

CODE OF PRACTICE REVIEW

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.

CLINICAL TRIAL DISCLOSURE – DECISION TREE UPDATED

The third in a series of studies was published online in Current Medical Research & Opinion (CMRO) on 25 November 2016, entitled 'Clinical trial transparency update: an assessment of the disclosure of results of company-sponsored trials associated with new medicines approved in Europe in 2013'. The medicines were those approved by the European Medicines Agency but did not include vaccines. The study did not assess the content of disclosure against any specific requirements. The authors were B R Deane, a freelance consultant in pharmaceutical marketing and research and Dr J Sivarajah, Head of Medical Affairs, ABPI. Publication support for the study was funded by the ABPI.

As the results of the study suggested that some companies might have breached the Code, the Director decided, in accordance with Paragraph 5.1 of the Constitution and Procedure, to take the matter up as a complaint with those companies. Similar consideration had been given to the previous study published in May 2015, relating to medicines approved in 2012. A complaint had been received about the first study, published in November 2013, relating to medicines approved in 2009, 2010 and 2011.

Clause 13.1 of the Code states 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 Joint Positions were agreed 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).

Article 9 of the current IFPMA Code of Practice (which came into operation on 1 September 2012) includes 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). These are available at www.ifpma.org/en/ethics/clinical-trials-disclosure.html.

In considering the cases, the Code of Practice Panel first had to determine whether the matter was covered by the ABPI Code, ie whether there was any UK involvement. The next point for consideration was the date the product was first approved and commercially available anywhere in the world which would determine which version of the ABPI Code applied for trials completed prior to first approval. If a trial completed after the date of first approval, the completion date of the trial would determine which version of the ABPI Code applied. In instances where the ABPI Code did not apply, many of the companies listed in the studies were members of IFPMA and/or EFPIA and thus would be covered by other codes. Where the ABPI Code did apply, companies were mainly ruled in breach of Clauses 13.1 in relation to not disclosing within the required timeline, in addition to Clause 9.1 for failing to maintain high standards.

PUBLIC REPRIMAND FOR ASTELLAS UK

Astellas UK has been publicly reprimanded by the Code of Practice Appeal Board for a lamentable lack of concern for patient safety and wholly unsatisfactory oversight and control of two patient support programmes and of the nurses employed to deliver them (Case AUTH/2883/10/16).

Astellas UK had voluntarily admitted multiple failings in this case concerning its patient support programmes, Fresh Start and VIP which related to Betmiga (mirabegron) and Vesicare (solifenacin succinate) respectively. Both medicines were for patients with overactive bladder syndrome. The Code of Practice Panel was extremely concerned and noted its rulings including breaches of Clause 2. Some of the matters raised went to the heart of self-regulation and patient safety. Notwithstanding the fact that Astellas UK was currently suspended from membership of the ABPI and already undergoing a series of audits of its procedures under the Code (Case AUTH/2780/7/15), the Panel reported Astellas UK to the Appeal Board. The Appeal Board considered that this case raised serious concerns which were entirely unacceptable.

The Appeal Board was minded to report Astellas UK to the ABPI Board but given the exceptional circumstances, including that the re-audits in Case AUTH/2780/7/15 were due to be carried out very shortly, it decided that the issues that had arisen in this case (AUTH/2883/10/16) should be looked at as part of the upcoming re-audit of Astellas UK. On consideration of the report of the re-audits the Appeal Board decided to report Astellas UK to the ABPI Board.

Full details of Case AUTH/2883/10/16 can be found on the PMCPA website.

Continued overleaf...

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.

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

Thursday 15 June, 2017

Friday 7 July, 2017

Friday 15 September, 2017

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
Facsimile: 020 7747 8881

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

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

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

CLINICAL TRIAL DISCLOSURE – DECISION TREE UPDATED

(Continued from cover)

The cases which have arisen as a result of the three studies published in CMRO led the PMCPA to develop a decision tree which took into account the dates of the various ABPI Codes, Joint Positions, date the product was first licensed and available and completion date of the trial. The first decision tree was published in 2014 and updated and republished in 2015. The recent cases led to a further update to the decision tree which is included in the relevant case reports (Cases AUTH/2898/11/16, AUTH/2901/11/16, AUTH/2906/11/16 and AUTH/2908/11/16), published in the May 2017 Code of Practice Review and available on the PMCPA website. Companies are encouraged to use the decision tree to aid their compliance with clinical trial disclosure requirements.

ANONYMOUS, NON-CONTACTABLE v GEDEON RICHTER

Esmya patient support leaflet

An anonymous, non-contactable complainant, who described him/herself as a senior grade doctor in obstetrics and gynaecology, complained about a patient support leaflet for Esmya (ulipristal acetate) produced by Gedeon Richter. Esmya was indicated for the pre-operative or intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

The complainant noted that the leaflet advised patients to use an alternative contraceptive method to 'oral hormonal contraception' whilst taking Esmya due to an interaction that would influence the efficacy of both medicines. The leaflet did not refer to other widely used hormonal methods such as contraceptive injections etc; the complainant noted that any type of hormonal contraceptive, regardless of delivery route, would interfere with the efficacy of Esmya and more worryingly, contraception. Patients could thus potentially conceive whilst taking Esmya; the patient support leaflet should be corrected as a matter of urgency in the interest of patient safety.

The detailed response from Gedeon Richter is given below.

The Panel noted that one of the contraindications listed in Section 4.3 of the Esmya summary of product characteristics (SPC) was 'pregnancy'. Section 4.5, Interaction with other medicinal products and other forms of interaction, stated that hormonal contraceptives and progestogens were likely to reduce the efficacy of Esmya and that Esmya might interfere with the action of hormonal contraceptives (progestogen only, progestogen-releasing devices or combined oral contraceptive pills). The patient support leaflet in question, however, only referred to the inadvisability of taking oral contraceptives whilst on Esmya treatment because the two medicines might interact.

The Panel noted Gedeon Richter's submission that as both Esmya and contraceptives had to be prescribed by a health professional, women would be unlikely to receive a prescription for both at the same time. Nonetheless, the Panel considered that given the extreme importance that such concomitant administration did not occur, the failure of the patient support leaflet to alert women to the fact that they should not use any form of hormonal contraception whilst taking Esmya was a serious matter. Although the Esmya package leaflet dealt with the matter, each piece of material should be capable of standing alone. In the Panel's view the statement in the patient support leaflet was inaccurate and misleading. High standards had not been maintained. Breaches of the Code were ruled. In the Panel's view that such a serious and fundamental error existed at all was such as to reduce confidence in the industry being able to produce even simple material to the required quality standards. A breach of Clause 2 was ruled.

Gedeon Richter provided the requisite undertaking and assurance and as the case

completed at Panel level the Appeal Board received the case report as set out in Paragraph 13.4 of the Constitution and Procedure.

The Appeal Board noted the Panel's comments and rulings above. The Appeal Board considered that this case raised serious issues regarding patient safety and was of the view that further sanctions should be imposed under Paragraph 11.1 of the Constitution and Procedure such as the issuing of a corrective statement and recovery of the material from health professionals.

The detailed response from Gedeon Richter to the possibility of further sanctions being imposed is given below.

The Appeal Board noted its previous comments and that Esmya was likely to be initiated in secondary care when the misleading patient support leaflet would be available for health professionals to give to patients. The Appeal Board considered that when Esmya was initiated it was unlikely that contraception methods would be discussed in any great detail. The Appeal Board noted that there was also the potential that repeat prescriptions for Esmya would be referred to general practitioners. Reading the leaflet, patients might not think to raise that they were using non-oral hormonal contraception and GPs would not necessarily be aware of the incomplete information that their patients might have been given via the patient support leaflet about the use of contraception and Esmya. The Appeal Board noted that whilst the onus was on the GPs to ensure that they prescribed appropriately, women might not necessarily source their contraception from their GP.

In accordance with Paragraph 11.3 of the Constitution and Procedure, the Appeal Board decided to require Gedeon Richter to issue a corrective statement to health professionals who had received the leaflets in question. [The corrective statement, which was agreed by the Appeal Board prior to use, appears at the end of this report].

An anonymous, non-contactable complainant, who described him/herself as a senior grade doctor in obstetrics and gynaecology, complained about a patient support leaflet for Esmya (ulipristal acetate) (ref UK/ESM5/0416/0033) produced by Gedeon Richter (UK) Ltd. Esmya was indicated for the pre-operative or intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

COMPLAINT

The complainant explained that the leaflet advised patients to use an alternative contraceptive method to 'oral hormonal contraception' whilst taking Esmya due to an interaction that would influence the efficacy of both medicines. The complainant noted that the leaflet did not refer to other widely used hormonal methods such as the Mirena coil, contraceptive injections etc. The complainant

submitted that any type of hormonal contraceptive, regardless of delivery route, would interfere with the efficacy of Esmya and more worryingly, contraception. This could potentially result in patients becoming pregnant whilst taking Esmya.

The complainant submitted that the mistake was brought to his/her attention by a colleague who assured him/her that Gedeon Richter knew about the error and would take appropriate action. However, the complainant noted that the leaflet was still in circulation.

The complainant strongly recommended that the patient support leaflet was corrected as a matter of urgency in the interest of patient safety.

When writing to Gedeon Richter, the Authority asked it to consider the requirements of Clauses 7.2, 9.1 and 2 of the Code.

RESPONSE

Gedeon Richter stated that it took compliance with the Code very seriously. The company regularly trained staff on the Code including most recently a two day meeting in October 2016 for the UK head office staff and senior managers. Further commitment to compliance and high standards was evidenced by the fact that the company still required two signatories (medical signatory and non-medical) to approve all materials before they were used or disseminated.

Gedeon Richter noted that the complainant had taken issue with reference to the need to avoid reliance on 'oral hormonal contraception' rather than referring to all forms of hormonal contraception in that regard in a patient support leaflet. The patient support leaflet which was provided as 50 identical tear off sheets stated: 'You should not take oral contraceptives whilst you are on ESMYA treatment because the two drugs might interact. Ask your healthcare professional if you are not sure'.

Gedeon Richter submitted that the leaflet was electronically certified in May 2016 and the printed version was approved in June; it was first disseminated in July, the associated briefing document having been certified two days previously. A copy of the leaflet was provided, along with the associated briefing document and related certificates. The tear off leaflet was certified for use by health professionals to hand to patients prescribed Esmya so the 'audience' was patients prescribed Esmya but delivery to the patients would be via their health professional. Gedeon Richter submitted that the text on the leaflet itself was very clear as to the audience.

