaxoSmithKline's general allegation that the omission of both key clinical data and the placebo data meant that the conclusion on efficacy and safety would be different, the Panel considered that this allegation had been addressed by its rulings of breaches of the Code above. It would be relevant in considering the allegations of breaches below. It therefore ruled no breach in relation to the broad allegation.

With regard to the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' the Panel considered that this was a broad, strong claim for the medicine. It was a quotation from the AstraZeneca executive vice president, global medicines development and chief medical officer. The Panel considered that readers of the press release would be clear that the benralizumab was to be dosed every eight weeks. However, it was not clear that the first 3 doses were to be given every 4 weeks. The Panel did not accept AstraZeneca's submission that the use of the word 'potential' meant that readers would be aware that any clinical benefits observed in studies to date were not applicable to all patients.

Patients using Fasenra would need to continue with other asthma medication as stated in the package information leaflet (high doses of corticosteroids). Use of Fasenra might allow patients to reduce or stop daily OCS. This would be done gradually under supervision of a doctor.

On balance, the Panel did not consider that the claim in the press release was an advertisement for Fasenra, a prescription only medicine, to the public. The medicine was unlicensed at the time of the press release and thus not classified as a prescription only medicine and ruled no breach. It considered that the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' might raise unfounded hopes of successful treatment, particularly given the lack of information about the need to be monitored before changing the doses of a patient's current medication.

The Panel noted the allegations about the speed of onset and the data for FEV1, and the changes at 4 weeks for patients with baseline eosinophils ≥ 300 cells per mcl. The Panel queried whether adding in an additional therapy was convenient for patients. It was not clear until page two of the press release that benralizumab was a subcutaneous injection. The Panel noted that there were other medicines available, one of which was GlaxoSmithKline medicine, mepolizumab (Nucala), which was to be given every 4 weeks. The basis of the claim for convenience in the press release was not clear to the Panel. AstraZeneca submitted that it related to the 8 week maintenance dosing schedule which the Panel noted was longer than for GlaxoSmithKline's medicine. The Panel considered that, given AstraZeneca's product had 3 doses at 4 week intervals, it was possible that maintenance treatment at 8 weeks would not be seen as convenient compared to treatment at 4 weeks. The Panel considered that, overall, the claim could be read as a comparison with inhalers and/or oral medication and compared to inhalers or oral medication, benralizumab was not convenient. Overall, it considered that the claim for convenience was misleading and that information to the public had not been presented in a balanced way. Breaches of the Code were ruled.

The Panel did not consider that GlaxoSmithKline had provided evidence that when a health professional asked for substantiation this was not provided and ruled no breach.

Noting all its rulings above, the Panel ruled a breach as high standards had not been maintained.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such use. The Panel noted that one of the reasons for GlaxoSmithKline to support a breach of Clause

2 was AstraZeneca's alleged failure to address GlaxoSmithKline's concerns. The Panel did not consider that this was relevant to its consideration regarding Clause 2. The Panel noted its rulings of breaches of the Code. It considered that it was extremely important that press releases were accurate, balanced and not misleading. On balance, the Panel considered that the circumstances did not warrant a ruling of a breach of Clause 2 and ruled accordingly.

GlaxoSmithKline complained about an AstraZeneca PLC press release dated 10 November 2017. The press release was entitled 'Benralizumab receives positive EU CHMP [Committee for Medicinal Products for Human Use] opinion for severe, uncontrolled eosinophilic asthma'. The press release referred to the European Medicines Agency (EMA) positive opinion which recommended the marketing authorization of benralizumab as an add-on maintenance treatment in adults with severe eosinophilic asthma inadequately controlled, despite high dose inhaled corticosteroids (ICS) plus long-acting beta-agonists (LABA).

COMPLAINT

GlaxoSmithKline alleged that the press release was in breach of Clauses 2, 7.2, 7.3, 7.4, 7.9, 7.10, 9.1, 26.1, 26.2 and 26.3 of the Code due to a number of misleading and/or unsubstantiated statements.

Inter-company dialogue

GlaxoSmithKline stated that in line with PMCPA guidance on inter-company dialogue it contacted AstraZeneca's UK medical director to outline the basis of GlaxoSmithKline's complaint on 6 December 2017. This was followed by a letter on 7 December 2017 to raise its detailed concerns. AstraZeneca's UK medical director subsequently informed GlaxoSmithKline that AstraZeneca UK would not be responding but AstraZeneca's global functions would which it did on 20 December. GlaxoSmithKline noted that AstraZeneca's response did not originate from the UK affiliate, nor from a person responsible for certifying material, activity, etc under the Code as recommended in the guidance on inter-company dialogue.

GlaxoSmithKline stated that AstraZeneca failed to address any of its detailed concerns and stated that, 'The Release was factual and balanced and met the standards required by applicable law and regulation' although which standards were considered was not stated. GlaxoSmithKline considered this response to be wholly unsatisfactory and not in keeping with the guidance on inter-company dialogue that the (initial) response should address all of the points raised and include any proposed amendments or actions and timelines.

GlaxoSmithKline wrote again to AstraZeneca on 4 January 2018 offering AstraZeneca another opportunity and respectfully requesting a detailed response to the concerns raised. The subsequent response of 11 January again made no attempt to address the detailed concerns now raised twice by GlaxoSmithKline and again questioned the applicability of the Code in this matter and referred to Case AUTH/2046/9/07, Takeda v GlaxoSmithKline.

During a conference call on 12 January AstraZeneca was not willing to discuss the specific details of the points raised in GlaxoSmithKline's letter of 7 December 2017 and again underlined AstraZeneca's position that the press release did not fall under the Code and therefore the jurisdiction of the PMCPA. Both companies had failed to reach an agreement on this fundamental point, which was key to the complaint. AstraZeneca offered to meet and discuss further but requested that the meeting be in conjunction with discussing global press releases in a broader context including a consideration of their overall governance. In GlaxoSmithKline's view, in order to have meaningful inter-company dialogue about the press release, the matter should be discussed separately. GlaxoSmithKline was disappointed and surprised that AstraZeneca had refused to respond to any of the specific issues outlined, given that in response to a complaint about an almost-identical press release to AstraZeneca's German affiliate, AstraZeneca had provided undertakings which addressed many of GlaxoSmithKline's concerns.

Since no agreement had been reached on whether the press release fell under the remit of the PMCPA, and AstraZeneca had failed to address the substantive concerns, despite two formal letters and a teleconference at a senior level, GlaxoSmithKline had no alternative but to bring the matter to the PMCPA.

Jurisdiction of the PMCPA

GlaxoSmithKline noted that, AstraZeneca, in its first response, drew attention to the fact that the press release was issued by AstraZeneca PLC, the global holding company of the AstraZeneca Group. It went on to state that this was done to meet its disclosure obligations under the UK Listing Rules and indeed GlaxoSmithKline recognised that this was a global press release which principally affected European markets as a similar press release relating to the FDA approval of benralizumab for the USA market was issued a few days later on 14 November 2017.

However, the press was released on the legal domain of www.astrazeneca.com (www.astrazeneca.com/Legal-notice) which clearly stated that 'This website was operated by AstraZeneca UK Limited'. As such, this was a web page hosted by the UK affiliate of a multinational company which was obliged to abide by the Code as well as the Medicines and Healthcare products Regulatory Agency (MHRA) Blue Guide for the Advertising and Promotion of Medicines. Moreover, AstraZeneca PLC was a member of the ABPI and had therefore committed to adhere to the Code as was clear from the ABPI website full membership list where Astra Zeneca was listed with a link to the global website.

GlaxoSmithKline stated that in Case AUTH/2046/9/07 the Panel ruled that the disputed press release did not fall within the Code, since it was not issued in the

UK and it did not specifically refer to the availability or the use of a medicine within the UK. Hence it did not meet the requirement of what was now Clause 28.2 of the Code. GlaxoSmithKline believed that Case AUTH/2046/9/07 was not applicable as it related to a US corporate press release covering FDA regulatory activity for a US and financial audience. The AstraZeneca press release in this case concerned a CHMP opinion which related directly to the availability and use of benralizumab in the UK and was without question published in the UK. However, in Case AUTH/2046/9/07 GlaxoSmithKline responded to the concerns about the press release being factual, balanced and non-promotional, whilst AstraZeneca had never offered any explanation as to why it believed the press release similarly complied with the Code.

In the letter of 11 January, AstraZeneca stated that its UK affiliate separately issued a UK-specific press release about the positive CHMP opinion, which was sent to UK pharmaceutical trade and medical media outlets. GlaxoSmithKline stated, however, that when trying to access a UK press release on the EU CHMP opinion for benralizumab through AstraZeneca's UK website (www.astrazeneca.co.uk/media-press-releases.html), the link led back to the global press release website, with a link to the global press release only, for a UK audience.

Finally, the supplementary information to Clause 14.3 stated that 'material issued by companies which relates to medicines but which is not intended as promotional material for those medicines *per se*, ..., press releases, ..., financial information to inform shareholders, the Stock Exchange and the like, ..., should be examined to ensure that it does not contravene the Code or the relevant statutory requirements'.

GlaxoSmithKline therefore believed that the publication of the press release was a matter regulated by the Code and any question of its compliance with requirements of the Code was subject to the jurisdiction of the PMCPA.

Complaint

GlaxoSmithKline stated that in line with the Code, press releases should be non-promotional and the information provided in them should also be non-promotional. They must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Any data should be presented in a balanced and appropriate way to avoid the audience reaching any misleading conclusions due to omission of evidence. In particular, the supplementary information to Clause 26.2 made it clear that information made available in order to inform shareholders, the Stock Exchange and the like by way of annual reports and announcements etc must be factual and presented in a balanced way.

GlaxoSmithKline alleged that the data on the clinical endpoints presented in the press release (including annual asthma exacerbations rate [AAER], lung function [LF] and median reduction in daily oral corticosteroids [OCS] use and adverse events [AE]) based on clinical trials SIROCCO, CALIMA and ZONDA were unbalanced and misleading due to the omission of the full available evidence.

GlaxoSmithKline alleged that the statement 'Up to 51% reduction in the annual asthma exacerbations rate (AERR) versus placebo' did not give a balanced picture of benralizumab efficacy. It was data from only one of the two regulatory studies (SIROCCO) with the more favourable efficacy result. In CALIMA, the other regulatory study, there was a 28% reduction vs placebo. Both regulatory studies were considered by the EMA for marketing authorisation. GlaxoSmithKline alleged that to only present the endpoint from the study which showed a greater reduction was misleading, unbalanced and did not reflect the entirety of the data in breach of Clause 7.2 and 26.2.

GlaxoSmithKline alleged that the statement 'Rapid improvement in lung function (290mL increase in forced expiratory volume in one second (FEV1) from baseline at 4 weeks) after the first dose, providing an early indication of effectiveness' did not give a balanced picture of the onset of benralizumab efficacy in a placebo-controlled trial and was misleading as it was not corrected for the placebo response. An improvement in the placebo arm was relevant to this claim. Also, secondary endpoints in CALIMA and in SIROCCO showed respectively a 116ml and 159ml improvement vs placebo in FEV1 at the end of the studies. 'Rapid improvement' was alleged to be an all-encompassing claim without the context of whether this was sustained or how efficacy in this case related to effectiveness. GlaxoSmithKline alleged therefore, this was an exaggerated and misleading claim, in breach of Clauses 7.2, 7.4 and 7.10 as well as an unbalanced statement of the findings of these studies in breach of Clause 26.2.

GlaxoSmithKline alleged that the statement '75% median reduction in daily OCS use and discontinuation of OCS use in 52% of eligible patients' was unbalanced and misleading for a number of reasons firstly the exacerbation reduction was presented as 'versus placebo' while FEV1 improvement and OCS reduction data were presented as 'from baseline'. Furthermore, in the '75% median reduction in daily OCS use' statement it was not explicit as to how the data had been presented as 'from baseline' had been omitted. The placebo arm had a 25% reduction, to give a true representation of OCS reduction, efficacy vs placebo data should be presented as a 'median reduction in daily OCS use of 50% versus placebo'. GlaxoSmithKline alleged that this unbalanced and misleading representation of data was in breach of Clauses 7.2 and 26.2.

GlaxoSmithKline was also concerned that the statement 'An overall adverse event profile similar to placebo' was misleading with respect to patient safety. Without any context of the adverse event profile, and any differences with placebo, it was inappropriate to present the safety profile of a new, black triangle medicine in this way. It raised

false hopes and could result in inappropriate prescribing and have an impact on patient safety. GlaxoSmithKline alleged a breach of Clauses 7.9, 7.10, 26.2 and 26.3 and of the MHRA Blue Guide Section 6.6 which stated 'Advertising which states or implies that a product is "safe" is unacceptable. All medicines have the potential for side-effects and no medicine is completely risk free as individual patients respond differently to treatment. For example, the term "placebo-like" in relation to safety or side-effects in general is considered to be misleading as it implies that there are no drug associated side-effects'.

GlaxoSmithKline stated that indeed, any medicine related adverse events in CALIMA were 8% for placebo vs 13% in the benralizumab arm, 10 benralizumab patients (2%) and 4 (<1%) who received placebo discontinued treatment because of adverse events and 2 patients had an adverse event leading to death vs none in the placebo arm. A comparable trend could be observed in SIROCCO: 18 benralizumab patients (2%) and 3 (1%) who received placebo discontinued treatment because of adverse events. Although these might be low numbers it was not only a factually incorrect statement but also not acceptable to state they were similar to placebo without any detail or context.

GlaxoSmithKline stated that if key clinical data had not been omitted and the vs placebo data had been included, the conclusion on clinical efficacy and safety would have been different. This was not acceptable in any press release, albeit to the financial or medical media. GlaxoSmithKline alleged that the press release raised unfounded hopes of successful treatment and misled with respect to the safety of the product in breach of Clause 26.2.

In addition, GlaxoSmithKline alleged that the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' was inappropriate as in particular 'speed of onset', 'convenience' and would 'make a real difference' were promotional and could not be substantiated by clinical trial data. GlaxoSmithKline alleged a breach of Clauses 26.1 and 26.2. The press release must be capable of being substantiated and based on actual data and therefore a breach of Clause 7.5 was also alleged. GlaxoSmithKline stated that this also set unfounded hopes and misled the media into believing that all patients would have a response with no context of the response rate nor any clinical context regarding the speed of onset. In addition, GlaxoSmithKline alleged that to claim that benralizumab was convenient when it was administered by subcutaneous injection, every 4 weeks for 3 doses and then every 8 weeks, compared with inhalers or oral medication, was misleading in breach of Clause 7.3.

In summary, GlaxoSmithKline alleged breaches of Clauses 7.2, 7.3, 7.4, 7.9, 7.10, 26.1, 26.2 and 26.3 of the Code as well as of the MHRA Blue Guide Section 6.6. To present clinical trial data in a misleading way and to issue a promotional press release did not maintain the high standards expected from a pharmaceutical company in breach of Clause 9.1. In addition, to the intent to promote in a misleading manner and the incorrect and misleading presentation of safety data had a potential impact on patient safety, and the failure to address GlaxoSmithKline's concerns, brought discredit upon, and reduced confidence in, the pharmaceutical industry, in breach of Clause 2.