Gedeon Richter stated that when it received the complaint, the leaflet was already in the late stages of revision/certification following customer feedback received via the sales team. The revised version, which addressed the matter now at issue ie reference to 'oral [hormonal] contraception' rather than the broader term 'hormonal contraception', was certified on 4 November 2016. Copies of this revised and certified version and associated briefing document, together with the corresponding certificates, were provided.

Gedeon Richter noted that Clause 7.2 required, *inter alia*, that 'Information, claims and comparisons must be accurate, balanced, fair, objective and

unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis'.

Gedeon Richter further noted that the complaint was that 'oral [hormonal] contraception' was inappropriately specific as other forms of hormonal contraception could interact with Esmya to reduce the efficacy of medicines.

Gedeon Richter submitted that it now realised that the wording on the patient support leaflet could potentially cause confusion but emphasised that this was certainly not intended; on the contrary, the company had hoped to simplify language for the patient in order to clearly convey the relevant information. In laymen's terms it was not unusual to use the term oral contraception to cover hormonal contraception in general. Gedeon Richter acknowledged that the outcome had inadvertently caused a misunderstanding which was unfortunate and regrettable. Gedeon Richter submitted that it had already revised the wording in the leaflet and the updated version was now in use following the withdrawal of the previous version which was the subject of this complaint.

Gedeon Richter submitted that the leaflet was the only piece of Esmya patient material it had produced and so the wording in question only appeared in that leaflet.

Gedeon Richter noted that the package leaflet for Esmya, which under the heading 'What you need to know before you take Esmya', clearly stated 'Warnings and precautions: - If you are currently taking hormonal contraception (for example birth control pills) (see "Other medicines and Esmya") you should use an alternative reliable barrier contraceptive method (such as a condom) while taking Esmya'. Gedeon Richter submitted that it was clear that the statement in the patient support leaflet was factually correct but inadvertently did not extend to other forms of hormonal contraception. However the leaflet text did include the clear and prominent statements 'You should not take oral contraceptives whilst you are on ESMYA treatment because the two drugs might interact. Ask your healthcare professional if you are not sure' and 'Further information on Esmya is available in the leaflet inside the product pack'.

Gedeon Richter denied a breach of Clause 7.2 on the basis that the combined information provided by the patient support leaflet, its reference to the package leaflet and that the package leaflet itself provided the information needed for the patient to understand the need for non-hormonal contraception while taking Esmya.

Gedeon Richter noted that in addition to the specific wording cited, the complaint related to the continued use of the patient support leaflet; the complaint was dated 1 November 2016 and referred to the material being in use 'last week'.

Gedeon Richter submitted that it was first made aware of the wording at issue by a health professional on 20 October and steps were then taken to draft a revised version which had now been certified for subsequent distribution. The previous version was withdrawn from use on 4 November.

Gedeon Richter submitted that all of its health professional materials and the prescribing information covered that concomitant hormonal contraceptives were not recommended with Esmya. As all hormonal contraception (oral or other routes) was available by prescription only, no patient would receive hormonal contraception without an interaction with her health professional who would follow due process with regards to checking medicine interactions before prescribing any hormonal contraceptive. Additionally, the patient support leaflet directed the patient to her health professional and/or the package leaflet for further information.

On that basis, Gedeon Richter did not accept that the continued use of the leaflet while its replacement was in preparation, represented an actual risk to patient safety as (a) patients could only obtain hormonal contraception on prescription from a health professional as described above, and (b) all other materials, including those for health professionals, referred to the need to avoid 'hormonal contraception' and not specifically 'oral hormonal contraception'. Gedeon Richter therefore refuted a breach of Clause 9.1.

Gedeon Richter submitted that it acted reasonably and not in a manner which would bring discredit upon, or reduce confidence in, the pharmaceutical industry. It had taken steps to ensure appropriate withdrawal and turnaround of revised materials following external feedback, which was nearing completion on receipt of this complaint.

Gedeon Richter submitted that once the wording was brought to its attention, it was subsequently revised; the previous version of the leaflet was withdrawn as soon as the revised version was certified. All other materials relating to Esmya were checked and no other instance identified where the same wording was used. As access to hormonal contraception was solely via consultation with a health professional, it obviated the possibility that a woman could take hormonal contraception concomitantly with Esmya. Taking this into account, Gedeon Richter submitted that the complainant had not demonstrated that, on the balance of probabilities, patient safety would be compromised by the wording in question.

Based on the company's actions and lack of impact on patient safety as described above, Gedeon Richter denied a breach of Clause 2.

PANEL RULING

The Panel noted that one of the contraindications listed in Section 4.3 of the Esmya SPC was 'pregnancy'. Section 4.4, Special warnings and precautions for use, stated that with regard to contraception, concomitant use of progestogen-only pills, a progestogen-releasing intra-uterine device or combined oral contraceptive pills was not recommended. Section 4.5 of the SPC, Interaction with other medicinal products and other forms of interaction, stated that hormonal contraceptives and progestogens were likely to reduce the efficacy of Esmya and that Esmya might interfere with the action of hormonal contraceptives (progestogen only, progestogen-releasing devices or combined oral contraceptive pills). The patient support leaflet in question, however, only referred to the inadvisability of taking oral contraceptives whilst on Esmya treatment because the two medicines might interact.

The Panel noted that the quality standards set out in Clause 7 of the Code for promotional information also applied to information for the public. Clause 7.2 required information, claims and comparisons to be, *inter alia*, accurate and not misleading. The Panel noted Gedeon Richter's submission that as both Esmya and contraceptives had to be prescribed by a health professional, women would be unlikely to receive a prescription for both at the same time. Nonetheless, the Panel considered that given the extreme importance that such concomitant administration did not occur, the failure of the patient support leaflet to alert women to the fact that they should not use any form of hormonal contraception whilst taking Esmya was a serious matter. Although the Esmya package leaflet dealt with the matter, each piece of material should be capable of standing alone. In the Panel's view the statement at issue in the patient support leaflet was inaccurate and misleading. A breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. In the Panel's view that such a serious and fundamental error existed at all was such as to reduce confidence in the industry being able to produce even simple material to the required quality standards. A breach of Clause 2 was ruled.

APPEAL BOARD CONSIDERATION OF CASE REPORT

Gedeon Richter provided the requisite undertaking and assurance and as the case completed at Panel level the Appeal Board received the case report as set out in Paragraph 13.4 of the Constitution and Procedure.

The Appeal Board noted the Panel's comments and rulings above. The Appeal Board considered that this case raised serious issues regarding patient safety. It noted Gedeon Richter's submission that as both Esmya and contraceptives had to be prescribed by a health professional, women would be unlikely to receive a prescription for both at the same time. The Appeal Board was of the view that further sanctions should be imposed under Paragraph 11.1 of the Constitution and Procedure such as the issuing of a corrective statement and recovery of the material from health professionals.

[Post meeting note: Following the Appeal Board meeting the Chairman was asked by the Director to reconsider the process in Paragraph 11 of the Constitution and Procedure regarding the arrangements when the Appeal Board considered imposing additional sanctions in cases which completed at Panel level. The Chairman noted that in such cases the Appeal Board was not provided with all the papers, further the respondent company had no opportunity to put its view or appear before the Appeal Board as it would have done if there had been an appeal or a report from the Panel to the Appeal Board. The Chairman also noted this aspect of the process in Paragraph 11 had not been used previously. In the interests of fairness, the Chairman decided that the company should be advised that the Appeal Board was considering imposing additional sanctions and asked to respond in writing, as well as be given the opportunity to attend the next meeting of the Appeal Board when the matter of sanctions would be considered afresh.]

COMMENTS FROM GEDEON RICHTER

Gedeon Richter entirely accepted the Panel's ruling of breaches of Clauses 2, 9.1 and 7.2 of the Code.

The patient support leaflet in question had been withdrawn from use within the required timeline and all relevant staff and third parties briefed as detailed below. Gedeon Richter sincerely regretted the error and accepted the sanctions already placed upon it.

Gedeon Richter submitted that it was committed to abiding by the Code and took its responsibilities under the Code extremely seriously. Gedeon Richter's existing key focus on patient safety and the maintenance of high standards within the industry had sharpened following the Panel's ruling. Gedeon Richter was taking appropriate steps to ensure there was no repetition of this failure.

Gedeon Richter noted that the head office and senior management team had received compliance training in late October 2016 and further compliance training was undertaken in early January 2017 for the entire company including the field force. Training records were provided.

Gedeon Richter submitted that it was placing considerable additional emphasis on its compliance with the Code and was in the process of appointing a compliance and regulatory affairs officer to provide additional support and ensure increased rigour to its processes, training schedules and records maintenance.

Gedeon Richter fully recognised that when its field teams made it aware of the issue, it had not acted quickly enough. Gedeon Richter sincerely regretted that it had not immediately withdrawn the patient support leaflet at issue. A number of factors caused this delay. The increased resource within its compliance team would help to ensure such an unfortunate and regrettable incident, with its attendant consequences for patient safety, did not reoccur.

Gedeon Richter submitted that it had audited and checked all of its current materials to ensure similar wording was not present in any other material and all standard operating procedures (SOPs) had been reviewed and updated. Additional SOP training was ongoing and would be completed by the end of February 2017.

On receipt of the complaint, Gedeon Richter submitted that it had withdrawn the patient support leaflet at issue; details of the actions taken and the number of leaflets destroyed were provided.

Gedeon Richter noted that it had previously provided details of the revised material.

Gedeon Richter submitted that the sales team were instructed verbally to brief customers on the revision to the patient support leaflet and to retrieve the superseded version from customers wherever possible. This direction to the sales team was repeated at a team meeting held in

January 2017 with a follow-up email requesting confirmation of these actions. To summarise, the company had withdrawn, amended and replaced the patient support leaflet in question. All relevant staff had been briefed on the complaint, its outcome and ensuing actions including further Code training and roll-out of revised SOPs and policies relating to the Code.

Finally, Gedeon Richter reiterated its sincere regret that the patient support leaflet had been found in breach of the Code; this was entirely unintended and fell far short of the standards by which the company operated. Gedeon Richter recognised the serious nature of the error and had not appealed the ruling but had focussed its energies in upskilling the team and making its processes more robust.

APPEAL BOARD CONSIDERATION

The Appeal Board noted the Panel's rulings of breaches of Clauses 2, 7.2 and 9.1 regarding the patient support leaflet which only told women that they should not use oral contraception whilst taking Esmya when in fact they should not use any form of hormonal contraception. The Appeal Board noted that Esmya might interfere with the action of all hormonal contraceptives which were also likely to reduce the efficacy of Esmya. The Appeal Board considered that this case raised serious issues regarding patient safety.

The Appeal Board noted that Esmya was likely to be initiated in secondary care when the misleading patient support leaflet would be available for health professionals to give to patients. The Appeal Board considered that when Esmya was initiated it was unlikely that contraception methods would be discussed in any great detail. The Appeal Board noted that there was also the potential that repeat prescriptions for Esmya would be referred to general practitioners. Reading the leaflet, patients might not think to raise that they were using non-oral hormonal contraception and GPs would not necessarily be aware of the incomplete information that their patients might have been given via the patient support leaflet about the use of contraception and Esmya. The Appeal Board noted that whilst the onus was on the GPs to ensure that they prescribed appropriately, it noted that women might not necessarily source their contraception from their GP.

In accordance with Paragraph 11.3 of the Constitution and Procedure the Appeal Board decided to require Gedeon Richter to issue a corrective statement to health professionals who had received the leaflets in question. [The corrective statement, which was agreed by the Appeal board prior to use, appears at the end of this report].

Complaint received 2 November 2016

Undertaking received 6 December 2016

Appeal Board consideration 11 January and 9 February 2017

On 30 March 2017, Gedeon Richter sent the following corrective statement to relevant hospital doctors

'Corrective statement

Between July and November 2016, a patient support leaflet for Esmya (ulipristal acetate) (ref UK/ESM5/0416/0033) produced by Gedeon Richter (UK) Ltd was circulated. Esmya is indicated for the pre-operative or intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

You are being sent this corrective statement because you may have received the Esmya patient support leaflets to pass on to your patients when you prescribed them Esmya.

Following a complaint under the ABPI Code of Practice for the Pharmaceutical Industry, the Code of Practice Panel ruled that the patient support leaflet

was inaccurate and misleading in that it only told the woman that she should not take oral contraceptives whilst on Esmya whereas she should have been told not to use hormonal contraceptives whilst taking Esmya. The Panel ruled that Gedeon Richter had failed to maintain high standards and had brought discredit upon and reduced confidence in the pharmaceutical industry. As a result of the above and concerns about patient safety, the Code of Practice Appeal Board has required Gedeon Richter to issue this corrective statement and to circulate a copy of the published report for the case which contains full details. This is enclosed.

If you have any remaining copies of the above patient support leaflet please dispose of them.

In addition, where relevant, please draw this issue to the attention of any GP to whom you might have referred patients for repeat prescriptions of Esmya.

Details of this case (Case AUTH/2885/11/16) are also available on the PMCPA website (www.pmcpa.org.uk).

PHARMACOSMOS v VIFOR

Promotion of Ferinject

Pharmacosmos UK complained about a Ferinject (iron carboxymaltose) leavepiece entitled 'Their world awaits' issued by Vifor Pharma UK. Ferinject was an intravenous (IV) iron preparation for the treatment of iron deficiency where oral therapy had been ineffective or could not be used. Pharmacosmos marketed Monofer (iron isomaltoside) which was similarly indicated.

Pharmacosmos stated that many of its concerns might be reflected in other promotional material. There appeared to be a clear intention to indirectly compare Ferinject and Monofer. The manner of the implied comparison resulted in claims that were alleged to be misleading as outlined below.

Page 1 of the leavepiece featured a red highlighted box which contained the following claims:

'Ferinject is the only high dose rapid infusion IV iron that;

- has simplified dosing for all patients
- contains product specific safety data in the Summary of Product Characteristics
- is licenced [*sic*] for ages 14 years and over
- can be administered up to 1g as a bolus injection

Ferinject is the UK and Europe's market leading IV iron.'

Pharmacosmos alleged that the layout of the phrase within the red box implied that Ferinject was the only product that could offer any of the points in the bullets, which was not true. A breach of the Code was alleged. By stating that Ferinject was the 'only high dose rapid iron infusion', the unstated but only comparison being made was with Monofer.

With regard to the claim that Ferinject was the only high dose rapid infusion IV iron that had simplified dosing for all patients, Pharmacosmos stated that there were two ways to calculate iron need based on patient body weight and haemoglobin levels; the Ganzoni formula or a simplified dosing table. Ferinject dose was based on the simplified table exclusively while clinicians could determine the dose of Monofer using either method. The Monofer summary of product characteristics (SPC) recommended but did not mandate the use of the Ganzoni formula in certain patients. Therefore, the Monofer SPC also allowed simplified dosing in all patients, and subsequently the implied comparison was alleged to be inaccurate and misleading in breach of the Code.

Pharmacosmos further alleged that the claim that Ferinject 'can be administered up to 1g as a bolus injection' was not accurate. The Ferinject SPC stated that 'Ferinject may be administered by

intravenous injection using undiluted solution up to 1,000 mg iron (*up to a maximum of 15 mg/kg body weight*)' (emphasis added). By failing to include the 15mg/kg limit Pharmacosmos alleged that an important safety consideration was omitted, in breach of the Code.

The detailed response from Vifor is given below.

The Panel agreed with Pharmacosmos that the claims in the red box on page 1 of the leavepiece were an implied comparison with Monofer. By referring to Ferinject as 'the only high dose rapid infusion IV iron' implied that there was at least one other with which to draw a comparison. The claims were not presented simply as 'Ferinject offers etc'. The Panel noted the allegation that the layout of the claims in the red box implied that only Ferinject, unlike Monofer, could offer any of the attributes stated. In that regard the Panel noted that only Ferinject had simplified dosing for all patients; Monofer did not as the Ganzoni formula was recommended in certain patient groups. Only Ferinject was licensed for ages 14 years and over; Monofer could only be given to patients aged 18 years and over. Only Ferinject could be administered (in some circumstances – see below) up to 1g as a bolus injection; bolus injections of Monofer should not exceed 500mg. In the Panel's view, however, Ferinject was not the only high dose rapid infusion IV iron that contained product specific safety data in its SPC as claimed. The statement in the Monofer SPC that due to limited clinical data the side effects stated were *primarily* (emphasis added) based on the safety data for other parenteral iron solutions, implied that at least some of the safety data in the Monofer SPC was product specific. The Panel thus did not consider that Ferinject was the only product which provided all of the attributes listed in the red box. In that regard the claim in the highlighted red box was not accurate as alleged. A breach of the Code was ruled.

The Panel noted the allegation that the claim that Ferinject was the only high dose rapid infusion iron that had simplified dosing for all patients was inaccurate and misleading. As referred to above, the Panel noted that Monofer did not have simplified dosing for all patients as the Ganzoni formula was recommended in certain patient groups. The Panel noted Pharmacosmos' comment that the Ganzoni formula was not mandated for particular patients; only recommended. In that regard, however, simplified dosing was not a given for Monofer, prescribers would have to make a clinical decision to ignore the recommendation to use the Ganzoni formula for certain patients. The Panel did not consider that the claim was inaccurate or misleading as alleged. No breach of the Code was ruled.

With regard to the allegations about the claim that Ferinject 'can be administered up to 1g as a

bolus injection', the Panel noted that Section 4.2 of the Ferinject SPC stated that a single Ferinject administration should not exceed 15mg iron/kg body weight (for IV injection) or 20mg iron/kg body weight (for IV infusion), nor should a single administration exceed 1,000mg iron. In that regard, patients with a body weight of less than 66.6kg could not receive a bolus injection of 1,000mg Ferinject. The Panel noted Vifor's submission that page 5 of the leavepiece contained the necessary detail but also noted that the Code required claims to be able to stand alone. In the Panel's view, the unqualified claim at issue implied that every patient could receive 1,000mg Ferinject as a single bolus injection and that was not so. The Panel considered that the claim was not accurate as alleged and it ruled a breach of the Code. The Panel did not consider that the claim was misleading about the side effects of Ferinject and in that regard it ruled no breach of the Code.

Pharmacosmos noted that page 3 of the leavepiece was headed 'Ferinject vs. oral iron therapy' and featured two graphs adapted from Onken *et al* (2014).

According to the simplified dosing in the Ferinject SPC, patients could receive a total dose of 500, 1,000, 1,500 or 2,000mg based on their weight and haemoglobin values. Onken *et al*, however, had dosed all patients with 2 x 750mg (1,500mg) completely independent and irrespective of the patient's weight and haemoglobin. This was an arbitrary and incorrect method of dosing patients and was not in-line with the licensed Ferinject dosing regimen. Pharmacosmos alleged that the presentation of data from Onken *et al* was thus in breach of the Code.

The Panel noted that the Ferinject SPC clearly stated that the determination of dose was based upon the patient's weight (below 35kg, 35-<70kg and 70kg and over) and his/her haemoglobin levels (<10g/dL, 10-14g/dL and >14g/dL). A table in the SPC showed the doses which should be given according to which of nine categories a patient fell within. A single dose of Ferinject should not exceed 15mg/kg/body weight for an IV injection and 20mg/kg bodyweight for an IV infusion. The maximum cumulative dose should not exceed 1,000mg of iron (20ml Ferinject) per week).

The Panel noted, however, that Onken *et al* administered Ferinject 15mg/kg to a maximum of 750mg on days 0 and 7 regardless of the patient's haemoglobin level. This was not in accordance with the SPC and meant that if a patient in the study weighed 70kg and had a haemoglobin level of $\leq 9\text{g/dL}$ in Onken *et al* would administer a total dose of 1,500mg. The SPC stated that for a patient of that weight and haemoglobin level, a total dose of 2,000mg should be given. Similarly if a patient weighed 68kg and had a haemoglobin level of $\geq 10.1\text{g/dL}$, Onken *et al* would still administer Ferinject in two doses of 750mg (1,500mg in total) whereas the SPC gave a dose of only 1,000mg.

The Panel noted that page 5 of the leavepiece stated that the Ferinject dose was calculated according

to the patient's weight and current haemoglobin level. Nonetheless, the Panel considered that the use of Onken *et al* on page 3 promoted a dose of Ferinject which was not in accordance with the SPC. The Panel ruled a breach of the Code. The Panel considered that the leavepiece was misleading in that regard. A breach of the Code was ruled.

Pharmacosmos referred again to page 3 of the leavepiece and the depiction of the Onken *et al* data discussed above. Pharmacosmos alleged that the only safety data in the leavepiece was in the prescribing information on the final page which was insufficient on this occasion.

Given that there was clearly an efficacy difference between Ferinject and oral iron demonstrated, it was appropriate and important to highlight that approximately 1 in 4 of the Ferinject study population experienced side effects compared with a much lower proportion of patients experiencing side effects with oral iron. Whilst Pharmacosmos recognised the comments of the authors, which explained the impact of the study run-in period, it was clear that the authors did not believe the study protocol accounted for all of the differences between IV and oral treatment. Given that the front page of the leavepiece drew attention to safety considerations in the SPC, Pharmacosmos believed that the difference in the safety profiles between Ferinject and oral iron in Onken *et al* should accordingly be highlighted. Pharmacosmos alleged that the absence of the balancing of safety data was in breach of the Code.