RESPONSE

As the press release was issued by AstraZeneca's global organisation, that organization responded rather than the UK marketing organisation. Whilst AstraZeneca was headquartered in the UK, its global and corporate teams were located around the world, in the US and Sweden as well as the UK. AstraZeneca had taken the same approach throughout its correspondence with GlaxoSmithKline as it was most appropriate for the organisation which was responsible for the press release to respond directly.

AstraZeneca disagreed with GlaxoSmithKline's implication that this conflicted with the guidance on inter-company dialogue and submitted this was a deliberately narrow interpretation of the guidance which provided that communication 'should be between appropriate levels of relevant departments of the companies concerned. This will vary given the size and resources available within each company, but ideally those responsible for certifying the material, activity etc under the Code should be involved in the initial contact'.

AstraZeneca did not understand why a response from its global organisation had been characterized as inappropriate given that GlaxoSmithKline acknowledged that the material at issue was a global press release.

AstraZeneca stated that it took very seriously its compliance with all applicable laws and regulations, including pharmaceutical industry codes. AstraZeneca submitted that it had always addressed this matter in accordance with the high standards expected of a pharmaceutical company.

In summary AstraZeneca stated that:

- the press release was a non-promotional mandatory announcement issued pursuant to AstraZeneca PLC's obligations under the UK Listing Rules to disclose potentially share price sensitive information to investors and potential investors.

- the press release fell outside the scope of the ABPI Code because it was issued by AstraZeneca's headquarters and did not specifically refer to the availability of benralizumab in the UK. The treatment of financial information under the Code was different compared with other information made available to the public.

- even if the Code applied, the press release complied with the relevant provisions – and

specifically that neither the press release nor AstraZeneca's actions breached the Code or the MHRA Blue Guide.

- it was concerned at a number of inaccuracies in GlaxoSmithKline's descriptions of AstraZeneca's statements, actions and its websites, which it addressed in detail below.

- it was disappointed to have received a complaint from GlaxoSmithKline alleging multiple breaches of the Code in a case with numerous similarities to Case AUTH/2046/9/07 (Takeda v GlaxoSmithKline) and where GlaxoSmithKline sought to take an opposite position to that taken in that case. AstraZeneca questioned GlaxoSmithKline's motivation for making such an extensive complaint.

- GlaxoSmithKline had not engaged in inter-company dialogue as envisaged by the procedure and guidance on inter-company dialogue. The complaint had been made prematurely. The company regretted that it did not have the opportunity to complete inter-company dialogue and attempt to resolve these issues with GlaxoSmithKline.

Background on the release and information requested by the PMCPA

AstraZeneca PLC issued the press release on 10 November 2017; it was a mandatory announcement issued pursuant to AstraZeneca PLC's obligations under the UK Listing Rules to disclose potentially share price sensitive information to investors and potential investors. It was issued through the Regulatory News Service and to AstraZeneca's media distribution list for corporate business releases (aimed at financial and business media covering the pharmaceutical industry and AstraZeneca PLC).

The press release, which gave notice of the positive EU CHMP opinion for benralizumab for severe uncontrolled eosinophilic asthma, did not specifically refer to the availability or use of benralizumab in the UK and was available on the global website (astrazeneca.com) which was clearly labelled as intended for people seeking information on AstraZeneca's global business. Country-specific information, including for the UK, was available via country-specific websites. Further information on the website location of the release was set out in the section below (Jurisdiction of the Code). AstraZeneca separately issued a UK-specific press release in respect of the positive CHMP opinion to UK pharmaceutical trade and medical media outlets which was not available on any of AstraZeneca's websites.

AstraZeneca submitted that the press release was not promotional in nature. The information and data included in the press release was intended to inform investors, not patients or health professionals.

When the press release was issued, benralizumab was not approved in the UK or elsewhere in Europe. It was approved by the European Commission on 10 January 2018 (brand name Fasenra) as an add-on maintenance treatment in adults with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists.

AstraZeneca stated that the release did not fall within the materials for which certification was required by Clause 14 of the Code and therefore no certificate was produced and Clause 14.3 was not breached. Details of the process by which the release was examined were provided. A copy of the benralizumab summary of product characteristics (SPC) was provided. It was not available when the press release was issued as benralizumab was not approved until 10 January 2018.

Jurisdiction of the Code

AstraZeneca submitted that the press release fell outside the scope of the Code because it did not specifically refer to the availability of benralizumab in the UK (as per Clause 28 and Case AUTH/2046/9/07 as analysed below). In addition, the Code treated financial information differently compared with other information made available to the public (Clause 26 and its supplementary information).

AstraZeneca believed that this was in line with the overarching purpose of the Code as set out in Clause 1 and its supplementary information. Those provisions made it clear that the Code captured product promotion and product information when directed at, or otherwise influenced, an audience that played any part in the decision-making unit about the promotion of medicines, including the public as consumers and patients.

Information on the Internet

GlaxoSmithKline's complaint was based on the location of the press release on the Internet, with GlaxoSmithKline suggesting that the operation or hosting of the relevant website by a UK based company determined the jurisdiction of the Code. As such, Clause 28 (The Internet) was the relevant part of the Code. AstraZeneca, however, found GlaxoSmithKline's reasoning on this subject confused, as it had not explained how Clause 28 operated to bring the press release in scope. This was one of the topics on which clarification was sought during the truncated inter-company dialogue. In this regard, AstraZeneca stated that:

- GlaxoSmithKline's first letter (7 December 2017) stated that the press release was subject to the Code because it was released on 'a web page hosted by the UK affiliate of a multinational company which was obliged to abide by the Code and the MHRA Blue Guide.

- GlaxoSmithKline's second letter (5 January 2018) stated that the press release was clearly an activity regulated by the Code and suggested that the release was in fact a UK-specific release because it was possible to navigate to its location on AstraZeneca's global website from AstraZeneca's UK-specific website (astrazeneca.co.uk).

- GlaxoSmithKline's complaint to the PMCPA (15 January 2018) repeated the above statements and then included an additional line of reasoning (which did not appear in the letters of 7 December or 5 January) that the Code applied because AstraZeneca PLC was a member of the ABPI.

AstraZeneca did not dispute the location of the release on the Internet. The release was made available on AstraZeneca's global website which clearly stated that 'This website is intended for people seeking information on AstraZeneca's worldwide business. Our country sites can be located in the AZ Network'. When the press release was issued the Legal Notice and Terms of Use link incorrectly stated that the website was 'operated by AstraZeneca UK Limited'; that had since been corrected to refer to AstraZeneca PLC.

AstraZeneca submitted that the following was the correct interpretation of the Code in assessing whether the release was caught by Clause 28:

- promotional materials directed to a UK audience were within the scope of the Code (Clause 28.1).

- information or promotional materials placed on the Internet outside the UK were within the Code if they were placed on the Internet by an ABPI member or an affiliate and made specific reference to the availability or use of the medicine in the UK (Clause 28.2).

- AstraZeneca noted that the Code did not expressly deal with the situation under discussion where information (as distinct from promotional material) was placed on the Internet within the UK by an ABPI member or an affiliate, for global circulation, and which did not refer specifically to the availability or use of the medicine in the UK. AstraZeneca suggested that the correct interpretation of the Code, its intent and previous rulings (including Case AUTH/2046/9/07) was that the same principles should apply whether the relevant information was placed on the Internet within or outside the UK – ie that the Code only applied if it contained specific reference to the availability or use of the medicine in the UK.

In support of this interpretation, AstraZeneca referred to the facts and the decision in Case AUTH/2046/9/07 where information was placed on the GlaxoSmithKline corporate website which was UK based. In that case, the Panel found that a global press release was not subject to the Code because it did not make specific reference to the availability or use of the medicine in the UK. It was noted that the relevant medicine was actually available in the UK at the time. AstraZeneca noted GlaxoSmithKline's attempts to distinguish this case because the relevant press release was placed on the GlaxoSmithKline corporate website by GlaxoSmithKline's US affiliate and that the subject of that release was a meeting of the FDA Advisory Committee rather than a European event. AstraZeneca did not consider these to be distinguishing features in the current matter:

- a positive CHMP opinion was not a specific reference to a medicine being available in the UK. There was no reference to benralizumab being available in the UK as it was not approved when the press release was issued. It was therefore incorrect to suggest that a positive CHMP opinion was somehow a proxy for specific reference to a medicine being available in the UK. The release was for global consumption and was not specific to any particular market as the positive CHMP opinion was relevant for the investment community.

- the legal entity responsible for GlaxoSmithKline's press release should be irrelevant. Clause 28 applied to ABPI members and their affiliates, so whether it was one of GlaxoSmithKline's UK entities or its US affiliates was irrelevant. In addition, GlaxoSmithKline argued in Case AUTH/2046/9/07 that the press release was a corporate release relevant to its investors and it was issued on its global corporate website – as was the release for AstraZeneca.

AstraZeneca noted that GlaxoSmithKline, in concluding its arguments on jurisdiction, had referred to Clause 14.3 (supplementary information) and suggested that because of that provision the release was regulated by the Code. This reference was not made expressly in either of GlaxoSmithKline's letters to AstraZeneca. In addition, it contradicted GlaxoSmithKline's allegation that the release was promotional. Whilst AstraZeneca agreed the release was not promotional, it did not agree that, as a result, Clause 14 applied automatically. AstraZeneca submitted this interpretation was inconsistent with the meaning and effect of Clause 28 and the outcome of Case AUTH/2046/9/07. Clause 14 could not be the determining factor in the jurisdiction of the Code and should only apply if the information in question otherwise fell within the Code (eg pursuant to Clause 28).

Accessibility of the press release

With regard to GlaxoSmithKline's suggestion that the release was in fact a UK-specific release because it was possible to navigate to its location on AstraZeneca's global website from AstraZeneca's UK-specific website (astrazeneca.co.uk), whilst that potential navigation route was factually correct, GlaxoSmithKline had mischaracterised how that would happen. AstraZeneca alleged that GlaxoSmithKline was wrong to state 'However, when trying to access a UK press release on the EU CHMP opinion for benralizumab through AstraZeneca's UK website … the link leads back to the global press release website, with a link to the global press release only, for a UK audience'. AstraZeneca noted:

- there was no reference to the positive CHMP opinion for benralizumab on the AstraZeneca UK-specific website.

- if someone looked for any AstraZeneca news on the UK-specific website, he/she was directed to contact various AstraZeneca media teams. The

same page also provided a link to the global website homepage, beneath the statement 'For media information about our Global operation please visit our global website'. This link went through to the global website www.astrazeneca.com. It did not, as GlaxoSmithKline suggested, link directly to the global press release website – or even UK-focused information.

- the global website was clearly labelled with the following disclaimer on the bottom of each webpage, 'This website is intended for people seeking information on AstraZeneca's worldwide business. Our country sites can be located in the AZ Network'.

- on the global website homepage, news releases were found either via (i) Investor Relations/ Stock Exchange Announcements or (ii) Media/ Media Centre. As such, a visitor who looked for an AstraZeneca global release and who arrived at that site from the UK-specific website, would have to navigate several pages and make at least two clicks before reaching a global release. In addition, the two most recent corporate news releases were also featured at the bottom of the global website homepage. The press release was featured in this location from 10 to 15 November 2017 (labelled as a corporate press release).

GlaxoSmithKline provided exactly this path in its complaint and AstraZeneca was unclear why GlaxoSmithKline mischaracterised these matters.

Treatment of financial information under the Code

AstraZeneca stated that even if GlaxoSmithKline was correct in its assertion that the press release was within the scope of the Code, it did not believe that it would be appropriate to assess the release with reference to the provisions of Clause 7 (Information, Claims and Comparisons). In those circumstances the release would fall within the classification of financial information (as referred to in the supplementary information to Clause 26.2), which was treated differently to other information made available to the public. Clause 26.2 covered information made available to the public. The supplementary information to Clause 26.2, Information to the Public, specifically applied the provisions of Clause 7 to such information and press releases. However, supplementary information for Clause 26.2 (Financial Information) provided only that the relevant information must be factual and presented in a balanced way. There was no reference to Clause 7 and therefore Clause 7 did not apply to financial information.
GlaxoSmithKline made a similar submission in Case AUTH/2046/9/07; the case report recorded that 'GlaxoSmithKline submitted that a press release clearly intended for business and financial media was not promotional and as such was not subject to the promotional aspects of the Code'. AstraZeneca was surprised that GlaxoSmithKline's complaint conflicted with submissions that it had made to the PMCPA in respect of its own conduct.

AstraZeneca submitted that its position was consistent with the MHRA Blue Guide (section 7.7) and the EFPIA code (page 6 and also section 2, content of websites page 21) in that financial press releases were treated differently from advertisements to persons qualified to prescribe or supply medicines.

Content of the press release

AstraZeneca submitted that the press release was not within the scope of the Code. In the event that the Panel disagreed, AstraZeneca asserted that the press release complied with the Code, and that neither the press release nor AstraZeneca's actions breached the Code (Clause 7) or the MHRA Blue Guide (Section 6.6).

The press release was a non-promotional communication, aimed at a worldwide audience and sent to business and financial media. The information provided in the release was factual, presented in a balanced way, of clear commercial importance and was sufficient to inform the investment decisions of the financial and investment audience to which it was directed. In addition, for completeness, transparency and to ensure that readers who wished to see further detail, active hyperlinks within the press release directed readers to the study publications for each of the relevant clinical trials (CALIMA, SIROCCO, and ZONDA) (both ahead of the high level bulleted attributes and again in the section 'About the WINDWARD Programme).

AstraZeneca responded to each of GlaxoSmithKline's concerns about statements in the press release:

1 **'Up to 51% reduction in the annual exacerbations rate (AERR) versus placebo'**

AstraZeneca stated that the reduction in AERR vs placebo in the two registrational studies, SIROCCO and CALIMA, were 51% and 28% respectively. The inclusion of 'up to' ensured that the claim was factually correct and not misleading: 51% was the maximum response observed across both studies. The claim was therefore accurate, balanced and provided in a succinct and easily comprehensible manner for the intended audience to inform investment decisions.

2 **'Rapid improvement in lung function (290mL increase in forced expiratory volume in FEV1 from baseline at 4 weeks) after the first dose, providing an early indication of effectiveness'.**

AstraZeneca disagreed that the claim was unbalanced or misleading for the intended audience. It was acceptable to provide the improvement in FEV1 at the 4 week time point as it was relevant to the reader's understanding of the medicine's profile.

AstraZeneca disagreed that the phrase 'Rapid improvement' was an all-encompassing claim because it was not a claim but a factual statement in non-promotional material. It was also not all-encompassing as it did not cover all endpoints, but referred specifically to lung function using FEV1 as a surrogate. The context was very clear.

The statement specifically described the benralizumab mechanism of action with respect to the timing of effect on lung physiology, as indicative of a rapid FEV1 response. The statement was that this was 'providing an early indication of effectiveness' not all-encompassing effectiveness. GlaxoSmithKline queried how 'efficacy relates to effectiveness'. AstraZeneca submitted that it was appropriate to use the word 'effectiveness' given the intended financial audience. The statement did not represent an all-encompassing claim of clinical efficacy.