The Panel noted the comments above regarding the trial design and how it might have contributed to the relatively low frequency of drug-related treatment-emergent adverse events in the oral iron treatment group (6.3%) vs the Ferinject treatment group (22.8%). The run-in part of the trial had already screened out those patients who could not tolerate oral iron. The Panel noted that the authors had stated that the safety profile of Ferinject was generally comparable to that of oral iron.

Overall, the Panel did not consider that the leavepiece was misleading as to the relative safety of Ferinject vs oral iron as alleged. No breach of the Code was ruled.

The Panel noted that there were no claims about the adverse reactions of Ferinject nor was it stated that the medicine had no side effects. Ferinject was not described as safe. No breach of the Code was ruled.

Pharmacosmos UK Limited complained about a Ferinject (iron carboxymaltose) leavepiece entitled 'Their world awaits' (ref UK/FER/16/0116) issued by Vifor Pharma UK Limited. Ferinject was an intravenous (IV) iron preparation for the treatment of iron deficiency where oral therapy had been ineffective or could not be used. Pharmacosmos marketed Monofer (iron isomaltoside) which was similarly indicated.

Pharmacosmos raised a number of concerns, stating that many might be reflected in other promotional material. There appeared to be a clear intention to

indirectly compare Ferinject and Monofer and raise doubts about the safety of the latter. Pharmacosmos alleged that the manner of the implied comparison resulted in misleading claims. Pharmacosmos was also concerned about the fair representation of Ferinject in relation to a number of specific claims.

Vifor stated that it was extremely disappointed to again be required to answer a complaint made by Pharmacosmos. The company stated that its views on the continued abuse by Pharmacosmos of both the letter and the spirit of the UK pharmaceutical industry self-regulatory system were in the public domain.

Vifor again stated that the case preparation manager should not have accepted this complaint as Pharmacosmos did not have standing with the PMCPA. As stated in the Memorandum of Understanding between the ABPI, the PMCPA and the Medicines and Healthcare products Regulatory Agency (MHRA):

'Compliance with the Code is a condition of membership of the ABPI and, in addition, about 60 pharmaceutical companies that are not members of the Code have agreed to comply with the Code and submit to the jurisdiction of the PMCPA. **Members of the ABPI and non-members of the ABPI who have agreed to comply with the Code should send their complaints to the PMCPA'** (emphasis added).

Vifor submitted that this clearly implied that non-member companies which had not agreed to comply with the Code should refer their complaints to the MHRA.

The basis of Pharmacosmos's complaint was that Vifor had indirectly compared Ferinject and Monofer. There were only two high dose, short infusion time IV irons with marketing authorizations in the UK. Pharmacosmos seemed to assert that any and all Ferinject claims made in the leavepiece were by definition automatically also a comparison with Monofer. Vifor disputed this stance as such an assertion, if upheld, would *de facto* deprive the company of its right to promote its product on its own merits, as was the case with this leavepiece. Vifor noted that the Pharmacosmos 'ONE Visit' promotional campaign claimed, misleadingly, that all patients could be treated fully for their iron deficiency with Monofer in only one hospital visit. Vifor did not claim this for Ferinject. Vifor queried whether Pharmacosmos had therefore made indirect comparisons to Ferinject in its promotional materials.

Vifor was concerned that Pharmacosmos selected specific complaints to refer to the PMCPA without acknowledging Vifor's comments during inter-company dialogue some of the alleged breaches of the Code considered in inter-company dialogue had not been included in the complaint to PMCPA; Vifor had not received any confirmation from Pharmacosmos that its response to these components of the complaint had been accepted.

Vifor stated that this and other discrepancies between the substance and content of the

Pharmacosmos complaint during inter-company dialogue and that submitted to the PMCPA, illustrated Pharmacosmos's clear manipulation of the self-regulatory system of medicines promotion in the UK. Vifor was not able to complain to the PMCPA about this situation, nor was it able to raise issues against Pharmacosmos via the PMCPA.

In summary, Vifor did not consider that this complaint should have been accepted by the Authority because Pharmacosmos lacked standing and the inconsistencies inherent in the inter-company dialogue process followed by Pharmacosmos. Furthermore, Vifor submitted that the leavepiece was not in breach of the Code as alleged.

1 Page 1

Page 1 of the leavepiece featured a red highlighted box which contained the following claims:

'Ferinject is the only high dose rapid infusion IV iron that;

- has simplified dosing for all patients
- contains product specific safety data in the Summary of Product Characteristics
- is licenced [*sic*] for ages 14 years and over
- can be administered up to 1g as a bolus injection

Ferinject is the UK and Europe's market leading IV iron.'

COMPLAINT

Pharmacosmos alleged that the layout of the phrase within the red box implied that Ferinject was the only product that could offer *any* of the points in the bullets, which was not true. A breach of Clause 7.2 was alleged. By stating that Ferinject was the 'only high dose rapid iron infusion', the unstated but only comparison being made was with Monofer.

With regard to the claim that Ferinject was the only high dose rapid infusion IV iron that had simplified dosing for all patients, Pharmacosmos stated that iron need was estimated based on patient body weight and haemoglobin levels, and there were two primary ways to calculate this; the Ganzoni formula or a simplified dosing table. The summary of product characteristics (SPC) for Ferinject was based on the simplified table exclusively while Monofer's SPC allowed for both options and clinicians could select between the two at their discretion. The Monofer SPC recommended but did not mandate the use of the Ganzoni formula in certain patients. Therefore, the Monofer SPC also allowed simplified dosing in all patients, and subsequently the implied comparison was alleged to be inaccurate and misleading in breach of Clause 7.2.

Pharmacosmos further alleged that the claim that Ferinject 'can be administered up to 1g as a bolus injection' was not accurate and omitted important safety caveats. The Ferinject SPC stated that 'Ferinject may be administered by intravenous

injection using undiluted solution up to 1,000 mg iron (**up to a maximum of 15 mg/kg body weight**)' (emphasis added). By failing to include the 15mg/kg limit Pharmacosmos alleged that an important safety consideration was omitted, in breach of Clause 7.9.

RESPONSE

Vifor noted that Pharmacosmos had emphasised the word 'any' in its complaint. All of the attributes listed were taken directly from the Ferinject SPC and were indeed true only for Ferinject. Hence, Vifor did not see how this could be a breach of Clause 7.2 as all of these statements were fact, properly referenced and based on Ferinject's individual substantiable attributes. These statements highlighted Ferinject's properties and were not a comparison, direct or indirect, to Monofer.

Vifor fundamentally disagreed with Pharmacosmos's reasoning and stated that the Ferinject claims were based on its own attributes one of which was that it was the only high dose intravenous iron that had simplified dosing for all patients. Pharmacosmos stated that '... Monofer's SPC allows for both options and clinicians can select between the two at their discretion ...' (*sic*). The Monofer SPC actually stated '... The cumulative iron need can be determined using either the Ganzoni formula (1) or the Table below (2). It is recommended to use the Ganzoni formula in patients who are likely to require individually adjusted dosing such as patients with anorexia nervosa, cachexia, obesity, pregnancy or anaemia due to bleeding ...'. Vifor submitted there was a major difference in regulatory documents between 'recommended' and Pharmacosmos's interpretation of this, 'discretion'. There was no such recommendation (or discretion) in the Ferinject SPC. Vifor denied a breach of Clause 7.2.

With regard to the claim that Ferinject 'can be administered up to 1g as a bolus injection', Vifor noted that the leavepiece was a six page document, the final page of which was Ferinject prescribing information. The claim at issue was on the first page. The fifth page included the statement '... A maximum single dose of 15mg/kg body weight up to 1000mg of iron can be administered by intravenous injection'. This was factual, accurate and very clearly referenced, Vifor therefore submitted that no breach of Clause 7.9 had occurred as there was no omitted important safety consideration.

PANEL RULING

The Panel disagreed with Vifor's submission that as Pharmacosmos was neither a member of the ABPI nor a non member that had agreed to comply with the Code and accept the jurisdiction of the Authority, it was not able to complain under the Code. This point was previously raised by Vifor in its appeal in Case AUTH/2830/4/16. In that case the Appeal Board noted that the Memorandum of Understanding between the ABPI, the PMCPA and the MHRA did not exhaustively detail who could submit complaints under the Code, referring only to the position of ABPI member companies and non members that had agreed to comply with the Code. Paragraph

5.1 of the Constitution and Procedure was clear that the complaints procedure could commence once the Director had received information that certain companies might have contravened the Code. Paragraph 5.1 of the Constitution and Procedure only required the respondent company to be either an ABPI member or a non member company which had agreed to comply with the Code and accept the jurisdiction of the Authority. There was thus nothing in the Constitution and Procedure to preclude Pharmacosmos from submitting a complaint; indeed if there were, the Appeal Board considered that such provision might encourage some companies to submit complaints anonymously. In the Appeal Board's view, the Authority had been correct to allow the complaint in Case AUTH/2830/4/16 to proceed.

Turning to the present case, Case AUTH/2886/11/16, the Panel agreed with Pharmacosmos that the claims in the red box on page 1 of the leavepiece were an implied comparison with Monofer. By referring to Ferinject as 'the only high dose rapid infusion IV iron' implied that there was at least one other with which to draw a comparison. The claims were not presented simply as 'Ferinject offers etc'. The Panel noted the allegation that the layout of the claims in the red box implied that only Ferinject, unlike Monofer, could offer any of the attributes stated. In that regard the Panel noted that only Ferinject had simplified dosing for all patients. Monofer did not have simplified dosing for all patients as the Ganzoni formula was recommended in certain patient groups such as those with anorexia nervosa or with anaemia due to bleeding. Only Ferinject was licensed for ages 14 years and over; Monofer could only be given to patients aged 18 years and over. Only Ferinject could be administered (in some circumstances – see below) up to 1g as a bolus injection; bolus injections of Monofer should not exceed 500mg. In the Panel's view, however, Ferinject was not the only high dose rapid infusion IV iron that contained product specific safety data in its SPC as claimed. The statement in the Monofer SPC that due to limited clinical data the side effects stated were *primarily* (emphasis added) based on the safety data for other parenteral iron solutions, implied that at least some of the safety data in the Monofer SPC was product specific. The Panel thus did not consider that Ferinject was the only product which provided all of the attributes listed in the red box. In that regard the claim in the highlighted red box was not accurate as alleged. A breach of Clause 7.2 was ruled.