AstraZeneca submitted that the statement was accurate, balanced and presented in succinct manner which was easily comprehensible for the intended audience.

3 **'75% median reduction in daily OCS use and discontinuation of OCS use in 52% of eligible patients'**

AstraZeneca strongly disagreed that this claim was misleading or unbalanced. It was factually correct and appropriate given the audience. Additional context was provided in the press release in the section titled 'About the WINDWARD Programme'. There was also no reason why the data relating to reduction in daily OCS use must be presented in exactly the same way as the exacerbation reduction data.

4 **'An overall adverse event profile similar to placebo'**

AstraZeneca was committed to patient safety and took any communications relating to all its medicines (both marketed and in development) very seriously, especially when safety profiles were discussed. AstraZeneca strongly refuted the allegations that the above claim was misleading or that it raised false hopes and could lead to inappropriate prescribing. Indeed, the intended financial and investment nature of the audience precluded this.

AstraZeneca submitted that the claim was factually correct and in line with relevant study reports. In the press release, the term 'overall' adverse events referred to the 'any' adverse event analysis for the studies. During the treatment period in the SIROCCO study, adverse events were reported by similar percentages of patients who received benralizumab Q8W (71%) or placebo (76%). The ZONDA study reported that 'Frequencies of adverse events were similar between each Benralizumab group and placebo group'. In CALIMA, the percentage of any reported adverse events for patients who received placebo was 78% and 75% for benralizumab (Q8W).

It was generally well accepted that adverse events were observed in the placebo arms of studies, and so it was reasonable to present an overall comparison of the adverse events observed in the placebo and active comparator arms of the study in a succinct and easily comprehensible manner that was tailored to the audience and would be appropriately understood. In addition, the press release did not state or imply that benralizumab was 'safe' or that there was an observed lack of side-effects and did not, therefore, breach Clause 7 of the Code or Section 6.6 of the MHRA Blue Guide. As stated above, links to the full study publications for the data presented were included in the press release.

5 **'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use'**

This claim was used with the knowledge that in the registration trials benralizumab had demonstrated efficacy, the ability to reduce oral corticosteroids usage and speed of onset in relation to both reduction of FEV1 and eosinophil depletion beginning after the first dose.

AstraZeneca believed that the word 'potential' ensured that the audience knew that any clinical benefits observed in studies to date were not applicable to all patients.

The suggestion by GlaxoSmithKline that the word 'convenience' was intended as a comparison of benralizumab with oral medications and inhalers was incorrect, and not an obvious conclusion to draw about the phrasing of that sentence. The use of the 'convenience' referred to the every 8-week maintenance dosing schedule and this was acknowledged in GlaxoSmithKline's letter of 7 December 2017. Every 8-week dosing was currently the longest dosing interval for a marketed asthma biologic.

Inter-company dialogue

AstraZeneca did not believe that GlaxoSmithKline had engaged in inter-company dialogue as envisaged by the PMCPA guidance. AstraZeneca therefore believed that the complaint was submitted prematurely.

GlaxoSmithKline had never suggested an in-person conversation regarding the issues raised and it had ignored or declined AstraZeneca's repeated offers of conversations and requests for specific clarification of issues, as explained below:

- GlaxoSmithKline's first letter (7 December 2017) did not include an offer of inter-company dialogue. Instead, it referred to inter-company dialogue but demanded that AstraZeneca agree to specified steps (providing information on distribution and examination of the release; giving an undertaking; and, issuing a corrective statement).

- AstraZeneca's response (20 December 2017) concluded with a statement that if GlaxoSmithKline had any further concerns, AstraZeneca would be happy to discuss them. AstraZeneca acknowledged that it did not deal with the detailed complaints raised by GlaxoSmithKline but instead focused on the detailed background of the release which it hoped

would help clarify that the release was global in nature and intended for a financial and business audience.

- GlaxoSmithKline's letter of 5 January 2018 (emailed on 4 January) demonstrated that it continued to have further concerns but it did not take up AstraZeneca's offer of a conversation. This second letter reiterated GlaxoSmithKline's demand that AstraZeneca agreed to the specified steps, again without any suggestion of a conversation.

- AstraZeneca's response (11 January) explicitly stated that it needed further information to respond to GlaxoSmithKline's concerns. Specific reference was made to dates and attendees for that meeting which demonstrated AstraZeneca's continued commitment to have a genuine dialogue.

- GlaxoSmithKline and AstraZeneca spoke by telephone on 12 January. AstraZeneca stated that GlaxoSmithKline's account above did not accurately represent that telephone conversation.

    - AstraZeneca requested that call to amplify the request for a meeting made in its 11 January letter and to emphasise that the complexities around global financial releases meant that appropriate attendees included corporate personnel as well as medical. It was not to rehearse the dialogue intended for the proposed meeting, nor were all of the relevant AstraZeneca personnel on that conference call to enable that dialogue to occur.

    - The relevant AstraZeneca personnel were not all on the call. Whilst it was correct that AstraZeneca was 'not willing to discuss the specific detail of the points raised in the GlaxoSmithKline letter' on the call, it was misleading to imply that such unwillingness displayed an overall refusal to engage in a dialogue. AstraZeneca had expressly requested a separate meeting to do so and to obtain the requested clarification. AstraZeneca gave assurances that each point of the complaint would be addressed at such a meeting, with the relevant personnel present.

    - It was not correct that AstraZeneca had 'underlined its position that the press release did not fall under the ABPI Code'. No such statement was made.

    - AstraZeneca had suggested that the proposed face-to-face meeting also covered the broader question of global press releases but did not believe that that suggestion automatically rendered the proposed meeting redundant. If GlaxoSmithKline was interested in pursuing an inter-company dialogue but had issues with that topic, it could have proposed excluding that topic from the meeting; instead, it rejected the meeting in its entirety.

- Following the 12 January telephone conversation, GlaxoSmithKline and AstraZeneca corresponded by email. AstraZeneca believed that such correspondence was relevant background and it noted that GlaxoSmithKline had not provided that correspondence with its complaint. The email exchange was provided.

    - GlaxoSmithKline's email on 12 January declined AstraZeneca's proposed meeting on the grounds that 'GlaxoSmithKline and AstraZeneca fundamentally have a different view on this matter and that our concerns raised will not be adequately resolved through further intercompany dialogue'. AstraZeneca stated that it did not discuss its view of the specific detail of GlaxoSmithKline's complaints on the 12 January telephone call. It was therefore difficult to see how GlaxoSmithKline could have concluded that the positions were irreconcilable and pre-empt the outcome of such a meeting by concluding that GlaxoSmithKline and AstraZeneca would not be able to agree.

    - AstraZeneca's response to that email (15 January 2018) restated its request for clarification of GlaxoSmithKline's position on several matters in order to respond to GlaxoSmithKline's issues. It also reaffirmed AstraZeneca's commitment to a genuine dialogue and AstraZeneca's continued availability for a face-to-face meeting.

Further details

AstraZeneca explained that the press release was prepared in line with its procedures for the generation of a Regulatory News Service disclosure.

In anticipation of the positive CHMP opinion, drafting of the press release began in early November 2017. The press release was developed and approved by the global team responsible for benralizumab. Details of the roles involved in this process were provided.

The press release was issued through the Regulatory News Service. It was also distributed electronically to AstraZeneca's media distribution list for corporate business releases (aimed at financial and business media covering the pharmaceutical industry and AstraZeneca PLC). The media distribution list was provided.

In response to a request for further information AstraZeneca confirmed that the 290ml increase in FEV1 from baseline at week 4 seen in the benralizumab 30mg every eight weeks arm was taken from the SIROCCO study. The data on file created was provided. The pooled post-hoc analysis (for SIROCCO and CALIMA studies) mentioned in the press release FitzGerald, *et al* 2018, was provided. This was published in September 2017 (ahead of print).

AstraZeneca stated that the study explored the relationship between benralizumab efficacy and baseline patient characteristics including blood eosinophil counts, historical exacerbations, OCS use and the history of nasal polyps, among other baseline factors.

PANEL RULING

The Panel noted that its role was to consider matters in relation to the Code and not the MHRA Blue Guide; GlaxoSmithKline's allegations regarding the Blue Guide were thus not considered.

The Panel noted the comments from both parties about the inter-company dialogue and that there were clearly some differences of opinion. GlaxoSmithKline contacted AstraZeneca on 7 December 2017, 5 January 2018 and 12 January. It appeared that AstraZeneca had not responded to the detailed points raised. In an email dated 15 January, AstraZeneca requested further clarification of GlaxoSmithKline's position and interpretation to be able to respond in more detail and offered to address each matter at a proposed meeting. GlaxoSmithKline had not agreed to the meeting and had submitted a complaint to the PMCPA approximately a month (allowing for the Christmas break) after first raising detailed points when it had not received a response. The matter had been referred to the Panel by the case preparation manager who by accepting the complaint was satisfied that the requirements for inter-company dialogue had been met.

This had not changed following receipt of further details from AstraZeneca.

The Panel noted the requirements of Clause 1.11. The supplementary information to Clause 1.11, Applicability of Codes, stated that pharmaceutical companies must ensure that they complied with all applicable codes, laws and regulations to which they were subject. This was particularly relevant when activities/materials involved more than one country or when a pharmaceutical company based in one country was involved in activities in another country.

Activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European country as well as the national code of the country in which the activities took place or the materials were used. In the event of a conflict of requirements the more restrictive requirements would apply. The only exemption for companies based in the UK not to follow the UK Code was with regard to the limits on subsistence set in European countries.

Clause 1.11 and its supplementary information were based on requirements in the EFPIA Health Professional Code. The Panel considered that, as a minimum, companies located in the UK were clearly required to comply with the UK Code and this would apply to AstraZeneca global. There might be occasions when it could be clearly demonstrated that the ABPI Code did not apply. In the Panel's view the press release at issue came within the scope of the ABPI Code; it had been produced by a company located in the UK (AstraZeneca global) and placed on a UK website described at the time as operated by AstraZeneca UK Limited. This had since been changed to AstraZeneca PLC. The Panel considered that the fact there was a UK specific press release did not mean that the press release in question was not covered by the ABPI Code.

The Panel did not accept AstraZeneca's submission that the Code did not expressly deal with the current situation where information was placed on the Internet within the UK for global circulation. In the Panel's view, for the reasons outlined above, the UK Code applied.

The Panel considered the points made by both GlaxoSmithKline and AstraZeneca about the relevance of Case AUTH/2046/9/07 when GlaxoSmithKline US had placed a press release on the GlaxoSmithKline corporate website. That press release referred to use of the product in the US and a meeting of the FDA Advisory Committee. The Panel at the time had decided that Clause 21.2 applied (now Clause 28.2) as the press release was placed on the Internet by a company outside the UK but as it did not meet the second requirement, ie specifically refer to its availability or use in the UK, then there was no breach of that clause of the Code and the press release was not within the scope of the Code. The Panel now noted, however, that in considering Case AUTH/2046/9/07, no reference was made to what was then Clause 1.7 but now Clause 1.11 ie that activities carried out and materials used in a European country by a pharmaceutical company located in a country other than a European country must comply with the EFPIA Code as well as the national code of the country in which the activities are carried out and materials are used. It appeared that no account had been taken of the fact that GlaxoSmithKline Global was based in the UK. The Panel's rulings of no breach of the Code were not appealed.

The Panel noted that Clause 28.2 of the Code stated that information or promotional material about medicines covered by Clause 28.1 which was placed on the Internet outside the UK would be regarded as coming within the scope of the Code if it was placed there by a UK company or an affiliate of a UK company or at the instigation or with the authority of such a company and it made specific reference to the availability or use of the medicine in the UK. The Panel, however, did not consider that Clause 28.2 was relevant in the case now before it as the AstraZeneca press release was not placed on the Internet outside the UK. In any event, the press release at issue referred to a product with a positive EU opinion recommending a marketing authorization which would be valid in the UK.

The Panel noted AstraZeneca's submission regarding the EFPIA Guidelines for Internet Websites Available to Healthcare Professionals, Patient and the Public in Europe. The Guidelines stated that member associations might find it necessary to adapt these guidelines to meet their particular requirements or needs and were encouraged to adopt additional

measures which extended further than the EFPIA Guidelines. The EFPIA Guidelines stated that general information on the company was not regulated by the EFPIA Guidelines or provisions of medicines advertising law.

The Panel noted that unlike the EFPIA codes the ABPI Code had detailed requirements for relations with the public and the media (Clause 26). The Panel considered if general information on the company promoted a prescription only medicine then such information was likely to be covered by medicines regulation which prohibited the advertising of prescription only medicines to the public.
The Panel noted the supplementary information to Clause 26.2 that information made available in order to inform stakeholders, the Stock Exchange and the like by way of annual reports and announcements etc might relate to both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. Business press releases should identify the business importance of the information.

The Panel noted that the press release referred to the positive CHMP opinion. It referred to features of benralizumab and its potential to make 'a real difference to patients with its combination of efficacy, speed of onset, convenience and ability to reduce oral steroid use'. The results of studies were described and a quotation from a UK investigator included the use of benralizumab to 'help transform severe asthma care'.

The press release ended with notes to editors which covered severe asthma, benralizumab, the Windward Programme in asthma which consisted of Six Phase III trials, AstraZeneca in respiratory diseases, Medimmune (part of AstraZeneca), AstraZeneca and referred to the AstraZeneca.com website. After the list of contacts for media relations and investor relations it was stated that the announcement contained inside information. The Panel noted that the press release did not identify the business importance of the information at the start. The Panel did not consider, given its clinical content, that the press release was clearly a business press release.

The Panel noted the distribution of the press release which included business reporters/editors, markets reporters and a small number of health reporters/ editors. The circulation was not limited to financial journalists.

The Panel agreed with AstraZeneca that press releases were treated differently from advertisements to health professionals. This distinction was clear in the Code in that information to the public about prescription only medicines was covered by Clause 26 of the Code which referred to relations with the public and media. Clause 26.2 covered information made available to the public either directly or indirectly. The supplementary information to Clause 26.2, Information to the Public, was clear that Clauses 7.2, 7.4, 7.5, 7.8, 7.9, 7.10 and 7.11, which set out the information quality standards in the Code, also applied and thus whether the material was an advertisement to a health professional or information to the public, similar standards applied. That the specific supplementary information relating to financial information did not refer to the information quality standards did not mean that these standards did not apply to such material, the supplementary information added clarity that there was often a need for Stock Exchange announcements to refer to medicines not yet authorized. It also referred to the need to identify the business importance of the information and that the information must be factual and presented in a balanced way.

Taking all the circumstances into account as set out above, the Panel considered that the press release was subject to the Code. It then went on to consider the allegations made by GlaxoSmithKline.