The Panel noted the specific allegation that the claim that Ferinject was the only high dose rapid infusion iron that had simplified dosing for all patients was inaccurate and misleading. As referred to above, the Panel noted that Monofer did not have simplified dosing for all patients as the Ganzoni formula was recommended in certain patient groups such as those with anorexia nervosa or with anaemia due to bleeding. The Panel noted Pharmacosmos' comment that the Ganzoni formula was not mandated for particular patients; only recommended. In that regard, however, simplified dosing was not a given for Monofer, prescribers would have to make a clinical decision to ignore the recommendation to use the Ganzoni formula for certain patients. The

Panel did not consider that the claim was inaccurate or misleading as alleged. No breach of Clause 7.2 was ruled.

With regard to the specific allegations about the claim that Ferinject 'can be administered up to 1g as a bolus injection', the Panel noted that Section 4.2 of the Ferinject SPC stated that a single Ferinject administration should not exceed 15mg iron/kg body weight (for IV injection) or 20mg iron/kg body weight (for IV infusion), nor should a single administration exceed 1,000mg iron. In that regard, patients with a body weight of less than 66.6kg could not receive a bolus injection of 1,000mg Ferinject. The Panel noted Vifor's submission that page 5 of the leavepiece contained the necessary detail. However the supplementary information to Clause 7 of the Code stated that claims in promotional material must be capable of standing alone as regards accuracy etc. In the Panel's view, the unqualified claim at issue implied that every patient could receive 1,000mg Ferinject as a single bolus injection and that was not so. The Panel considered that the claim was not accurate as alleged and it ruled a breach of Clause 7.2. The Panel did not consider that the claim was misleading about the side effects of Ferinject and in that regard it ruled no breach of Clause 7.9.

2 Alleged off-label patients

Page 3 was headed 'Ferinject vs. oral iron therapy' and featured two graphs comparing Ferinject and oral iron. The first graph compared median serum ferritin saturation (mcg/L) and the second compared median haemoglobin saturation (g/dL). The data was at baseline and the change to day 35. Each graph was adapted from Onken *et al* (2014).

COMPLAINT

Pharmacosmos stated that the two graphs were intended to demonstrate that Ferinject was effective in treating iron deficiency. The company was concerned about the use of Onken *et al*.

As the leavepiece correctly stated, the simplified dosing table had to be used with all patients receiving Ferinject and this was the only option for estimating patient's iron need identified in the Ferinject SPC. According to this table, patients could receive a total dose of 500, 1,000, 1,500 or 2,000mg based on their weight and haemoglobin values. Onken *et al*, however, had dosed all patients with 2 x 750mg (1,500mg) completely independent and irrespective of the patient's weight and haemoglobin. This was an arbitrary and incorrect method of dosing patients that did not take into account their weight or haemoglobin values. This was not in-line with the licensed Ferinject dosing regimen. Pharmacosmos alleged that the presentation of data from Onken *et al* was thus in breach of Clause 3.2 and was also misleading in breach of Clause 7.2.

RESPONSE

Vifor noted that Onken *et al* was a multicenter, randomised, active-controlled study to investigate the efficacy and safety of Ferinject in patients with iron deficiency anemia; it was one of the registration

studies conducted in order to gain licence approval for Ferinject in the US. The average weights of the groups who received Ferinject were 82.8kg for Group A and 79.5kg for Group C. This was consistent with the Ferinject SPC and there was nothing in the SPC that prevented the administration of two doses of 750mg to make a total cumulative dose of 1,500mg being given to appropriate patients according to the dosing table in Section 4.2 of the SPC. The leavepiece clearly provided the dosing table from the SPC which described dose based on haemoglobin level and body weight.

Vifor submitted that Pharmacosmos's allegation that Ferinject had been promoted in an unlicensed manner was not correct and therefore there was no breach of Clauses 3.2 and 7.2.

PANEL RULING

The Panel noted that the Ferinject SPC clearly stated that the determination of dose was based upon the patient's weight (below 35kg, 35-70kg and 70kg and over) and his/her haemoglobin levels (<10g/dL, 10-14g/dL and >14g/dL). A table in the SPC showed the doses which should be given according to which of nine categories a patient fell within. A single dose of Ferinject should not exceed 15mg/kg/body weight for an IV injection and 20mg/kg bodyweight for an IV infusion. The maximum cumulative dose should not exceed 1,000mg of iron (20ml Ferinject) per week).

The Panel noted, however, that Onken *et al* administered Ferinject 15mg/kg to a maximum of 750mg on days 0 and 7 regardless of the patient's haemoglobin level. This was not in accordance with the SPC. The mean weight of patients in Group A was 82.8kg (\pm 22.5) and in Group C it was 79.5kg (\pm 20.4). The Panel noted that if a patient in the study weighed 70kg and had a haemoglobin level of \leq 9g/dL (there were 23/246 patients in Group A and 122/253 in Group C with that baseline haemoglobin level), Onken *et al* would administer a dose of 750mg on days 0 and 7 giving 1,500mg in total. The SPC stated that for a patient of that weight and haemoglobin level, a total dose of 2,000mg should be given. Similarly if a patient weighed 68kg and had a haemoglobin level of \geq 10.1g/dL (there were 175/246 patients in Group A and 71/253 patients in Group C with that haemoglobin level), Onken *et al* would still administer Ferinject in two doses of 750mg (1,500mg in total) whereas the SPC gave a dose of only 1,000mg.

The Panel noted that page 5 of the leavepiece stated that the Ferinject dose was calculated according to the patient's weight and current haemoglobin level. Nonetheless, the Panel considered that the use of Onken *et al* on page 3 promoted a dose of Ferinject which was not in accordance with the SPC in that doses had not been calculated according to bodyweight and haemoglobin level. The Panel ruled a breach of Clause 3.2. The Panel considered that the leavepiece was misleading in that regard. A breach of Clause 7.2 was ruled.

3 Balancing safety data

Pharmacosmos referred again to page 3 and the depiction of the Onken *et al* data discussed above.

COMPLAINT

Pharmacosmos alleged that the only safety data in the leavepiece was in the prescribing information on the final page which was insufficient on this occasion.

Given that there was clearly an efficacy difference between Ferinject and oral iron demonstrated, it was appropriate and important to highlight that approximately 1 in 4 of the Ferinject study population experienced side effects compared with a much lower proportion of patients experiencing side effects with oral iron. Whilst Pharmacosmos recognised the comments of the authors, which explained the impact of the study run-in period, it was clear that the authors did not believe the study protocol accounted for all of the differences between IV and oral treatment. Given that the front page of the leavepiece drew attention to safety considerations in the SPC, Pharmacosmos believed that the difference in the safety profiles between Ferinject and oral iron in Onken *et al* should accordingly be highlighted.

Pharmacosmos alleged that the absence of the balancing of safety data was in breach of Clauses 7.2 and 7.9.

RESPONSE

Vifor submitted that it managed all compliance with the utmost of seriousness, especially any complaint in relation to safety. That said, the argument used by Pharmacosmos to state that Vifor was not balanced in relation to safety data was fundamentally incorrect. During inter-company dialogue, Pharmacosmos stated '...it seems appropriate to highlight that 1 in 4 (28%) of the study population experienced side effects with Ferinject; we believe this is pertinent information, especially given the safety inference on the first page ...'. This was a clear misrepresentation of the Onken *et al* study data.

In Onken *et al*, the actual number of treatment-emergent adverse events that were considered drug related were 22.8% of subjects in group A (Ferinject), 6.3% in group B (oral iron), 25.3% in group C (Ferinject) and 26.5% in group D (standard of care IV iron). The 28% figure stated by Pharmacosmos was the number of subjects reporting a treatment-emergent adverse event during the run-in period, which used oral iron only and included all adverse events, not just drug-related ones.

In addition, the study included a primary composite safety end point which was generally comparable for Ferinject and oral iron. Furthermore, the authors stated that the relatively low frequency of drug-related treatment-emergent adverse events in group B could be explained by the trial design. Cohort 1 subjects, who formed groups A and B were pre-selected for lack of severe reaction to oral iron. In addition, events related to oral iron for subjects in group B (oral iron) that began during run-in would not have been counted as adverse events during treatment phase because the study medicine was the same, whereas all drug-related treatment-emergent adverse events in group A (Ferinject) after randomization to Ferinject were considered new events. Therefore, Vifor submitted that the only reliable measure of safety was the primary composite safety end point, which was generally comparable for Ferinject and oral iron. Vifor did not consider that there was an absence of balancing of safety data and there was no breach of Clauses 7.2 and 7.9.

PANEL RULING

The Panel noted the comments above regarding the trial design and how it might have contributed to the relatively low frequency of drug-related treatment-emergent adverse events in the oral iron treatment group (6.3%) vs the Ferinject treatment group (22.8%). The run-in part of the trial had already screened out those patients who could not tolerate oral iron. The Panel noted that the authors had stated that the safety profile of Ferinject was generally comparable to that of oral iron.

Overall, the Panel did not consider that the leavepiece was misleading as to the relative safety of Ferinject vs oral iron as alleged. No breach of Clause 7.2 was ruled.

Clause 7.9 stated that information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product had no adverse reactions, toxic hazards or risks of addiction or dependency. The word 'safe' must not be used without qualification. The Panel noted that there were no claims about the adverse reactions of Ferinject nor was it stated that the medicine had no side effects. Ferinject was not described as safe. No breach of Clause 7.9 was ruled.

Complaint received **7 November 2016**

Case completed **22 February 2017**

ANONYMOUS HEALTH PROFESSIONAL v ASTRAZENECA

Meeting attendees and speaker reference to Saxagliptin

An anonymous, contactable complainant, who described him/herself as a GP, complained that the parents of an AstraZeneca UK secondary care representative attended two promotional meetings organised by one of the company's primary care representatives. The complainant was concerned that on both occasions, the father of the secondary care representative (who was not General Medical Council (GMC) registered or practising) attended and had a meal. The complainant stated that GPs who were not active were no different from members of the public and should not be at such meetings.

The complainant stated that the secondary care representative's mother, who was a practice manager and a health assistant, discussed prescribing matters with other clinicians as she recommended medicines (including AstraZeneca's diabetes medicines). The complainant stated that the secondary care representative's mother asked the GP at the practice to sign the prescription which again, seemed wholly inappropriate as questions could arise linking sales of AstraZeneca's medicines without discussion from prescribing health professionals.

The complainant stated that the facts were that the secondary care representative's father had twice been brought to the meetings by his child who worked for AstraZeneca and it was wholly inappropriate for a practice manager who was not medically trained to recommend pharmaceutical products to other health professionals. As there was no section on quality outcome framework (QOF) or administration, the complainant queried what practice managers would have achieved from the session.

The complainant further noted that the speaker at the meeting referred to AstraZeneca's product Onglyza (saxagliptin) as 'sexygliptin' to get customers to remember it.

The Panel noted that there were differences between the parties' accounts, it was extremely difficult in such cases to know exactly what had transpired. The complainant bore the burden of proof on the balance of probabilities. A judgement had to be made based on the available evidence.

The Panel noted that according to AstraZeneca the representative's father did not attend either meeting as a delegate nor did he consume any subsistence. With respect to the second meeting neither the representatives nor he could recall whether he drove his wife to, or collected her from, the meeting and whether he entered the meeting venue. In relation to the first meeting, the secondary care representative and his/her father confirmed that he had dropped his wife off at the meeting. On collecting his wife he had arrived early and waited in the venue where he spoke to former colleagues. The Panel noted that the representative's father was no longer practising

or GMC registered and thus would be classified as a member of the public for the purposes of the Code. However, the Panel did not consider it unreasonable, in the circumstances, for him to merely greet former colleagues outside of the meeting's formal agenda and subsistence. There was no evidence that anything more than that had occurred. The Panel noted that the complainant bore the burden of proof and considered that there was no evidence that the representative's father had attended either meeting as a delegate or received subsistence as alleged. No breach of the Code was ruled. In addition, there was no evidence that either the representatives or the company had failed to maintain a high ethical standard. No breach of the Code was ruled.

The Panel noted that the secondary care representative's mother, attended both meetings in her role as a practice manager and a healthcare assistant. The Panel noted that the role of healthcare assistants in general practice varied but might include health promotion, blood pressure management and venepuncture; they were not registered with a professional body. The Panel had no information about the precise nature of the representative's mother's duties but noted that they would depend on the contractual relationship between her and the practice. The complainant alleged that the representative's mother recommended medicines including diabetes products. Nonetheless, the Panel noted that dependent on the details of her role the representative's mother could be a health professional and/or a relevant decision maker. The Panel noted the educational content of the meetings. The Panel also noted that the complainant bore the burden of proof. The Panel did not consider that there was any evidence before it to indicate that it was inappropriate for representative's mother to attend either of the meetings as a delegate as alleged. No breach of the Code was ruled. There was no evidence that either of the representatives or the company had failed to maintain high standards; no breach of the Code was ruled.

The Panel noted that the speaker at the second meeting had advised AstraZeneca that he had instead referred to 'sexygliptin' in an attempt at humour. The Panel noted that the speaker had been briefed in advance of the meeting and that his contract stated, *inter alia*, that statements 'must not cause offence either through the use of imagery or humour unbecoming the professional standing of the audience'. The Panel noted AstraZeneca's admission that it appeared that the speaker did not fulfil these requirements. The Panel considered that in this regard high standards had not been maintained; a breach of the Code was ruled.

An anonymous, contactable complainant, who described him/herself as a GP, complained that the parents of an AstraZeneca UK representative

attended two promotional meetings organised by the company. The complaint was copied to AstraZeneca.

COMPLAINT

The complainant stated that he/she had attended a number of AstraZeneca meetings in the last 10 years and was concerned about two diabetes meetings, held in November 2015 and November 2016 by two AstraZeneca representatives, one for primary care and one for secondary care. The complainant was concerned that on both occasions, that the father of the secondary care representative (who was not General Medical Council (GMC) registered or practising) attended and had a meal.

The complainant stated that the secondary care representative's mother, who was a practice manager and a health assistant, discussed prescribing matters with other clinicians as she recommended medicines (including AstraZeneca's diabetes medicines). The complainant stated that the secondary care representative's mother asked the GP at the practice to sign the prescription which again, seemed wholly inappropriate as questions could arise linking sales of AstraZeneca's medicines without discussion from prescribing health professionals.

No manager was present at either meeting and the complainant stated that if one had attended, then this issue would have been dealt with. GPs who were not active were no different from members of the public and should not be at such meetings.

The complainant stated that whilst he/she had no written or photographic evidence of the secondary care representative's father attending, he/she was certain that his presence would not have been recorded. In the past, the complainant had attended many meetings sponsored by AstraZeneca and other pharmaceutical companies with the secondary care representative's father attending and representatives failing to register his attendance due to compliance issues.

The complainant stated that the facts were that on these two occasions the AstraZeneca secondary care representative had brought his/her father to the meetings and it was wholly inappropriate for a practice manager who was not medically trained to recommend pharmaceutical products to other health professionals. The complainant stated that there was no section on quality outcome framework (QOF) or administration so he/she queried what practice managers would have achieved from the session.

In the complainant's view it was bizarre that the speaker at the meeting referred to AstraZeneca's product Onglyza (saxagliptin) as 'sexygliptin' to get customers to remember the medicine.

The complainant understood that now that the secondary care representative had advanced in his/her career he/she did not need to pay for these meetings but considered it was acceptable to bring his/her father as there was no trail leading to his/her father attending these meetings.

The complainant stated that with no manager present it would be a case of his/her report against that of the company, however, AstraZeneca needed to demonstrate that the representative's father did not attend. However, if no ruling was made to discipline the secondary care representative for breaching the Code in any capacity, the complainant stated that he/she would complain about every meeting that he attended. The only way the PMCPA might get any truth was to call the customers directly.

When writing to AstraZeneca the Authority asked it to consider the requirements of Clauses 11.1, 22.1, 9.1, 15.2 and 2 of the Code.

RESPONSE

AstraZeneca stated that it took its obligations under the Code seriously and had conducted an investigation to address the points raised.

The two meetings referred to by the complainant were promotional events for Forxiga (dapagliflozin). A primary care representative organised and invited delegates to these meetings. A secondary care representative, attended both meetings. Both representative's reported to the same manager: while one was more senior he/she did not have authority to direct the others work. The representatives' both stated during interviews that they were professional colleagues and did not socialise outside work.

As part of his/her activities as a representative, the primary care representative invited health professionals, from a practice on the local prioritised list, to attend both meetings referred to by the complainant. The secondary care representative's mother was invited in her capacity as a health professional (healthcare assistant and practice manager). The secondary care representative's name appeared on attendee lists for both meetings. The primary care representative knew the health professional was the secondary care representative's mother.

The secondary care representative's father, was a retired GP who most recently worked at the practice on the local prioritised list. He no longer practised or was GMC registered. As part of its investigation AstraZeneca reviewed its customer relationship management (CRM) records and conducted interviews to ascertain whether the secondary care representative father attended either of the meetings; his name did not appear on attendee lists for either. During interviews, the representatives and the health professional each stated that he had not attended either meeting as a delegate and did not consume any subsistence provided. With respect to the 2015 meeting, neither the secondary care representative or his/her father remembered whether he drove his wife to or from the meeting, or whether he entered the restaurant to drop her off or pick her up. With respect to the 2016 meeting, both the secondary care representative and his/her father stated during interviews that he dropped off and collected his wife, from the meeting venue; he arrived early to collect his wife and waited for her at the meeting venue. The secondary care representative's father also

stated that he spoke with several meeting attendees who were former colleagues before departing with his wife. An attendee at the 2016 meeting, further confirmed that the secondary care representative's father arrived to collect his wife and stopped to speak with former colleagues who had attended the meeting. Other attendees interviewed did not know the secondary care representative's father and could not comment on his attendance. AstraZeneca concluded that the secondary care representative's father had no meaningful contact or interaction with the meetings nor could he rightfully be described as an attendee at either.

AstraZeneca submitted that, to the best of its knowledge, the secondary care representative's father did not attend either meeting. Breaches could not therefore have arisen in relation to his attendance. The secondary care representative's mother's attendance and consumption of subsistence at these meetings was appropriate. AstraZeneca's representatives maintained high standards in this regard. Furthermore, high standards were maintained more generally. No events took place which could be considered to have brought the industry into disrepute. AstraZeneca therefore denied breaches of Clauses 11.1, 22.1, 15.2, 9.1 and 2.

On a separate point, while neither the 2015 nor the 2016 slide deck referred to saxagliptin, AstraZeneca understood that the medicine was mentioned by a speaker at the 2016 meeting. The speaker reported in an interview that he referred to 'saxagliptin' in an attempt at humour. Notably, the speaker was briefed regarding his obligations as a speaker in advance of the meeting. The Fee for Service Contract signed by the speaker in relation to this meeting stated that 'You will perform the Services diligently and conscientiously using your best efforts with the highest professional standards and in compliance with all applicable laws, regulations and codes of practice relevant to the pharmaceutical industry'. This document also stated that 'I have been adequately briefed by AstraZeneca and read and understood the 'Guidelines for External Speakers'. His document included wording that statements must 'not cause offence either through the use of imagery or humour unbecoming the professional standing of the audience'. It would appear that the speaker did not fulfil these requirements. AstraZeneca would suspend work with the speaker until he had been thoroughly re-briefed as to requirements for speaking at AstraZeneca meetings.

To prevent recurrence AstraZeneca submitted that it would complete the following actions by 31 December 2016:

- Ensure that all future meeting invitations were specific regarding intended recipients
- Review all briefing documents accompanying currently approved promotional slide decks to ensure specific appropriate audiences were identified
- Retrain originators and signatories on the importance of detailing the specific intended audience in briefing documents accompanying promotional slide decks

- Brief representatives as to the importance of only allowing specified groups of attendees to be present at promotional meetings and of the need to vigilantly monitor the conduct of meetings and intervene should inappropriate language be used.

PANEL RULING

The Panel noted that there were differences between the parties' accounts, it was extremely difficult in such cases to know exactly what had transpired. The complainant bore the burden of proof on the balance of probabilities. A judgement had to be made based on the available evidence.

The complaint concerned the attendance of the secondary care representative's parents at two Forxiga promotional meetings organised by the local primary care representative and held in November 2015 and November 2016.

The complainant alleged that the father of the secondary care representative, had stayed for the duration of each meeting and consumed subsistence. The Panel noted that the secondary care representative's father was a retired GP who no longer practised or held GMC registration. According to AstraZeneca he did not attend either meeting as a delegate nor did he consume any subsistence provided. With respect to the meeting held in November 2015, neither the representatives nor he could recall whether he drove his wife to, or collected her from, the meeting and whether he entered the meeting venue. In relation to the meeting held in November 2016 both the secondary care representative and his/her father confirmed that he had both dropped off and collected his wife from the meeting. On collecting his wife he had arrived early and waited in the venue where he spoke to former colleagues before departing. A meeting attendee had confirmed the accounts of the secondary representative and his/her father. The Panel noted that the secondary care representative's father was no longer practising or GMC registered and thus would be classified as a member of the public for the purposes of the Code. However, the Panel did not consider it unreasonable, in the circumstances, for him to merely greet former colleagues outside of the meeting's formal agenda and subsistence. There was no evidence that anything more than that had occurred. The Panel noted that the complainant bore the burden of proof and considered that there was no evidence that the secondary care representative's father had attended either meeting as a delegate or received subsistence as alleged. No breach of Clause 22.1 was ruled. In addition, there was no evidence that either of the representatives or the company had failed to maintain a high ethical standard. No breach of Clauses 9.1 and 15.2 was ruled.