The Panel noted that the SPC available on the electronic medicines compendium (eMC) stated that Fasenra (benralizumab) was first authorised on 8 January 2018. The recommended dose of benralizumab was 30mg every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. Fasenra was intended for long-term treatment. A decision to continue the therapy should be made at least annually based on disease severity, level of exacerbation control and blood eosinophil counts. The SPC stated, under special warnings and precautions for use, that abrupt discontinuation of corticosteroids after initiation of Fasenra therapy was not recommended. Reduction in corticosteroid doses, if appropriate, should be gradual and performed under the supervision of a physician.

The Panel noted that the press release stated that patients in SIROCCO and CALIMA received standard of care medicine (including high dose inhaled corticosteroids and long acting beta 2 agonists) and were randomized to receive benralizumab 30mg every 4 weeks, 30mg every 4 weeks for the first 3 doses followed by 30mg every 8 weeks or placebo via a subcutaneous injection.

With regard to the claim 'Up to 51% reduction in the annual asthma exacerbations rate (AERR) versus placebo', the Panel noted this was from the SIROCCO trial (Bleecker *et al* 2016). The CALIMA trial (FitzGerald *et al* 2016) stated that annual exacerbation rates were approximately 28% lower than with placebo. The Panel considered that the use of the phrase 'up to 51%' was misleading as it did not reflect the range. The balance of the data had not been reflected and a breach of Clause 7.2 was ruled.

The Panel considered that the information made available to the public had not been presented in a balanced way and a breach of Clause 26.2 was ruled accordingly.

With regard to the claim 'Rapid improvement in lung function (290mL increase in forced expiratory volume in FEV1 from baseline at 4 weeks) after the first dose, providing an early indication of effectiveness', the Panel noted that SIROCCO concluded that both benralizumab dosing regimens significantly improved pre-bronchodilator FEV1 in patients at week 48 compared with placebo. The

difference between benralizumab 30mg every 8 weeks and placebo (in patients with baseline eosinophils ≥ 300 cells per mcl was 159ml (p = 0.0006). The Panel noted AstraZeneca's submission that the 290ml increase in FEV1 from baseline at week 4 data as stated in the press release came from SIROCCO. Data on file had been created which stated that at week 4 there was a 290ml increase in FEV1 for benralizumab and a 209ml increase for placebo (p=0.039) versus baseline. The estimated difference between benralizumab and placebo was 81ml.
CALIMA concluded that benralizumab significantly improved pre-bronchodilator FEV1. Improvements in pre-bronchodilator FEV1 were present within 4 weeks of treatment start and were maintained through the treatment period. At week 56 the difference between benralizumab 30mg every 8 weeks and placebo (in patients with baseline eosinophils ≥ 300 cells per mcl) was 116ml (p = 0.0102). The Panel noted that CALIMA stated that annual exacerbation rates, pre-bronchodilator FEV1 and total asthma scores were not affected by benralizumab for the subset of patients receiving medium-dosage inhaled corticosteroids plus LABA with blood eosinophils ≥ 300 cells per mcl at baseline.

The data on file for CALIMA at week 4 showed there was a 280ml increase in FEV1 for benralizumab 30mg every 8 weeks and 152ml for placebo (p=0.002) versus baseline. The estimated difference between benralizumab and placebo was 127ml.

The SIROCCO and CALIMA data on file stated that the analysis of these endpoints were not multiplicity protected and therefore p values were reported as nominal. Results were descriptive only.

The Panel noted that the ZONDA study (Nair *et al* (2017)) assessed the effects of benralizumab versus placebo on the reduction in oral glucocorticoid dose whilst maintaining asthma control in adults with severe asthma. ZONDA concluded that benralizumab showed significant clinically relevant benefits compared with placebo on oral glucocorticoid use and exacerbation rates. These effects occurred without a sustained effect on FEV1.

The Panel noted that the claim in the press release referred to a rapid improvement in lung function. It appeared to the Panel that if the improvements in FEV1 at 4 weeks in SIROCCO and CALIMA were seen as rapid improvement in lung function then there was evidence to support the change in both the treated and placebo groups. The Panel considered that it was misleading and exaggerated not to include the placebo data in the press release to ensure that the improvements from baseline were not confused with improvements compared with placebo. The Panel therefore ruled a breach of Clauses 7.2 and 7.10 of the Code. The data was capable of substantiation so no breach of Clause 7.4 was ruled.

The Panel considered that information to the public had not been presented in a balanced way and a breach of Clause 26.2 was ruled.

With regard to the claim '75% median reduction in daily OCS use and discontinuation of OCS use in 52% of eligible patients', the Panel considered that it was not clear that the reduction in daily OCS use difference was compared to baseline. It noted that the placebo data also showed a decrease in daily OCS use. The SPC published on the eMC gave the placebo reduction as 25%. The Panel considered that the data in the press release was not placed in context; the press release was misleading in this regard and the Panel therefore ruled a breach of Clause 7.2.
The Panel considered that information to the public had not been presented in a balanced way and a breach of Clause 26.2 was ruled.

With regard to the claim 'an overall adverse event profile similar to placebo', the Panel noted that the medicine was new and at the time of the press release it was not licensed in the UK. The intended audience would not necessarily be familiar with the incidence of adverse events with placebo. The claim referred to the addition of benralizumab rather than the overall incidence of adverse events when the medicine was used in addition to high-dose inhaled corticosteroids plus long acting beta agonists. The SPC published on the eMC stated that the most common adverse reactions during treatment were headache (8%) and pharyngitis (3%). Injection site reactions (eg pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with the recommended benralizumab dose compared with 1.9% in patients treated with placebo.

The Panel was concerned about the lack of context for the claim in the press release to an audience that were, in effect, members of the public. There was no further data in the press release about adverse events. The press release was misleading in this regard; it was not balanced and a breach of Clause 7.9 was ruled. The Panel considered that the claim exaggerated the properties of the product and thus it ruled a breach of Clause 7.10.

The Panel considered that information to the public about the adverse event profile had not been presented in a balanced way and a breach of Clause 26.2 was ruled.

The Panel noted that Clause 26.3 covered material which related to a medicine and which was intended for patients taking that medicine and required, *inter alia*, that when the material related to a medicine which was subject to additional monitoring, an inverted black equilateral triangle must be included on it together with a statement about additional monitoring and reporting of side-effects. The Panel considered that as the press release was not specifically intended for patients taking the medicine Clause 26.3 did not apply and the Panel ruled no breach of that clause.

With regard to GlaxoSmithKline's general allegation that the omission of both key clinical data and the placebo data meant that the conclusion on efficacy and safety would be different, the Panel noted that it had ruled various statements and claims in breach of Clause 26.2. It considered that this allegation had

been addressed by its rulings of breaches of the Code above. It would be relevant in considering the allegations of breaches of Clause 9.1 and 2 below. It therefore ruled no breach of Clause 26.2 in relation to the broad allegation.

With regard to the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' the Panel considered that this was a broad, strong claim for the medicine. It was a quotation from the AstraZeneca executive vice president, global medicines development and chief medical officer. The Panel considered that readers of the press release would be clear that the benralizumab was to be dosed every eight weeks. However, it was not clear that the first 3 doses were to be given every 4 weeks. The Panel did not accept AstraZeneca's submission that the use of the word 'potential' meant that readers would be aware that any clinical benefits observed in studies to date were not applicable to all patients.

Patients using Fasenra would need to continue with other asthma medication as stated in the package information leaflet (high doses of corticosteroids). Use of Fasenra might allow patients to reduce or stop daily OCS. This would be done gradually under supervision of a doctor.

On balance, the Panel did not consider that the claim in the press release was an advertisement for Fasenra, a prescription only medicine, to the public. The medicine was unlicensed at the time of the press release and thus not classified as a prescription only medicine. The Panel ruled no breach of Clause 26.1. It considered that the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' might raise unfounded hopes of successful treatment, particularly given the lack of information about the need to be monitored before changing the doses of a patient's current medication.

The Panel noted the allegations about the speed of onset and the data for FEV1, and the changes at 4 weeks for patients with baseline eosinophils ≥ 300 cells per mcl. The Panel queried whether adding in an additional therapy was convenient for patients. It was not clear until page two of the press release that benralizumab was a subcutaneous injection. The Panel noted that there were other medicines available, one of which was GlaxoSmithKline medicine, mepolizumab (Nucala), which was to be given every 4 weeks. The basis of the claim for convenience in the press release was not clear to the Panel. AstraZeneca submitted that it related to the 8 week maintenance dosing schedule which the Panel noted was longer than for GlaxoSmithKline's medicine. The Panel considered that, given AstraZeneca's product had 3 doses at 4 week intervals, it was possible that maintenance treatment at 8 weeks would not be seen as convenient compared to treatment at 4 weeks. The Panel considered that, overall, the claim could be read as a comparison with inhalers and/or oral medication and compared to inhalers or oral medication, benralizumab was not convenient. Overall, it considered that the claim for convenience was misleading and therefore ruled a breach of Clause 7.3.

The Panel considered that information to the public had not been presented in a balanced way and a breach of Clause 26.2 was ruled.

With regard to the alleged breach of Clause 7.5, the Panel noted that this required that substantiation be provided as soon as possible and within 10 working days following a request from a health professional. GlaxoSmithKline had provided no information in this regard. The Panel noted that GlaxoSmithKline was dissatisfied with AstraZeneca's response to the intercompany dialogue. The Panel did not consider that GlaxoSmithKline had provided evidence that when a health professional asked for substantiation this was not provided. The Panel ruled no breach of Clause 7.5.

Noting all its rulings above, the Panel did not consider that high standards had been maintained and therefore ruled a breach of Clause 9.1.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such use. The Panel noted that one of the reasons for GlaxoSmithKline to support a breach of Clause 2 was AstraZeneca's alleged failure to address GlaxoSmithKline's concerns. The Panel did not consider that this was relevant to its consideration regarding Clause 2. The Panel noted its rulings of breaches of the Code. It considered that it was extremely important that press releases were accurate, balanced and not misleading. On balance, the Panel considered that the circumstances did not warrant a ruling of a breach of Clause 2 and ruled accordingly.

Complaint received **17 January 2018**

Case completed **4 May 2018**

CASE AUTH/3012/1/18

VOLUNTARY ADMISSION BY PIERRE FABRE

Failure to certify material

Pursuant to Case AUTH/2962/7/17, Pierre Fabre voluntarily admitted that it had identified certain breaches of the Code in material related to Toviaz (fesoterodine), a treatment for the symptoms of overactive bladder syndrome. The material at issue included that used at a cycle meeting in April 2017, a Toviaz slide set and an email, with attachments, sent to the representatives after the cycle meeting.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Pierre Fabre.

Pierre Fabre noted that a slide deck, 'Marketing Focus: Strategy for UK & ROI' presented at the cycle meeting and subsequently emailed to the representatives bore no code number or date of preparation and there was no disclaimer regarding its use or distribution. Pierre Fabre submitted that the slides had not been certified before use and that the information on one slide was unbalanced and misleading and not always capable of substantiation.

With regard to the framework for the cycle meeting, agenda and objectives, Pierre Fabre again noted the absence of a code number, date of preparation and certification.

Pierre Fabre submitted that the Toviaz 'Meetings in a box' slides used at the cycle meeting had also not been certified and nor had an email sent to the sales force after the cycle meeting.

Pierre Fabre noted that one of the documents sent with the email was a corporate presentation for use with health professionals. The presentation charted the company's history and a slide which detailed strategic partnerships in 2015 (some of which existed, *inter alia*, to further the development of new medicines) referred to possible therapeutic targets and a licensing opportunity. Pierre Fabre submitted that such information might encourage an audience to enquire about medicines in development/ commercial opportunities. Further the sales force briefing material for the presentation referred to the healthy product pipeline which might encourage representatives to pay particular attention to the slide. Pierre Fabre also submitted that another slide of the corporate presentation referred the audience to the company's global website for further information. Pierre Fabre stated that the website was thus not addressed to a UK audience. Pierre Fabre stated that the briefing material was not certified.

Pierre Fabre submitted that the breaches above collectively demonstrated a failure to understand, to apply and to comply with certification of materials used to brief representatives, and other breaches. Pierre Fabre stated that the breaches above reflected the errors and confusion of accountability for responsibility for compliance with the Code that occurred during a period of dysfunctional management.

Pierre Fabre submitted however, that there had been no breach of Clause 2 as there were no risks for patient safety and the breaches had not brought discredit upon, or reduced confidence in, the industry.

Pierre Fabre apologised unreservedly for the breaches above. The company was fully committed to maintaining high standards and to taking all steps to both remedy the failings identified. Pierre Fabre UK and Europe had learned from these failings and were taking all available steps to prevent recurrence.

The details response from Pierre Fabre is given below.

The Panel noted that the marketing focus slide deck used at the cycle meeting did not include a date of preparation or guidance as to how it was to be used by representatives. The email dated 2 May 2017 did not give any instructions about the use of this presentation which the Panel considered was briefing material for representatives as required by the Code. The Panel noted the failure to certify the presentation and ruled a breach of the Code.

With regard to the date of preparation the Panel noted that the Code referred to promotional material. It was not clear whether the marketing focus presentation was to be shown to health professionals. In the Panel's view, as the presentation was briefing material it would have been helpful to include a date of preparation but as there was no requirement for it do so. The Panel did not consider Clause 4.8 applied so no breach of that clause was ruled.

One slide was headed 'Decision Tree' with three sub headings including'Mirabegron is better tolerated than any anticholinergic' beneath which was the claim 'European Warning – CV risk'. Pierre Fabre stated that the material failed to balance this with the statement in the Toviaz summary of product characteristics (SPC) that it should be used with caution in patients with risk of QT prolongation. The Panel thus considered that the briefing material was misleading and not capable of substantiation as required; breaches of the Code were ruled. The briefing material advocated a course of action which would be likely to lead to a breach of the Code if the representatives used this statement.

With regard to the framework for the cycle meeting, agenda and objectives, the Panel considered that this constituted briefing material as it referred to the quantity and quality of calls by representatives on health professionals. The failure to certify such material meant that it did not comply with the relevant requirement of the Code. A breach of the Code was ruled.

With regard to the date of preparation the Panel noted its comments above regarding briefing material and again ruled no breach of the Code.

With regard to the Toviaz 'meetings in a box' slides, the Panel noted that they were not certified at the time of the April cycle meeting. They were certified on 5 May. The first slide of the presentation in April was marked 'Draft'. The Panel considered that the slides should have been certified prior to being presented at the cycle meeting. Their use at the cycle meeting would constitute briefing material for the representatives and, as previously, the failure to certify briefing material was ruled in breach of the Code.

With regard to the email sent after the cycle meeting, which provided certain documents to the representatives, the Panel noted that it was not certified and considered that it should have been as it constituted briefing material. A breach of the Code was ruled.

The company profile presentation was to be used with health professionals. It gave an overview of the company's history. One slide referred to partnerships which were to 'Develop and commercialize two novel molecules in oncology'. The briefing material instructed representatives to use the slides at meetings prior to the presentation of main product slides with the key messages that the company had patient interest at its core and it was steadily growing with a healthy product pipeline. It was for promotional use.

The Panel was concerned that the presentation included focus on strategic partnerships which referred to developing and commercialising two novel molecules in oncology.

The Panel considered that the presentation went beyond general comments about Pierre Fabre's interests in oncology. The slide would elicit questions about the pipeline. The briefing material for representatives gave no instructions about the response to such questions nor did it give much information about how the slides were to be used. The Panel considered that slide at issue promoted unlicensed medicines and a breach of the Code was ruled. This presentation had been certified.

The Panel noted that the briefing material for the presentation had not been certified as required by the Code. The briefing material and the company profile presentation advocated a course of action that would lead to a breach of the Code and thus the Panel ruled a breach of the Code.

The Panel noted Pierre Fabre's submission that another slide from the company profile presentation referred the audience to the global website (www.pierre-fabre.com) which was not addressed to a UK audience. Pierre Fabre cited one clause in this regard but provided no further details or the website content. The voluntary admission implied that the website had not been certified and thus the Panel ruled a breach of the Code.

The Panel noted its comments and rulings above and considered that Pierre Fabre had failed to maintain high standards. A breach of the Code was ruled.

The Panel noted its ruling above of a breach of the Code with regard to the promotion of unlicensed medicines, an activity likely to be in breach of Clause 2. The Panel noted that a robust certification procedure underpinned self-regulation. The Panel considered that in advertising a medicine prior to the grant of a marketing authorization and failing to certify material meant that Pierre Fabre had brought discredit upon or reduced confidence in the pharmaceutical industry and a breach of the Code was ruled.

Pursuant to Case AUTH/2962/7/17, Pierre Fabre Limited voluntarily admitted that it had identified certain breaches of the Code in material related to Toviaz (fesoterodine). Toviaz was indicated for the treatment of symptoms of overactive bladder syndrome. The marketing authorization holder was Pfizer Limited.

In September 2017 Pierre Fabre suspended all promotion of Toviaz in the UK pending the completion of steps being implemented by it in close consultation with Pfizer. The material at issue included that used at a cycle meeting in April 2017, a Toviaz slide set and an email, with attachments, sent to the representatives after the cycle meeting.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Pierre Fabre.

VOLUNTARY ADMISSION

Pierre Fabre noted that a slide deck, 'Marketing Focus: Strategy for UK & ROI' presented at the cycle meeting and subsequently emailed to the representatives bore no code number or date of preparation and there was no disclaimer regarding its use or distribution. Pierre Fabre submitted that the slides had not been certified before use in breach of Clause 14.1. The company also submitted that the information on slide 9 was unbalanced and misleading and not always capable of substantiation. Pierre Fabre admitted breaches of Clauses 7.2 and 7.4.

With regard to the framework for the cycle meeting, agenda and objectives, Pierre Fabre again noted the absence of a code number and date of preparation; the material had not been certified in breach of Clause 14.1.

Pierre Fabre provided two copies of Toviaz 'Meetings in a box' slides. The first copy was that used at the cycle meeting and the second copy was the one certified in May 2017, after the April meeting. As

the slides used at the April meeting had not been certified, Pierre Fabre admitted a breach of Clause 14.1.

Subsequent to the April cycle meeting, Pierre Fabre emailed the sales force and attached a number of documents. Pierre Fabre submitted that the email had not been certified, in breach of Clause 14.1.

Pierre Fabre noted that one of the documents sent with the email above was a corporate presentation for use with health professionals. The presentation charted the company's history and one slide detailed strategic partnerships in 2015; some of those partnerships existed, inter alia, to further the development of new medicines. The slide referred to possible therapeutic targets and a licensing opportunity. Pierre Fabre submitted that such information might encourage an audience to enquire about medicines in development/commercial opportunities. Pierre Fabre admitted breaches of Clauses 3.1 and 15.9.

Pierre Fabre stated that the sales force briefing material for the corporate presentation included key messages, one of which referred to the healthy product pipeline which might encourage representatives to pay particular attention to the slide discussed above. Further, Pierre Fabre also submitted that another slide in the presentation referred the audience to the company's global website for further information. Pierre Fabre stated that the website was thus not addressed to a UK audience. Pierre Fabre acknowledge a breach of Clause 14.1 in that the briefing material was not certified before use.

Pierre Fabre submitted that the breaches above collectively constituted a breach of Clause 9.1 as they demonstrated a failure to understand, to apply and to comply with certification of materials used to brief representatives, and other breaches. The breaches above also reflected the errors and confusion of accountability for responsibility for compliance with the Code that occurred during a period of dysfunctional management. Pierre Fabre submitted, however, that there had been no breach of Clause 2 as there were no risks for patient safety and the breaches had not brought discredit upon, or reduced confidence in, the industry.

Pierre Fabre stated that it was sharing the learnings of Case AUTH/2962/7/17 with all its UK and European staff and senior management would remind all staff to fulfil their obligations under the Code. Compliance with the spirit and letter of the Code and Pierre Fabre's code of ethics were fundamental to activities in the UK.

Pierre Fabre apologised unreservedly for the breaches above. The company was fully committed to maintaining high standards and to taking all steps to both remedy and prevent further recurrence of the failings identified. Its policies and procedures were under review and it had recently trained and tested employees on the Code and had learned from the failings detailed above and were taking all available steps to prevent recurrence. Pierre Fabre would continue to implement its remedial plan and to voluntarily admit any further breaches of the Code that were identified as promptly as practicable. These steps included withdrawal of all materials in breach of the Code, including those referred to above.

In considering this matter, Pierre Fabre was asked in addition to the clauses it had cited in its admission to respond in relation to the requirements of Clause 4.8 in relation to all points where a failure to include a date of preparation was included and to Clause 15.9 in relation to the sales force briefing for the company profile presentation. The company was also asked to respond to Clause 2 in relation to the collective admissions.

RESPONSE

April 2017 cycle meeting

Pierre Fabre stated that the April 2017 cycle meeting was scheduled by the then national sales director and was attended by all representatives. On 7 April 2017, separate meetings were held for each of the two UK regions.

Briefings at these meetings were provided verbally and in slide format. This followed detailed written training materials provided to sales representatives in November 2016 on the Code.

The materials presented at the April 2017 cycle meeting were created to inform representatives about the progress of promotion of Toviaz and to provide verbal briefings, supported by slide presentations.

The national sales manager and regional sales managers had provided draft content for these materials. Due to the absence on sick leave of the two individuals with significant experience of the Code, the slides were not finalised in time for review and certification by Pfizer, or for prior certification on Zinc by Pierre Fabre. The slides were presented on 6 April 2017 with limited support on both content and on the requirements of the Code. The medical director was not present at this meeting, and it was explained that the presentations were in draft form, with the understanding that the presentations would follow by email.

Materials were circulated on 2 May 2017 by email, after review and certification of some materials via the Zinc platform. The list of recipients of these materials was the same as stated on the email of 2 May 2017.

Promotion of Toviaz was suspended in September 2017 and had not recommenced. As part of an ongoing process by new Pierre Fabre Management to review and where relevant withdraw all materials and meetings conducted under previous management in 2017, all the materials at issue described in the voluntary admission were withdrawn on 21 December 2017. This process started in November 2017.

Agreement between Pfizer and Pierre Fabre in relation to the certification of materials

Pierre Fabre was responsible for the marketing and promotion of Toviaz in the UK, with Pfizer remaining the marketing authorization holder. Pfizer and Pierre Fabre must certify all Toviaz material in line with Clause 14 of the Code.

The presentations and email referred to in the voluntary admission were however not shared with Pfizer for review and certification. This breach of both the agreement with Pfizer and of the Code occurred due to a combination of time pressure and of the culture of previous management of Pierre Fabre.

Breaches of the Code

Pierre Fabre stated it had now identified breaches of Clauses 3.1, 4.8, 7.2, 7.4, 14.1, 15.9 and 9.1 of the Code. It submitted that these collective breaches did not constitute a breach of Clause 2 of the Code.

The company apologised unreservedly for these breaches and had implemented changes and significant remedial steps to prevent their recurrence.

With regard to slide 9 of the presentation, Pierre Fabre submitted that the statement 'European warning – CV risk' for mirabegron [Betmiga, marketed by Astellas] was not balanced, and so in breach of Clause 7.2 because Section 4.4 of the Toviaz summary of product characteristic (SPC) included the statement that 'Toviaz should be used with caution in patients with risk for QT prolongation'.

The slide should have been reviewed in accordance with local codes and procedures. In this instance, the slide was not reviewed in accordance with the Code.

Pierre Fabre stated that one slide of the Company Profile Presentation breached Clause 15.9. The company initially considered that Clause 15.9 was more relevant to the presentation. On reflection, it was acknowledged that the briefing document referred to all of the slides in the presentation, including the one at issue, and also referred to a 'healthy product pipeline' as a key message, and therefore also breached Clause 15.9 of the Code.

Pierre Fabre acknowledged that the slide deck presented at the April 2017 meeting and the agenda and objectives for that cycle meeting should have included a date of preparation. The company apologised for not noting these as separate breaches of Clause 4.8 above.

On reflection, however, Pierre Fabre submitted that the further breaches of the Code identified (Clause 15.9 and 4.8) fell under the scope of the admitted breach of Clause 9.1 of the Code, as they provided further examples of failure to maintain high standards.

Pierre Fabre Limited apologised for the breaches and submitted that it had learned from the errors and breaches and had taken a number of steps to remedy them and to prevent recurrence.

Pierre Fabre submitted that the breaches did not overall constitute a breach of Clause 2 of the Code. No risk for patient safety occurred as a result of the breaches, and that these individual and collective breaches had not brought discredit upon or reduced confidence in the industry.

PANEL RULING

Slide deck 'Marketing Focus: Strategy for UK and ROI'

The Panel noted that the slide deck 'Marketing Focus: Strategy for UK & ROI' did not include a date of preparation or guidance as to how it was to be used by representatives.

The email dated 2 May 2017 did not give any instructions about the use of this presentation which had been discussed at the cycle meeting.

The Panel noted that the presentation was briefing material for representatives as required by Clause 15.9 of the Code. The supplementary information to Clause 14.1 required that briefing material be certified. The Panel noted that failure to certify the presentation was in breach of Clause 14.1 and a breach of that Clause was ruled.

With regard to the date of preparation the Panel noted that Clause 4.8 referred to promotional material. It was not clear whether the marketing focus presentation was to be shown to health professionals. In the Panel's view as the presentation was briefing material it would have been helpful to include a date of preparation. However, there was no requirement for briefing material to include a date of preparation. In the circumstances the Panel did not consider Clause 4.8 applied so no breach of Clause 4.8 was ruled.

The slide headed 'Decision Tree' had three sub headings which included 'Mirabegron is better tolerated than any anticholinergic' beneath which was the claim 'European warning – CV risk'. Pierre Fabre stated that the material failed to balance this with the statement in the Toviaz SPC that it should be used with caution in patients with risk of QT prolongation.

The Panel considered that by failing to balance the statement the briefing material was misleading and not capable of substantiation as required by Clauses 7.2 and 7.4 and breaches of those Clauses were ruled. The briefing material advocated a course of action which would be likely to lead to a breach of the Code if the representatives used this statement.

Framework April Cycle Meeting

With regard to the framework for the cycle meeting, agenda and objectives, the Panel considered that this constituted briefing material as it referred to

the quantity and quality of calls by representatives on health professionals. The failure to certify such meant that it did not comply with the relevant requirement of Clause 14. A breach of Clause 14.1 was ruled as acknowledged by Pierre Fabre.

With regard to the date of preparation the Panel noted that Clause 4.8 referred to promotional material. In the Panel's view, as the material was, in effect briefing material, it would have been helpful to include a date of preparation but as there was no requirement for it to do so the Panel did not consider that Clause 4.8 applied so no breach of that clause was ruled.

Toviaz Meeting in a Box Slide Set

With regard to the Toviaz 'meetings in a box' slides, the Panel noted that they were not certified at the time of the April cycle meeting. They were certified on 5 May. The first slide of the presentation in April was marked 'Draft'.

The Panel considered that the slides should have been certified prior to being presented at the cycle meeting. Their use at the cycle meeting would constitute briefing material for the representatives and, as previously, the failure to certify briefing material was ruled in breach of Clause 14.1.

The Panel noted that the slides when presented to health professionals would then be promotional material rather than briefing material.

Email

With regard to the email dated 2 May 2017 which provided certain documents to the representatives, the Panel noted that it was not certified and considered that it should have been as it constituted briefing material. A breach of Clause 14.1 was ruled. The email could have given clearer guidance about the use of the various materials.

Two of the documents sent with the email in question (Toviaz Marketing Focus: strategy for UK and ROI, the company profile presentation and its briefing material) were the subject of the voluntary admission.

Company profile presentation and representatives briefing material

The company profile presentation was to be used with health professionals. It gave an overview of the company's history. One slide referred to partnerships which were to 'Develop and commercialize two novel molecules in oncology'. The briefing material instructed representatives to use the slides at meetings prior to the presentation of main product slides with the key messages that the company had patient interest at its core and it was steadily growing with a healthy product pipeline. It was for promotional use.

The Panel was concerned that the presentation included focus on strategic partnerships which referred to developing and commercialising two novel molecules in oncology.

The Panel considered that the presentation went beyond general comments about Pierre Fabre's interests in oncology. The slide about partnerships would elicit questions about the pipeline. The briefing material for representatives gave no instructions about the response to such questions nor did it give much information about how the slides were to be used.

The Panel considered that the slide at issue promoted unlicensed medicines and a breach of Clause 3.1 was ruled. This presentation had been certified.

The Panel noted that the briefing material for the presentation had not been certified as required by Clause 14.1. The briefing material and the company profile presentation advocated a course of action that would lead to a breach of the Code and thus the Panel ruled a breach of Clause 15.9 of the Code.

The Panel noted Pierre Fabre's submission that another slide from the same presentation referred the audience to the global website (www.pierre-fabre.com) which was not addressed to a UK audience. Pierre Fabre raised Clause 14.1 in this regard but provided no further details or the website content. The voluntary admission implied that the website had not been certified and thus the Panel ruled a breach of Clause 14.1.

Overall

The Panel noted its comments and rulings above and considered that Pierre Fabre had failed to maintain high standards. A breach of Clause 9.1 was ruled.

The Panel noted its ruling of a breach of Clause 3.1 which was listed as an example of activities that were likely to be in breach of Clause 2. The Panel noted that a robust certification procedure underpinned self-regulation. The Panel considered that in advertising a medicine prior to the grant of a marketing authorization and failing to certify material meant that Pierre Fabre had brought discredit upon or reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

Voluntary admission received **18 January 2018**

Case completed **21 March 2018**

CASE AUTH/3013/1/18

ASTRAZENECA EMPLOYEE v ASTRAZENECA

Global training and advisory board

An anonymous, non-contactable complainant, who described him/herself as an employee of AstraZeneca UK Limited's marketing company, alleged that although one of AstraZeneca's values was 'we do the right thing', over the last five years the company had become solely focussed on profits ahead of its ethical obligations. Over the last couple of years, the trend had reversed in the UK marketing company and the focus on achieving AstraZeneca's goals through the right means had returned. However, the same was not so for AstraZeneca's global functions.