The Panel noted that the secondary care representative's mother, attended both meetings in her role as a practice manager and a healthcare assistant. The Panel noted that the role of healthcare assistants in general practice varied but might include health promotion, blood pressure management and venepuncture; they were not registered with a

professional body. The Panel had no information about the precise nature of the secondary care representative's mother's duties but noted that they would depend on the contractual relationship between her and the practice. The complainant had alleged that the secondary care representative's mother recommended medicines including diabetes products. AstraZeneca had not provided any detail about the secondary care representative's mother's professional responsibilities. Nonetheless, the Panel noted that dependent on the details of her role she could be a health professional and/or a relevant decision maker. The Panel noted the educational content of the meetings. The Panel also noted that the complainant bore the burden of proof. The Panel did not consider that there was any evidence before it to indicate that it was inappropriate for the secondary care representative's mother to attend either of the meetings as a delegate as alleged. No breach of Clause 11.1 was ruled. There was no evidence that either of the representatives or the company had failed to maintain high standards; no breach of Clauses 9.1 and 15.2 was ruled.

The Panel noted that the speaker had spoken at the November 2016 meeting; contrary to AstraZeneca's submission, at least one slide referred to saxagliptin. The speaker advised AstraZeneca that he had instead referred to 'sexygliptin' in an attempt at humour. The Panel noted that the speaker had been briefed regarding his obligations as a speaker in advance of the meeting. The Panel noted that the fee for service contract signed by the speaker stated that he had read and understood the Guidelines for External Speakers which stated, *inter alia*, that statements 'must not cause offence either through the use of imagery or humour unbecoming the professional standing of the audience'. The Panel also noted AstraZeneca's admission that it would appear that the speaker did not fulfil these requirements. The Panel considered that in this regard high standards had not been maintained; a breach of Clause 9.1 was ruled.

Complaint received **14 November 2016**

Case completed **10 February 2017**

NURSE v NAPP

Promoting a switch to Remsima

A hospital specialist nurse complained about a Remsima (infliximab) email from Napp Pharmaceuticals Limited. The subject of the email appeared in the email inbox as 'Why switch from Remicade to Remsima?' and was about switching from Remicade (infliximab, the originator product marketed by Merck Sharp & Dohme) to the biosimilar Remsima marketed by Napp. The body of the email, headed 'Don't get left behind – make the switch', informed the reader that 'Your colleagues from across the UK are switching from Remicade to Remsima and re-investing their savings to improve patient care' and that compared to Remicade, Remsima could offer highly similar clinical outcomes and that it was 'no different to what you're already used to with Remicade'. Remsima was indicated for, *inter alia*, rheumatoid arthritis (RA), Crohn's Disease and ulcerative colitis.

The complainant stated that he/she used this biosimilar; the hospital was considering a full scale switch but needed processes in place to ensure the safety and needs of its patients.

The complainant considered that Napp was pushing a switch with no consideration to patients' needs. Not all centres that had switched had been able to re-invest any cost savings into their services; the claim in this regard was wrong.

The complainant stated that the indications for use of this biosimilar and its efficacy should not be presented in the same advertisement to switch patients. In particular the complainant did not like the slogan 'Don't get left behind – make the switch'.

The detailed response from Napp is given below.

The Panel noted the complainant's concern that the email encouraged health professionals to switch from Remicade to Remsima with no consideration of patients' needs. In that regard the Panel further noted that readers could access four relevant case studies; each detailed, *inter alia*, stakeholder or clinical support, outcomes and benefits. Key learnings and advice included 'Before initiating the switch to an infliximab biosimilar, it is important to understand the safety, efficacy and economic arguments', 'Don't rush the switch process itself – give yourself time to resolve any technical issues and ensure that patient concerns have been addressed' and 'Engagement with all key-stakeholders is essential'. It seemed clear from the case studies that switches from Remicade to Remsima had taken place with due consideration of the patients' needs; in all cases the proposed switch was discussed with patients before their therapy was changed. The Panel considered that in referring to patients' needs and presenting a considered approach to switching, the email had encouraged the rational use of Remsima and in

that regard it ruled no breach of the Code. In the Panel's view, the material was sufficiently complete to allow recipients to form their own opinion of the therapeutic value of Remsima. No breach of the Code was ruled.

The Panel considered that, contrary to Napp's submission, the unequivocal claim that 'Your colleagues from across the UK are switching from Remicade to Remsima and re-investing their savings to improve patient care' implied that every organisation that switched had savings to reinvest. The Panel further noted that in support of that claim, readers were provided with a link to the four case studies discussed above all of which were based in England. Given the small number of case studies offered and their limited geographical spread, the Panel considered that the claim was unequivocal and exaggerated and thereby misleading. A breach of the Code was ruled. The Panel considered that such a broad claim could not be substantiated; a breach of the Code was ruled.

In the Panel's view, the complainant's submission that the indications for Remsima and its efficacy should not be presented in an advertisement which promoted switching from Remicade appeared to run counter to his/her concern that the email encouraged health professionals to switch to Remsima with no consideration of patients' needs. The Panel did not consider that in referring to the clinical aspect of Remsima, the email was misleading or that claims could not be substantiated. No breaches of the Code were ruled. The Panel noted its ruling of no breach of the Code above in that it considered that the email had encouraged the rational use of Remsima.

The email was headed with the emboldened phrase, 'Don't get left behind – make the switch' which in the Panel's view, implied that if the reader did not switch patients from Remicade to Remsima, they and their clinical practice were in some ways outdated. The Panel considered that the phrase did not recognise the professional standing of the audience and their ability to make their own decisions and was likely to cause offence. A breach of the Code was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of the Code was ruled.

A hospital gastroenterology specialist nurse complained about a Remsima (infliximab) email (Ref UK/REM-16038) from Napp Pharmaceuticals Limited. The subject of the email appeared in the email inbox as 'Why switch from Remicade to Remsima?' and was about switching from Remicade (infliximab, the originator product marketed by Merck Sharp & Dohme) to the biosimilar Remsima marketed by

Napp. The body of the email was headed 'Don't get left behind – make the switch'. The email stated that Remsima was infliximab, as 'proven by rigorous comparability testing vs Remicade (infliximab)' and informed the reader that 'Your colleagues from across the UK are switching from Remicade to Remsima and re-investing their savings to improve patient care'. The email stated that compared to Remicade, Remsima could offer highly similar clinical outcomes and that it was 'no different to what you're already used to with Remicade'.

Remsima was indicated for, *inter alia*, rheumatoid arthritis, Crohn's Disease and ulcerative colitis.

COMPLAINT

The complainant stated that he/she used this biosimilar but as yet had not switched for a number of reasons. The hospital was considering a full scale switch but needed processes in place to ensure the safety and needs of its patients.

The complainant did not like the content of the email and considered that Napp was pushing a switch with no consideration to patients' needs. Not all centres that had switched had been able to re-invest any cost savings into their services; the claim in this regard was wrong.

The complainant stated that the indications for use of this biosimilar and its efficacy should not be presented in the same advertisement to switch patients. In particular the complainant did not like the slogan 'Don't get left behind – make the switch'.

When writing to Napp the Authority asked it to respond in relation to Clauses 7.2, 7.4, 7.10, 9.1 and 9.2 of the Code.

RESPONSE

Napp stated that the email promoted switching from originator infliximab (Remicade) to biosimilar infliximab (Remsima) and focussed on the potential significant cost savings such a switch could provide and how these could be re-invested in service improvements. The email was sent to an identified list of 4,475 health professionals on 14 November 2016 who were appropriate to receive the information because they managed patients for whom infliximab was licensed and they had opted to receive promotional emails. It was sent to rheumatologists, rheumatology specialist nurses, gastroenterologists, gastroenterology specialist nurses and hospital pharmacists.

Napp identified four key points to the complaint:

- 1 Napp had pushed a switch with no consideration to patient needs
- 2 Napp had claimed that all UK centres were able to re-invest savings made by switching to services and the complainant considered that this was incorrect
- 3 That efficacy and therapeutic indications of a medicine should not be included in an advertisement which promoted a switch

- 4 The complainant disliked in particular the slogan 'Don't get left behind – make the switch'.

Napp strongly refuted the complaint and submitted that the Remsima email was not misleading, was capable of substantiation, promoted rational use of the medicine, did not cause offence and therefore did not breach Clauses 7.2, 7.4, 7.10 or 9.2.

Background

Napp explained that in the past 20 years biological medicines had brought significant therapeutic benefit to many patients but they accounted for a significant proportion of the annual NHS drug budget spend. For example, NHS expenditure on anti-TNF biological medicines in 2015 was £1.011 billion. Biosimilar medicines were being developed in line with rigorous EU requirements to provide therapeutic alternatives to their respective reference products at significantly reduced cost without jeopardising patient safety. NHS England defined a biosimilar medicine as:

'...a biological medicine which is highly similar to another biological medicine already licensed for use. It is a biological medicine which has been shown not to have any clinically meaningful differences from the originator biological medicine in terms of quality, safety and efficacy.'

CT-P13 (Remsima or Inflectra) was the world's first biosimilar monoclonal antibody, and was granted a licence in Europe in 2013 for the same clinical indications as the originator, Remicade.

Napp submitted that switching from originator to biosimilar infliximab was both rational and responsible. Increasing clinical evidence confirmed that switching from the originator to CT-P13 was clinically safe and effective, a view supported by key authoritative professional bodies within the UK. For example, the British Society for Gastroenterology published guidance in March 2016 confirming that 'There is sufficient data from observational studies to show that safety and clinical efficacy of CT-P13 are comparable to the originator drug, with similar immunogenicity, and that switching from Remicade to CT-P13 was also safe and effective'. The recent Royal College of Physicians audit of biological therapies for inflammatory bowel disease stated 'all new starters should commence treatment on infliximab biosimilars. Consideration should be given whether to switch those patients currently established on Remicade to infliximab biosimilars'.

Furthermore, the issue of switching to biosimilar infliximab was addressed by the National Institute for Health and Care Excellence (NICE) in 'Introducing biosimilar versions of infliximab: Inflectra and Remsima' which concluded that this was a rational and responsible course of action.