The complainant stated that as a UK company, and with many employees in the global functions based in the UK, AstraZeneca should comply with the Code for activities led by global. However, this was not so. Global functions did not receive appropriate training on the Code and did not have regular Code case updates as in the UK marketing company. Globally led activities thus usually did not comply with the Code. In particular, the complainant referred to an unspecified global advisory board, held in October 2017, with over 15 external advisors and a similar number of AstraZeneca employees. The UK nominated signatory who was asked to approve the meeting, as UK health professionals were advisors, refused to do so due to the excessive number of people and the view that this was not a genuine advisory board. However, the UK marketing company was put under pressure to approve this and the nominated signatory was told to approve the advisory board by two other staff even though they acknowledged that it was likely to be a breach of the Code.

The detailed response from AstraZeneca is given below.

With regard to the allegations about training, the Panel noted that AstraZeneca distributed training to staff based on their role, location and responsibilities. The Panel noted that although the materials provided by AstraZeneca did not demonstrate comprehensive training on the Code, the company nonetheless trained global staff and provided more detailed training to the nominated signatories. The Panel did not consider that there was evidence to show that on the balance of probabilities, AstraZeneca had not trained relevant global staff as alleged. The Panel therefore ruled no breach of the Code.

With regard to advisory boards, the Panel noted that it was acceptable for companies to pay health professionals and others for relevant advice. Nonetheless, the arrangements for such meetings had to comply with the Code. To be considered a legitimate advisory board the choice and number of participants should stand up to independent scrutiny; each should be chosen according to their expertise such that they would be able to contribute meaningfully to the purpose and expected outcomes of the advisory board. The number of participants should be limited so as to allow active participation by all. The agenda should allow adequate time for discussion. The number of meetings and the number of participants should be driven by need and not the invitees' willingness to attend. Invitations to participate should state the purpose of the meeting, the expected advisory role and the amount of work to be undertaken. If an honorarium was offered it should be made clear that it was a payment for such work and advice. Honoraria must be reasonable and reflect the fair market value of the time and effort involved.

AstraZeneca referred to an advisory board meeting, held in Amsterdam in November 2017, which, in the absence of details, it assumed was the one to which the complainant had referred. The Panel noted that the agenda for that advisory board, included in the presentation, started with a welcome coffee and the actual meeting started at 10.30am and ended at 5.30pm; there were breaks for lunch and tea. The meeting was co-chaired by an external speaker and a member of AstraZeneca staff. One of the two speakers in the morning session was from AstraZeneca and the moderators for the afternoon discussion groups were both from AstraZeneca.

The initial invitation described the advisory board as part of AstraZeneca's ongoing commitment to supporting health professionals and patients. The objective of the meeting was to gain expert feedback and insights on the role of selective sodium glucose co-transporter 2 (SGLT2) inhibitors in type 1 diabetes and specifically the Forxiga (dapagliflozin) programme studies (DEPICT-1 and -2). The external speaker was asked to critically evaluate the benefit/risk of dapagliflozin on type 1 diabetics and to provide recommendations for safe and effective use of dapagliflozin in type 1 diabetes.

The UK delegates were emailed 6 published papers as pre-reading 6 days before the meeting.

There were 78 slides to be used during the day. Twenty-eight slides were presented in the first session by an external speaker, one of the investigators of the DEPICT studies. This one-hour session, which focused on the results of the two studies included two periods for discussion. The second session of seventeen slides, presented by an AstraZeneca employee, focused on the safety results of the two studies and lasted for one hour and fifty minutes. In the afternoon the group was split into two (US and EU/International) and each group, moderated by AstraZeneca, discussed as session 3 (45 mins) the efficacy results. Session 4

(90 minutes) was a discussion of the benefit/risk of dapagliflozin in type 1 diabetes. The day ended with 30 minutes for summary and closing remarks. The short agenda provided included the sub heading 'Group discussion is 80% or more of each allocated session time and includes all participants'.

The Panel queried whether so many slides were needed on the DEPICT outcomes given the pre-reading included the published studies.

The Panel noted that the advisory board was to help AstraZeneca decide about an application for a new indication in the US and EU. In that regard, seven of the 16 advisors were from the US, eight came variously from five European countries (two from the UK, a doctor and a diabetes specialist nurse) and one advisor was from another country. In addition, there were 12 AstraZeneca staff.

The rationale for the attendance of AstraZeneca staff was provided. The stated business justification was to present and discuss DEPICT data, to critically evaluate benefit/risk of dapagliflozin on type 1 diabetes patients and to provide recommendations for the safe and effective use of dapagliflozin in type 1 diabetes. The business justification in this document was different to the objectives provided to the attendees. This document listed the 12 AstraZeneca staff and the rationale for their attendance. Five of the staff were to watch the first part of the advisory board via a video link and then three would actively participate in the breakout sessions. This was different to the submission from the company which stated that 9 of its staff joined the meeting and three listened in another room. Following a request for further information, the company stated that on the day there were 9 AstraZeneca staff in the room and the three listening in another room joined the main room about half way through the morning session due to a technical problem.

From the list of AstraZeneca attendees, four were assigned to participate in each of the breakout sessions; it was not stated if the other four were to participate in either session or not. The further information confirmed that all 12 AstraZeneca staff participated in the afternoon breakout sessions.

It was not clear to the Panel why AstraZeneca had not described what actually happened at the advisory board in the first instance. It was unacceptable and concerning that details of the arrangements for AstraZeneca attendees were only provided following a request for additional information.

The Panel was concerned about a number of aspects of the advisory board including the number of AstraZeneca attendees which was well outside the UK SOP. However, this did not necessarily mean that the advisory board failed to meet the requirements of the ABPI Code.
The Panel was concerned to note, given the compliance difficulties that companies could experience with advisory boards and the high profile given to such in the UK recently, that it appeared that the arrangements for the meeting were only submitted for local review 12 working days before the meeting took place. The Panel was also concerned that the day before the advisory board AstraZeneca made fundamental changes to the arrangements and increased the number of its staff in the meeting room. In the Panel's view, the timescales and last minute changes would put unnecessary pressure on the nominated signatory to approve a meeting for which all of the arrangements should have already been in place; the UK SOP stated that material should be submitted for approval at least 6 weeks before the meeting date.

The Panel noted that no evidence was supplied in relation to the alleged pressure on the UK signatory to certify the meeting. The Panel was concerned as this was a serious allegation and it was vital that signatories were free to decline certifying material if they did not think it met the requirements of the Code. It appeared from AstraZeneca's submission that there was discussion between UK and global. This was particularly concerning given that this was ongoing so close to the date of the advisory board and that advisory boards were high risk area for companies. The Panel queried whether the certification should have been completed before the UK advisors were first approached at the end of September. If the arrangements were not capable of certification, UK health professionals should not have been approached.

The Panel noted that the advisory board which was held outside the UK and involved UK delegates had not been certified. The Panel noted AstraZeneca's submission that this was due to a timing issue rather than because the signatory was concerned with compliance with the Code. The Panel ruled that the failure to certify was in breach of the Code as acknowledged by AstraZeneca.

The Panel noted the complainant alleged that the advisory board was not genuine. No evidence had been provided by the complainant who had not clearly identified the advisory board about which he/she was concerned. As noted above, the Panel was concerned about the advisory board identified by AstraZeneca but did not consider that the complainant had shown, on the balance of probabilities, that the advisory board held on 10 November 2017 failed to meet the requirements of the Code and thus that any payment was inappropriate. Thus, the Panel ruled no breach of the Code.

On balance, the Panel considered that the arrangements for certification and the short time frame increased the pressure on UK certifiers. This and the failure to certify meant that AstraZeneca had failed to maintain high standards and a breach was ruled.

Noting its rulings above the Panel 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 reserved for such use.

An anonymous, non-contactable complainant, who described him/herself as an employee of AstraZeneca UK Limited's marketing company, complained about compliance at AstraZeneca. The complainant referred to global activities and referred to an advisory board meeting held in 2017.

COMPLAINT

The complainant alleged that despite stating that one of AstraZeneca's values was 'we do the right thing', over the last five years the company had become solely focussed on profits ahead of its ethical obligations. Over the last couple of years, the trend had reversed in the UK marketing company and the focus on achieving AstraZeneca's goals through the right means had returned. However, the same could not be said for AstraZeneca's global functions.

The complainant stated that as a UK company, and with many of the employees in the global functions based in the UK, AstraZeneca should comply with the Code for activities led by global. However, this was not so. Global functions did not receive appropriate training on the Code and did not have regular Code case updates as in the UK marketing company. Global functions believed that they did have to know or comply with the Code (sic) and only had to follow AstraZeneca global standards which were loosely based on the Code. The complainant understood that all staff working in areas that were covered by the Code should have comprehensive Code training.

Due to this, globally led activities were usually conducted in a manner which was not in line with the requirements in the Code. The complainant was aware of a recent global advisory board, held in October 2017, with over 15 external advisors and a similar number of AstraZeneca employees. This was sent to the UK marketing company for approval as UK health professionals were advisors. The nominated signatory refused to approve this due to the excessive number of people and the view that this was not a genuine advisory board. However, the UK marketing company was put under pressure to approve this and the two other staff (roles named) in the UK told the nominated signatory to approve the advisory board, even though they acknowledged that it was likely to be a breach of the Code.

The complainant stated that there were likely to be a number of other global activities that were in breach of the Code but that AstraZeneca UK was not aware of them. The complainant asked that the PMCPA investigate this in order that the reputation of AstraZeneca and the wider pharmaceutical industry was not tarnished.

When writing to AstraZeneca, attention was drawn to the requirements of Clauses 2, 9.1, 14.2, 16.1, 18.1 and 23.1 of the Code.

RESPONSE

AstraZeneca submitted that it took compliance with all applicable laws and regulations very seriously, including pharmaceutical industry codes of practice. AstraZeneca believed that it had, at all times, addressed the advisory board referred to in the complaint in accordance with the high standards expected of a pharmaceutical company.

AstraZeneca was disappointed that the complainant had brought his/her concerns to the PMCPA rather than raising them internally. AstraZeneca noted that its commitment to ethics included training all staff on induction, and annually thereafter, on its internal escalation processes which also included details of its AZethics line, an externally hosted confidential online and telephone helpline, available 24 hours a day, 7 days a week. Whilst AstraZeneca did not deny the complainant's right to complain to the PMCPA, it was very important to note the reporting system which existed and to reiterate that AstraZeneca made every effort to encourage employees to report concerns and gave them a confidential route to do so. AstraZeneca submitted that it did this, because it was the right thing to do and because it was committed to continuous improvement across its organisation.

AstraZeneca refuted the complainant's general and unsubstantiated allegations about interactions between AstraZeneca's global and UK commercial functions and the general attitude of the global functions to compliance. As recognised in the complaint, 'Do the Right Thing' was one of AstraZeneca's five core values and underpinned all of its decisions. Like any organisation, there would always need to be discussions between colleagues to understand the implications of the underlying legal and regulatory requirements. It was grossly inaccurate to state that such discussions showed a disregard for the Code or a desire to put profit before compliance. The allegations suggested that the complainant did not have full insight into all the relevant and key discussions that took place about the advisory board, and did not have sufficient knowledge and experience of the organisation especially in relation to global processes.

AstraZeneca submitted that the only specific allegation related to an advisory board. Although the complainant did not specify a date, AstraZeneca believed that the advisory board to which he/she referred was the Global Dapagliflozin T1D Indication Advisory Board held in Amsterdam from 9.30am to 5.30pm on 10 November 2017. AstraZeneca submitted that this advisory board was conducted in a compliant fashion.

Issues to be addressed by the advisory board

AstraZeneca stated that as part of its commitment to science, it had recently conducted the DEPICT-1 and DEPICT-2 studies to investigate the efficacy and safety of the selective sodium-glucose co-transporter 2 (SGLT2) inhibitor, dapagliflozin (Forxiga) in patients with inadequately controlled type 1 diabetes. This was a new area of potential application for this class of product and relied on a mode of action which had not previously been used in type 1 diabetics.

The advisory board was arranged by AstraZeneca's global medical affairs team. Global medical affairs

looked to inform AstraZeneca's decision on an application for a potential new indication (US and EU) by gaining insight from key opinion leaders on the benefit/risk profile of Forxiga based on DEPICT-1 and DEPICT-2. The detailed objectives of the meeting were set out in a form for health professionals (copy provided).

The advisory board was a single advisory board required for insight gathering only. It was not part of a series.

Selection and invitation of participants

AstraZeneca selected the participants based upon:

- expertise and experience in the management of type 1 diabetes and its complications;
- experience with SGLT2 inhibitors and/or familiarity with diabetic ketoacidosis;
- the need to represent a diversity of advisor roles across the diabetes therapy area; and
- the need for representation from relevant geographies.

In order to meet the requirements, AstraZeneca selected seventeen potential participants. They were emailed by a global medical leader within global medical affairs in order to ascertain whether they were available (example email provided). A follow-up email invitation was sent by a third party agency based on confirmation of participant availability (copy provided).

Number of health professionals attendees and compensation

AstraZeneca stated that sixteen participants attended the advisory board. Compensation was paid to each in accordance with relevant local guidance and details were provided. It submitted that the compensation paid to the two UK health professionals was reasonable and in accordance with the UK marketing company's fair market value guidance.

Agenda and materials

Copies of the advisory board agenda, the presentations and the participants' pre-reading material were provided. AstraZeneca referred to the audio recording of the advisory board captured by the third party agency for the sole purpose of consolidating a report of the meeting.

The materials associated with this advisory board (agenda, presentations and discussion guide) were examined by a global medical affairs signatory in line with the requirements of the Code for non-promotional activities, and also a host country nominated signatory to ensure local host country regulations were adhered to.

Feedback from participants

There was no feedback form. Whilst AstraZeneca often sought feedback from attendees at its educational and promotional meetings, it was not standard practice to seek feedback from advisory board attendees.

Selection and attendance of AstraZeneca staff

Noting differences between the global and local standard operating procedures (SOPs), a compromise was agreed that only AstraZeneca attendees with a meeting relevant role were to be in the actual meeting room. Colleagues with a secondary requirement were allowed to listen remotely. Nine AstraZeneca staff were in the room along with 2 employees of the third party agency. A further three AstraZeneca staff listened to the advisory board from an adjacent room with a video link, together with a further 2 agency employees. AstraZeneca provided a rationale for attendance of its staff.

Discussions concerning AstraZeneca attendees

Discussions about the differences between the global and UK SOPs for advisory boards took place between global medical affairs and UK marketing company staff, in particular around the more prescriptive limit on the number of internal attendees that ordinarily applied under the UK SOP. Copies of both SOPs were provided. AstraZeneca submitted that neither of the two staff whose roles were mentioned by the complainant considered that the meeting was in breach of the Code. Furthermore, they did not pressurize the UK signatory to certify the meeting arrangements and AstraZeneca had found no evidence to the contrary. Team members confirmed that the one of these roles had made it clear on more than one occasion that AstraZeneca did not expect individuals to sign off any materials if they were not comfortable to do so. The UK nominated signatory confirmed that the two members of staff did not pressurize him/her to certify the meeting arrangements.

The advisory board was designed in line with AstraZeneca's relevant global SOP which AstraZeneca submitted was in accordance with the principles of the ABPI Code. The global SOP required adherence to local requirements including, where appropriate, the need for local approval of matters relating to the attendance of local health professionals. As two UK health professionals were to attend this advisory board, the global medical affairs team approached local UK marketing company signatories to arrange certification for their attendance. The local UK marketing company signatories reviewed the advisory board and requested that certain changes be made, including in relation to the number/role of attendees: discussions on the changes took place over a number of weeks following the submission of the advisory board for review by the local signatory on 24 October 2017. Eventually, only a request from the UK signatories to change the number of internal attendees present in the meeting in order for the arrangements to be certified under the UK SOP remained under discussion. They presented several options to resolve this, one of which was the option eventually settled upon. Unfortunately, although it was agreed and an amended health professional form submitted

by the global medical affairs team for approval on 9 November, they were not able to make a further resubmission of the health professional form before close of business that day owing to additional editorial changes to the form requested by the UK marketing company signatory. As a result, the UK signatory decided that it would not be appropriate to certify the arrangements of the advisory board on the following day (10 November) as the UK health professionals had already travelled and the activity had commenced: to do so would have been viewed as a retrospective certification. The UK signatory did not inform his manager of the lack of certification due to this timing issue until after the advisory board had started. This had been logged as a deviation and would be addressed in accordance with AstraZeneca's standard procedures for dealing with specific deviations.

Training of global personnel

AstraZeneca refuted the complainant's non-specific allegations concerning the level of training of global employees in the requirements of the Code; such allegations appeared to overlook the comprehensive training program in place for all staff across a wide range of topics, including regulatory compliance.

AstraZeneca maintained a web-based software solution to schedule and distribute training to staff based on their role, location and responsibilities. Various topics, including those related to medicines' promotional regulations, were made available to global employees on the network and these interactive modules allowed employees to work through training presentations on their own with trackable progress. An example of one, the training on scientific exchange was provided.

In addition, the global nominated signatories (GNSs) were tasked to train relevant global teams on topics related to the regulation of the promotion of medicines and their assigned therapy areas. Examples of summaries of such trainings were provided. All members of the GNS team were either UK registered pharmacists or registered physicians and they were registered with the Medicines and Healthcare products Regulatory Agency (MHRA) and PMCPA in line with Clause 14.4 of the Code. The majority had had extensive experience working in the medical affairs departments of UK pharmaceutical companies, and so had a deep understanding of the requirements of the Code. In addition, GNSs underwent robust training when they joined the company, and actively took part in various learning initiatives on the job to keep their knowledge up-to-date.

The AstraZeneca team used a variety of techniques to deliver training and these were reviewed regularly to ensure that training was up-to-date and effective. One of the methods used was WebEX for group training, called 'Nom Sig On- Air Sessions'. During these sessions, participants from global and affiliate countries dialled in to receive live audio training and follow visual presentations on their computer screens. The participants interacted with the presenters through the audio function or via webchat, with training sessions recorded to allow for easy make-up for employees who missed the group training or as useful on-demand refresher training. An example of a 'Nom Sig On-Air Session' on running a patient advisory board was provided.

AstraZeneca also used multimedia for training, typically videos that were widely available to all employees, not just those involved in the production and review of materials subject to the Code. These videos were mostly about 3 minutes each and provided succinct guidance. They allowed employees to build sufficient knowledge to know when they might be carrying out a regulated activity. An example of a transcript for one of the videos was provided.

Clause 14.2

AstraZeneca was disappointed that the arrangements for the attendance of the UK health professionals at the advisory board were not certified before it commenced, despite the scrutiny that was applied to this advisory board. AstraZeneca acknowledged that it did not meet the requirements of Clause 14.2 but noted that the failure to certify was based on a timing issue rather than a disregard of the requirements of the Code or the activity not being in accordance with the Code.

Clause 16.1

Given the extensive training regime described above, AstraZeneca denied a breach of Clause 16.2, whether generally in relation to the staff within global medical affairs or more specifically with relation to the staff involved in the advisory board.

Clause 18.1

The advisory board was appropriate and the remuneration provided to the health professionals represented a fair market value for their work, in accordance with AstraZeneca's internal guidance on fair market value. AstraZeneca denied any breach of Clause 18.1.

Clause 23.1

AstraZeneca denied any breach of Clause 23.1. In particular, the UK health professionals in question:

- had signed appropriate written contracts in respect of the advisory board;
- were selected based on appropriate criteria in order to enable AstraZeneca to fulfil a legitimate business need;
- were part of an appropriately sized group of health professionals contracted to provide the breadth of advice reflecting the scope of disease, complications of treatment and variation in geography for a global investment decision and
- were paid the fair market value for the services that they provided and were not hired as an inducement to prescribe.

Clause 9.1

Whilst AstraZeneca acknowledged and regretted the breach of Clause 14.2 referred to above, it did not accept that it failed to maintain high standards. The detailed discussions that took place over this one advisory board were a sign of the efforts that the company had made to maintain high standards.

Clause 2

AstraZeneca denied any breach of Clause 2. AstraZeneca believed that it had maintained high standards throughout and that the evidence demonstrated its commitment to upholding the reputation of the industry.

In summary, AstraZeneca stated that the advisory board was carried out for a legitimate business purpose, the arrangements were appropriate including a reasonable number of participants and AstraZeneca staff to achieve the stated business objectives. A difference in opinion based on variation in the UK and global SOPs was appropriately escalated and no pressure was put on the nominated signatory to approve an activity with which he/she was uncomfortable. Nevertheless, AstraZeneca accepted that the arrangements for the advisory board were not certified because the final amended forms were not submitted early enough for the UK signatory to certify them. However, AstraZeneca denied any other breach of the Code.

FURTHER INFORMATION FROM ASTRAZENECA

The Panel requested further information.

With regard to the changes to the arrangements for the advisory board requested by UK signatories, AstraZeneca submitted that during the initial review of travel arrangements for the two UK health professionals invited to attend the advisory board, the only point raised by UK signatories which required further discussion related to the number of AstraZeneca employees invited to attend the meeting and the need to clarify the rationale for their attendance. UK signatories requested that the internal attendee numbers be revised in line with requirements of the local UK SOP for advisory boards. This was in contrast to the global SOP which was not prescriptive regarding specific attendee numbers or ratios, but gave guidance to ensure the number of internal attendees was the minimum required to meet the objectives of the meeting. The ensuing discussion between global medical affairs and the UK focused on how to resolve the conflicting guidance. The compromise reached was to reduce the number of AstraZeneca attendees in the main room where the discussion was taking place during the morning session, with 5 staff members listening in from another room.

Once internal attendee numbers were agreed, the UK signatory requested the following additional changes, which were mostly editorial in nature, before final approval could be granted:

- a correction of an error which marked one of the UK health professional's fee for service as being outside acceptable fair market value limits when in fact it was within the limits;
- a request to attach the biography for one of the UK health professionals;
- a request to correct errors in the flight details for both UK attendees to accurately reflect the travel arrangements;
- a request to clarify job/role descriptions of AstraZeneca attendees and
- a request to clarify the final number of internal attendees.

With regard to the differences between AstraZeneca's letter of response and enclosed rationale for attendance of active AstraZeneca participants, AstraZeneca stated that a final internal preparatory meeting for the advisory board was conducted by global medical affairs on the day before the meeting. At that meeting, those present determined that two members of staff who had been due to listen from the neighbouring room would need to be in the main meeting room in order to answer questions and clarify points as part of the morning discussion. As a result, it was decided that three additional AstraZeneca employees would be present in the room as well. Although this increased the total number of AstraZeneca attendees inside the room to nine, AstraZeneca submitted it needed to exercise a degree of flexibility on this occasion to fulfil the requirements of the advisory board. About half way through the morning session, there was a problem with the listening device which led to the three remaining AstraZeneca participants joining the others in the main room until the end of that session.

Twelve AstraZeneca staff participated to facilitate the needs of the afternoon sessions which were split by region into the US and EU/International sessions. A list of advisors, AstraZeneca attendees and agency staff at each session was provided.

AstraZeneca stated that the welcome coffee was time allocated for coffee to be served outside the meeting room whilst advisors arrived. All twelve AstraZeneca attendees arrived at different times during the welcome coffee. No formal introductions or discussions took place between AstraZeneca staff and the advisors, most of whom used this time to settle in or catch up with their colleagues or prepare for the meeting.

AstraZeneca stated that emails to ascertain availability to attend the advisory board were sent to one UK health professional on 25 September 2017 and to the other on 3 October 2017. These emails did not constitute formal invitations to attend the advisory board. It was important to clarify that whilst this contact was prior to formal UK signatory involvement, the purpose and nature of this contact was purely to ascertain availability; this communication was appropriate and compliant because it did not contain any substantive content.

The global medical affairs team engaged the UK signatory team to approve attendance of the UK attendees on 24 October 2017, after receiving

confirmation of availability to attend. No formal invitation was sent to either UK health professional prior to involvement by UK signatories.

A formal invitation to attend the advisory board was sent to both UK health professionals on 6 November 2017.

A copy of correspondence sent with pre-read materials was provided.

The outcome and recommendations by the advisors were captured by the agency staff. The form containing the details of the information captured was provided. AstraZeneca submitted that this information clearly demonstrated a legitimate need for the advisory board, with relevant content, an appropriate agenda and aligned outputs.

AstraZeneca remained comfortable that the advisory board was entirely appropriate and that it was conducted in compliance with the ABPI Code.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure for the Prescription Medicines Code of Practice Authority stated that anonymous complaints would be accepted but that like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The Panel noted that the parties' accounts differed; the complainant had provided no evidence to support his/her allegations and could not be contacted for more information.

With regard to the allegations about training staff, the Panel noted that AstraZeneca distributed training to staff based on their role, location and responsibilities. Various topics including those related to medicines' promotional regulations were made available to global employees on the AstraZeneca network allowing them to work through training presentations on their own with trackable progress. The example training for scientific exchange, medical education and sharing off-label information was dated March 2015. Other training for global nominated signatories to use when training relevant global teams was a one-page summary on medicines promotion regulations. There were three versions for the different audiences, medical personnel, marketing personnel and communications personnel. The training for nominated signatories appeared to be more detailed. The screen shot provided dated September 2016 listed 10 training modules with links to AZlearn modules. The patient advisory board training was undated.

The Panel noted that although the materials provided did not demonstrate comprehensive training on the ABPI Code, Clause 16.1 required relevant personnel concerned in any way with the preparation or approval of material or activities covered by the Code to be fully conversant with the Code and the relevant laws and regulations. AstraZeneca provided training to global staff and more detailed training to the nominated signatories who, as required by the supplementary information to Clause 14.1, Suitable Qualifications for Signatories, must have an up-to-date detailed knowledge of the Code. The Panel did not consider that there was evidence to show that on the balance of probabilities, AstraZeneca had not trained relevant global staff as alleged. The Panel therefore ruled no breach of Clause 16.1 of the Code.

Turning to the allegations about the advisory board, the Panel noted that it was acceptable for companies to pay health professionals and others for relevant advice. Nonetheless, the arrangements for such meetings had to comply with the Code, particularly Clause 23. To be considered a legitimate advisory board the choice and number of participants should stand up to independent scrutiny; each should be chosen according to their expertise such that they would be able to contribute meaningfully to the purpose and expected outcomes of the advisory board. The number of participants should be limited so as to allow active participation by all. The agenda should allow adequate time for discussion. The number of meetings and the number of participants should be driven by need and not the invitees' willingness to attend. Invitations to participate should state the purpose of the advisory board meeting, the expected advisory role and the amount of work to be undertaken. If an honorarium was offered it should be made clear that it was a payment for such work and advice. Honoraria must be reasonable and reflect the fair market value of the time and effort involved.

The Panel noted that the agenda for the advisory board included in the presentation started with a welcome coffee from 9.30am until 10.30am and the actual advisory board started at 10.30am and ended at 5.30pm; there were breaks for lunch and tea. It was held in Amsterdam and was co-chaired by the external speaker and a member of AstraZeneca staff. One of the two speakers in the morning session was from AstraZeneca and the moderators for the afternoon discussion groups were both from AstraZeneca.

The initial invitation to one of the UK participants was provided (dated 25 September 2017). The initial invitation to the other UK participant (dated 29 September 2017) was provided following the Panel's request for further information. The invitation described the advisory board as part of AstraZeneca's ongoing commitment to supporting health professionals and patients. The objective of the meeting was to gain expert feedback and insights on the role of SGLT2 inhibitors in type 1 diabetes and specifically the DEPICT programme studies. The invitation to the external speaker set out the objectives as to critically evaluate the benefit/risk of dapagliflozin on type 1 diabetic patients and to provide recommendations for safe and effective use of dapagliflozin in type 1 diabetes.

The pre-reading consisted of 6 published papers including the 'American Association of Clinical

Endocrinologists and American College of Endocrinology Position Statement on the Association of SGLT-2 Inhibitors and Diabetic Ketoacidosis' and the published DEPICT study. It was sent to the UK participants on 4 November 2017. The email of 4 November referred to the recipient already receiving details of how to register for the meeting. The official invitation was sent on 6 November and this asked the participant to register for the meeting.

There were 78 slides to be used during the day. Twenty-eight slides were presented in the first session by an external speaker, one of the investigators of the DEPICT studies. This one-hour session, which focused on the results of the two studies and their clinical interpretation, included two periods for discussion. The second session of seventeen slides, presented by an AstraZeneca employee, focused on the safety results of the two studies and lasted for one hour and fifty minutes. In the afternoon the group was split into two (US and EU/International) and each group, moderated by AstraZeneca, discussed as session 3 (45 mins) the efficacy results, in a 'Focused discussion on efficacy elements including HbA1c, weight and continuous glucose monitoring'. Session 4 (90 minutes) was a discussion of the benefit/risk of dapagliflozin in type 1 diabetes patients in particular 'Guidance on insulin dose reduction, dose response 5mg vs 10mg dapagliflozin, special precautions, patient subgroups, labelling.' The day ended with 30 minutes for summary and closing remarks. The short agenda provided included the sub heading 'Group discussion is 80% or more of each allocated session time and includes all participants'.

The Panel queried whether so many slides were needed on the DEPICT outcomes given the pre-reading included the published studies.

The Panel noted that the advisory board was to help AstraZeneca decide about an application for a new indication in the US and EU. In that regard, seven of the 16 advisors were from the US, eight came variously from five European countries (two from the UK, a doctor and a diabetes specialist nurse) and one advisor was from Israel. In addition, there were 12 AstraZeneca staff.

The rationale for the attendance of AstraZeneca staff was provided. This indicated that the meeting ran from 9.30 until 17.30 whereas the first hour was spent on a welcome coffee with the advisory board starting at 10.30. The stated business justification was to present and discuss DEPICT-1 and -2 data, to critically evaluate benefit/risk of dapagliflozin on type 1 diabetes patients and to provide recommendations for the safe and effective use of dapagliflozin in type 1 diabetes. The business justification in this document was different to the objectives provided to the attendees. This document listed the names of the 12 AstraZeneca staff and their role as well as the rationale for their attendance. Five of the staff were to watch the first part of the advisory board in a separate room on video link and then three would actively participate in the breakout sessions. This was different to the submission from the company which stated that 9 AstraZeneca staff joined the meeting and three listened in another room. The further information from the company stated that on the day there were 9 AstraZeneca staff in the room and the three listening in another room joined the main room about half way through the morning session due to a technical problem.

From the list of AstraZeneca attendees four were assigned to participate in each of the breakout sessions; it was not stated if the other four were to participate in either session or not. The further information confirmed that all 12 AstraZeneca staff participated in the afternoon breakout sessions.

It was not clear to the Panel why AstraZeneca had not described what actually happened at the advisory board in its first letter of response. It was unacceptable and concerning that details of the arrangements for AstraZeneca staff attendees were only provided following a request for additional information.

The AstraZeneca UK marketing company guideline, 'UKMC Advisory Board Standard' stated that an advisory board should generally consist of no more than 10 advisors and that generally no more than 3 AstraZeneca employees might attend. Additional employees might attend only if they could show a legitimate and documented need.

The Panel was concerned about a number of aspects of the advisory board including the number of AstraZeneca attendees which was well outside the UK SOP. However, this did not necessarily mean that the advisory board failed to meet the requirements of the ABPI Code.

The Panel was concerned to note, given the compliance difficulties that companies could experience with advisory boards and the high profile given to such in the UK recently, that it appeared that the arrangements for the meeting were only submitted for local review on 24 October – only 12 working days before the meeting took place. The Panel was also concerned that the day before the advisory board AstraZeneca was making fundamental changes to the arrangements and increasing the number of AstraZeneca staff in the meeting room. In the Panel's view, the timescales and last minute changes would put unnecessary pressure on the nominated signatory to approve a meeting for which all of the arrangements should have already been in place; the UK SOP stated that material should be submitted for approval at least 6 weeks before the meeting date.

The Panel noted that no evidence was supplied in relation to the alleged pressure on the UK signatory to certify the meeting. The Panel was concerned as this was a serious allegation and it was vital that signatories were free to decline certifying material if in their opinion it did not meet the relevant requirements of the Code. It appeared from AstraZeneca's submission that there was discussion between the UK company and the global company. This was particularly concerning given that this was ongoing so close to the date of the advisory board and that advisory boards were high

risk area for companies. The Panel queried whether the certification should have been completed before the UK advisors were first approached at the end of September. If the arrangements were not capable of certification, UK health professionals should not have been approached.

The Panel noted that the advisory board which was held outside the UK and involved UK delegates had not been certified. The Panel noted AstraZeneca's submission that this was due to a timing issue rather than because the signatory was concerned with compliance with the Code. The Panel ruled that the failure to certify was a breach of Clause 14.2 of the Code as acknowledged by AstraZeneca.

The Panel noted the complainant alleged that the advisory board was not genuine. No evidence had been provided by the complainant who had not clearly identified the advisory board about which he/she was concerned. As noted above, the Panel was concerned about the advisory board identified by AstraZeneca but did not consider that the complainant had shown, on the balance of probabilities, that the advisory board held on 10 November 2017 failed to meet the requirements of the Code and thus that any payment was inappropriate. Thus, the Panel ruled no breach of Clauses 23.1 and 18.1.

On balance, the Panel considered that the arrangements for certification and the short time frame increased the pressure on UK certifiers. This and the failure to certify meant that AstraZeneca had failed to maintain high standards. The Panel ruled a breach of Clause 9.1 of the Code.

Noting its rulings above the Panel 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 reserved for such use. The Panel therefore ruled no breach of Clause 2.

Complaint received **22 January 2018**

Case completed **10 April 2018**

HEALTH PROFESSIONALS v SERVIER

Alleged sponsorship of a meeting

Two health professionals separately complained about a weekend meeting which they alleged had been sponsored by Servier. The meeting, of a learned society, took place within the grounds of Windsor Castle. The complainants both provided a copy of a letter and its attachments sent to Servier from the organisers, asking for sponsorship.

Both complainants referred to Windsor Castle as a 'luxurious venue' and considered more suitable professional venues were available locally. The complainants noted that although the meeting programme ran from Friday to Sunday, all education was finalised by lunchtime on the Saturday; they both noted that the programme stated that delegates could 'enjoy the rest of their weekend'.

The complainants stated that public perception of the industry and of health professionals would be extremely poor; both referred to sleaze.

The details response from Servier is given below.

The Panel noted that the complainants had each provided a request for sponsorship form apparently completed and naming a person at Servier with his/her contact details indicating sponsorship for a morning session and that artwork accompanied the sponsorship form to show a logo to be displayed between speakers' slides. Nonetheless, the Panel noted that the complainants had not provided any evidence that Servier had sponsored the meeting.

The Panel noted Servier's submission that it had not sponsored any part of the meeting and no-one from the company had attended it. A response to the organiser's request for sponsorship clearly stated that the company was unable to support the meeting because to do so at the venue in question would expose the company 'to a high degree of risk'. Servier also declined a further request to sponsor the dinner before the meeting. No breach of the Code was ruled.

Two contactable health professionals, an anonymous 'concerned oncologist' (Case AUTH/3022/2/18) and an oncologist specialising in gastro-intestinal (GI) tumours who wanted to maintain his/her anonymity (Case AUTH/3023/2/18), complained about the alleged sponsorship by Servier Laboratories Limited of a learned society weekend meeting which took place in October 2017 within the grounds of Windsor Castle. The complainants both provided a copy of a letter sent to Servier from the meeting organisers, asking for sponsorship.

Case AUTH/3022/2/18

COMPLAINT

The complainant stated that the organiser had invited Servier to sponsor the meeting which was to be held at a luxurious venue ie Windsor Castle. The complainant stated that the meeting could have been held at one of many other suitable professional venues locally. The complainant considered that a failure to maintain high standards and the elitist attitude did not reflect well on the NHS or Servier.

The complainant stated that from the programme the meeting appeared to start on Friday and end on Sunday. Closer scrutiny, however, revealed that there was some education on the Friday followed by a social event and a dinner. All education was completed by Saturday, after 1pm and the programme encouraged 'delegates either to stay and enjoy the rest of their weekend or return home'. In effect, by sponsoring this event Servier had used the high class, luxury venue as an excuse for attracting attendance. This sleazy behaviour brought both health professionals and the industry into disrepute; the public would see the relationship between the pharmaceutical industry and the NHS as one of excess, outright arrogance, and not about the science or care of the patient. The complainant stated that if such details were to get out to the media, health professionals would hang their heads in shame.

Overall, the complainant did not believe Servier should have become star struck by the venue and should have noted that the meeting was not about science and research, but about having a weekend at Windsor Castle, wined and dined by the pharmaceutical industry; this meeting was organised by an elitist for the elite.

Case AUTH/3023/2/18

COMPLAINT

The complainant alleged that Servier had sponsored the meeting in question. The complainant considered that, of all the venues around Windsor and the surrounding M4 corridor, the venue was luxurious and distracted from the main purpose of the meeting which was to discuss research in an important solid tumour type. A more professional venue would have meant sincere attendees; Servier should have adopted due diligence to ensure that the venues it sponsored were professional and not elitist or appealing to a certain class of health professional.

The complainant noted that the educational content was complete by 1pm on the second day of the three day meeting. The complainant queried whether Servier had thus effectively paid for an elitist group of doctors to get together at a luxurious venue (effectively the Queen's backyard) and spend most of their time at a social event and a banquet. The

programme stated 'delegates are free to enjoy the rest of their weekend' in return for a bit of education.

The complainant did not consider that Servier should have sponsored the meeting as it did not meet the high standards expected and the venue and social aspects (ie the social event mentioned, the luxury dinner and the amount of free time to explore the grounds) all pointed to elitism, demonstrated by a group of health professionals who could have held the meeting at a hotel nearby.

The complainant stated that he/she valued the relationship with pharmaceutical companies but considered that if this was to be made public, all parties would hang their heads in shame. The public's perception of health professionals getting together in Windsor Castle to discuss the serious topic of GI cancers at a meeting where a huge proportion of time was dedicated to a social event and a free weekend of fun, pointed to non-seriousness, sleaze and a lack of respect for patients and the hardworking jobbing oncologists who had not had a pay rise in years! The complainant asked the Authority to ensure that Servier did not put its own reputation or the reputation of working oncologists into disrepute.

When writing to Servier about both cases attention was drawn to the requirements of Clauses 2, 9.1, 22.1 and 22.2 of the Code.

RESPONSE

Servier strongly denied the allegations and considered that the complainants had misled the Authority by suggesting that it had collaborated with the NHS to sponsor such an event. The complainants had not supplied any evidence that the company had supported the meeting; they had only provided a request for sponsorship form addressed to Servier.

Servier stated that it placed the highest value on being an ethical pharmaceutical company and regarded adherence to the Code with the utmost importance. Equally it considered that it was important to appropriately support the development and education of health professionals.

Servier noted that it initially received a request to support the meeting in November 2016. Given the international standing of the organisation and the scientific merit of the meeting to the research community and ultimately patients, Servier wanted to ensure that it knew all the facts about the meeting and venue before it agreed to sponsor the event. This involved a face-to-face meeting between two senior managers and the organisers (two NHS clinicians) as well as requests for information. Servier noted that it was concerned about the venue given the availability of other business venues nearby and the possibility that the choice of venue could be misconstrued. On careful review of all information available, Servier decided not to support the meeting either financially or by any Servier presence at the meeting (in the audience or by a stand). Copies of relevant correspondence were provided.

Servier therefore considered that it had followed the correct processes for the support and hospitality of meetings, it had maintained high standards and had not discredited the industry. The company, therefore, did not consider it had breached the Code.

PANEL RULING

The Panel noted that the complainants had each provided a request for sponsorship form apparently completed and naming a person at Servier with his/her contact details indicating sponsorship for a morning session and that artwork accompanied the sponsorship form to show a logo between speaker slides. Nonetheless, the Panel noted that the complainants had not provided any evidence that Servier had proceeded to sponsor the meeting.

The Panel noted Servier's submission that it had not sponsored the meeting either in whole or in part and no-one from the company had attended the meeting. A response to the organiser's request for sponsorship clearly stated that the company was unable to support the meeting because to do so at the venue in question would expose the company 'to a high degree of risk'. Servier also declined a further request to sponsor the dinner before the meeting. The Panel ruled no breach of Clauses 2, 9.1, 22.1 and 22.2 of the Code.

Complaint received **23 February 2018**

Case completed **10 April 2018**

CODE OF PRACTICE REVIEW – May 2018

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

AUTH/2831/4/16	**Voluntary admission by Celgene**	**Meetings organised by representatives**	**Breach Clause 2** **Two breaches Clause 4.1** **Two breaches Clause 4.10** **Breach Clause 9.1** **Three breaches Clause 14.1** **Breaches Clauses 15.2, 18.1 and 26.1**	**No appeal** **Report from Panel to Appeal Board** **Audit required by Appeal Board** **Two further re-audits required by Appeal Board**	**Page 3**
AUTH/2961/6/17	**Indivior v Martindale**	**Promotion of Espranor and information to the public**	**Two breaches Clause 2** **Sixteen breaches Clause 7.2** **Five breaches Clause 7.3** **Sixteen breaches Clause 7.4** **Breach Clause 7.9** **Four breaches Clause 9.1**	**No appeal**	**Page 18**
AUTH/2962/7/17	**Anonymous sales representative v Pierre Fabre**	**Call rates and certification of meetings**	**Breaches Clauses 2, 9.1, 14.1 and 15.9** **Public reprimand required by the Appeal Board**	**Appeal by complainant**	**Page 45**
AUTH/2969/8/17	**Senior practice nurse v AstraZeneca**	**Conduct of a representative**	**Breach Clauses 9.1 and 15.2**	**No appeal**	**Page 58**
AUTH/2970/8/17	**Anonymous, non-contactable v Janssen**	**Promotional email**	**Breach Clauses 9.1 and 15.2**	**No appeal**	**Page 67**
AUTH/2978/9/17	**Anonymous, non-contactable consultant dermatologist v Janssen**	**Promotion of Tremfya**	**Breaches Clauses 2, 3.1 and 9.1**	**Appeal by respondent**	**Page 75**
AUTH/2982/10/17	Anonymous, non-contactable member of the public v Leo	Alleged promotion of Kyntheum to the public	No breach	No appeal	Page 84
AUTH/2988/10/17	**Employee v Otsuka**	**Use of LinkedIn to promote medicines**	**Breaches Clauses 3.1, 3.2, 4.1, 7.2, 9.1, 14.1 and 26.1**	**No appeal**	**Page 90**

AUTH/2991/11/17 and AUTH/2992/11/17	Anonymous, non-contactable v Pfizer and Bristol-Myers Squibb	Meeting arrangements	No breach	No appeal	Page 98
AUTH/2993/11/17	Complainant v Napp	Asthma review service	No breach	No appeal	Page 103
AUTH/3005/12/17	**Director v Biogen**	**Clinical trial disclosure (Tecfidera)**	**Breach Clause 9.1**	**No appeal**	**Page 108**
AUTH/3008/1/18	**Teva v Pharmasure**	**Provision of a chocolate hamper**	**Breaches Clauses 2, 9.1 and 18.1**	**No appeal**	**Page 116**
AUTH/3011/1/18	**GlaxoSmithKline v AstraZeneca**	**Press release issued by AstraZeneca**	**Three breaches Clause 7.2** **Breaches Clauses 7.3 and 7.9** **Two breaches Clause 7.10** **Breach Clauses 9.1 and 26.1** **Four breaches Clause 26.2**	**No appeal**	**Page 120**
AUTH/3012/1/18	**Voluntary admission by Pierre Fabre**	**Failure to certify material**	**Breaches Clauses 2, 3.1, 7.2, 7.4 and 9.1** **Five breaches Clause 14.1** **Breach Clause 15.9**	**No appeal**	**Page 135**
AUTH/3013/1/18	**AstraZeneca employee v AstraZeneca**	**Global activities**	**Breaches Clauses 9.1 and 14.2**	**No appeal**	**Page 140**
AUTH/3022/2/18 and AUTH/3023/2/18	Health professionals v Servier	Alleged sponsorship of a meeting	No breach	No appeal	Page 149

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 other relevant decision makers 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 any printed or electronic material used by them
- the supply of samples
- the provision of inducements in connection with the promotion of medicines and 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, social media 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 the Internet
- relationships with patient organisations
- disclosure of tranfers of value to health professionals and organisations
- joint working between the NHS and pharmaceutical companies
- 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, donations and benefits in kind to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of three 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 does not participate and is not present 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, must be 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.

Further information about the Authority and the Code can be found at www.pmcpa.org.uk

Complaints under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 7th Floor, Southside, 105 Victoria St, London SW1E 6QT

telephone 020 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.

CODE OF PRACTICE REVIEW

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