In light of the above, Napp submitted that the focus of the email was designed to:

- Share the experiences of UK clinical centres which had switched to biosimilar infliximab

- Highlight the potential cost savings that switching to Remsima could provide should health professionals choose to switch and how these could be re-invested in services, focusing particularly on those in their own departments eg more specialist nurses
- Provide the clinical comparison between Remicade and Remsima, including efficacy, safety and administration.

The Code did not prohibit companies from promoting a simple switch from one medicine to another. Indeed, in Case AUTH/2795/9/15 about a Remsima switch leavepiece, the PMCPA stated 'it is not unacceptable under the Code for a company to promote a simple switch from one product to another; companies could not, however, assist a health professional in implementing a switch'. Napp was not found in breach of the Code.

Point 1

Napp disagreed that the email promoted a switch with no consideration for patient needs. The email presented comprehensive information, references and resources to health professionals, to potentially help the switch process in their centres, and the patient was considered in all of these. Firstly, health professionals were directed to four case studies on the Remsima website via a link highlighted in the email. Each clinical case study shared the experience of switching in different centres across the UK and was structured into five parts: i) stakeholder support; ii) gain-share; iii) the change process; iv) outcomes and benefits and v) key learnings and advice. In section iii (change process) of each case study, there was a focus on how the clinical centres involved had informed the patient about the switch process, including examples of how this was managed. The outcomes and benefits section (iv) also discussed how many patients were switched and if any adverse events occurred. Finally, the key learnings and advice section (v) included a comment recognising the importance of the patient in the process.

The email also provided health professionals with the relevant clinical evidence comparing Remsima with Remicade. Specific reference was made to the fact that the biosimilar Remsima had highly similar clinical outcomes in terms of efficacy, safety, quality and immunogenicity. These claims were fair, balanced, accurate and substantiated by references to the European Public Assessment Report (EPAR) and the pivotal clinical trials (PLANETAS (Park *et al* 2013) and PLANETRA (Yoo *et al* 2013)).

A highlighted link in the email directed the health professional to the resources page on the Remsima website via which he/she could download or request resources to support patients as part of the switch process. In particular the health professional could request patient support packs specific to each of the diseases for which Remsima was licensed. Napp thus refuted that it had promoted a switch to Remsima without regard to patients' needs, and the decision to switch to Remsima remained firmly in the hands of the health professional. Napp submitted that the email promoted the rational use of Remsima and it thus denied breaches of Clauses 7.2, 7.4 and 7.10.

Point 2

Napp submitted that the statement 'Your colleagues from across the UK are switching from Remicade to Remsima and re-investing their savings to improve patient care' did not state or infer that all colleagues who had switched to Remsima from Remicade had been able to re-invest savings in their departments. Instead Napp's intent was to share the experiences from four centres which had achieved gain-share agreements to the benefit of their clinical service such that other centres could learn from them and hopefully implement some of the learnings in their own centres should they decide to switch. The statement was immediately followed by a link to the case studies on the Remsima website.

Napp did not agree that the statement was misleading. It did not claim that all colleagues were switching nor that all were re-investing in patient care. Napp denied a breach of Clause 7.2. The statement could also be substantiated by the experiences provided in the four case studies. Napp thus refuted a breach of Clause 7.4.

Point 3

Napp disagreed with the complainant that therapeutic indications and efficacy data should not be included in an email which promoted a switch to Remsima. On the contrary, companies must present adequate information on the efficacy including indications and safety of a medicine in order for health professionals to make an informed clinical decision.

As stated previously, companies were permitted under the Code to promote a simple switch from one medicine to another. However, materials which promoted a switch should also provide health professionals with all the information necessary such that they could form their own opinion of the therapeutic benefit of switching with regards to their patients. Napp submitted that the email provided health professionals with the appropriate information to allow them to make an informed decision about switching to Remsima. The email referenced the EPAR to reassure health professionals that 'Remsima is infliximab as proven by rigorous testing vs Remicade'. In addition, health professionals were directed to the pivotal clinical trials comparing Remicade with Remsima in terms of clinical efficacy, safety, quality and immunogenicity (Park *et al* and Yoo *et al*). Napp submitted that it was important to inform readers that Remsima was licensed for the same therapeutic indications as Remicade and had the same dosing, posology and infusion schedule. Taking the above into consideration, health professionals could then determine whether a switch was appropriate for their patients.

Napp submitted that the email promoted the rational use of the medicine and provided health professionals with accurate, balanced, fair information which was fully substantiated and hence did not contravene Clauses 7.2, 7.4 and 7.10.

Point 4

Napp stated that although the complainant had not specified exactly what he/she disliked about the

opening strapline 'Don't get left behind – make the switch', it explained the reasoning and intent behind its use.

It was clear from IMS commercial market share data in March 2016 (when the email was conceived) that there was a large disparity across the UK in the uptake and usage of biosimilar infliximab; it was as high as 82.3% usage of biosimilar infliximab CT-P13 (either Inflectra or Remsima) in some regions and as little as 3.2% in others. The email, with the subject title of 'Why switch from Remicade to Remsima' was meant to help address some of the reasons why a switch to Remsima had not occurred in some areas of the UK despite clinical and regulatory bodies considering switching to CT-P13 a rational use of the medicine.

Napp was aware that switching to a biosimilar and involvement in gain-share negotiations was new for many health professionals. The aim of the email was to:

- reassure that switching patients from Remicade to Remsima was a rational use of the medicine
- highlight the potential substantial cost savings to the NHS and how some of these savings could be re-invested in their services and finally
- provide health professionals with tools and information to help them understand the switch should they choose to do so.

The bold opening strapline 'Don't get left behind – make the switch' was used to draw the attention of readers to start to think about three things:

- 1 How to switch patients from Remicade to Remsima without jeopardising patient safety
- 2 Cost savings that switching to Remsima could generate
- 3 How the savings could be re-invested in patient services.

The strapline was a call to action for health professionals to consider the facts if it was right for them and their patients to make the switch, and Napp provided the literature resources for them to make an informed decision. Indeed, the strapline was in bold letters and in larger font than the rest of the text to gain the health professionals' attention, but never to offend. Napp's experience was that those units where clinicians/nurses/pharmacists were involved and took a lead in gain-share negotiations were more likely to see some of the savings re-invested in their departments rather than simply decreasing budget deficits within the NHS trust.

The strapline was immediately followed by evidence that many colleagues across the UK were switching. The statements 'Biosimilar infliximab volume market share in the South West of England was 82.3% for the month of March 2016' and 'Your colleagues from across the UK are switching from Remicade to Remsima and re-investing their savings to improve patient care', with a link to the four case studies described previously, were intended to re-assure readers that other centres in the UK were switching, that switching did not jeopardise clinical efficacy

or patient safety and to give examples of how they implemented the switch.

As well as reading about the experiences of other centres, health professionals were provided with a link to the Remsima cost calculator to begin to realise what cost savings they could potentially achieve if they switched. The cost calculator allowed them to enter their own hospital data and their own vial acquisition prices (these would vary from hospital to hospital depending on local tenders) to simply calculate how much money their departments could potentially save from switching from Remicade to biosimilar Remsima. The calculator then gave an example of how this money might be re-invested in patient care by highlighting how many band 6 nurse salaries it could potentially fund.

As noted above, the email provided health professionals with the appropriate information to allow them to make a clinically informed decision about switching to Remsima. The email referenced the EPAR to reassure health professionals that 'Remsima is infliximab as proven by rigorous testing vs Remicade'.

In summary, the email provided appropriate clinical and financial information upon which health professionals could base a decision on whether to switch their patients to Remsima. The strapline was to gain attention and stimulate the health professionals' thinking and not to offend. It then went on to provide information and resources for clarity which would help health professionals make informed clinical decisions. Napp strongly believed the information provided was fair, balanced and accurate, capable of substantiation and promoted the rational use of Remsima and hence did not breach Clauses 7.2, 7.4 or 7.10. It also refuted that the email content, and in particular the strapline, caused offence and hence did not breach Clause 9.2.

Furthermore, Napp believed high standards had been maintained at all times by careful consideration of how to promote switching without jeopardising patient's safety or causing offence and hence it also refuted a breach of Clause 9.1.

PANEL RULING

Point 1 The Panel noted the complainant's concern that the email encouraged health professionals to switch from Remicade to Remsima with no consideration of patients' needs. In that regard the Panel further noted that readers could access four case studies about the switching of patients from Remicade to Remsima. Each of those case studies detailed, *inter alia*, stakeholder or clinical support, outcomes and benefits and key learnings and advice. Some of the key learnings and advice included 'Before initiating the switch to an infliximab biosimilar, it is important to understand the safety, efficacy and economic arguments', 'Don't rush the switch process itself – give yourself time to resolve any technical issues and ensure that patient concerns have been addressed' and 'Engagement with all key- stakeholders is essential'. It seemed clear from the case studies that switches from Remicade to Remsima had taken place with due

consideration of the patients' needs; in all cases the proposed switch was discussed with patients before their therapy was changed. The Panel considered that in referring to patients' needs and presenting a considered approach to switching, the email had encouraged the rational use of Remsima and in that regard it ruled no breach of Clause 7.10. In the Panel's view, the material was sufficiently complete to allow recipients to form their own opinion of the therapeutic value of Remsima. No breach of Clause 7.2 was ruled. The Panel did not consider that Clause 7.4 was relevant within the context of this matter and so it made no ruling in that regard.

Point 2 The Panel considered that, contrary to Napp's submission, the unequivocal claim that 'Your colleagues from across the UK are switching from Remicade to Remsima and re-investing their savings to improve patient care' implied that every organisation that switched had savings to reinvest. The Panel further noted that in support of that claim, readers were provided with a link to the four case studies discussed above at Point 1. None of those case studies, however, were based in Scotland, Wales or Northern Ireland. Given the small number of case studies offered and their limited geographical spread (England only), the Panel considered that the claim was unequivocal and exaggerated and thereby misleading. A breach of Clause 7.2 was ruled. The Panel considered that such a broad claim could not be substantiated; a breach of Clause 7.4 was ruled.

Point 3 The Panel noted that the supplementary information to Clause 19.1 stated that it was

acceptable for companies to promote a simple switch from one product to another. In the Panel's view, the complainant's submission that the indications for Remsima and its efficacy should not be presented in an advertisement which promoted switching from Remicade appeared to run counter to his/her concern that the email encouraged health professionals to switch to Remsima with no consideration of patients' needs. The Panel did not consider that in referring to the clinical aspect of Remsima, the email was misleading or that claims could not be substantiated. No breach of Clauses 7.2 and 7.4 were ruled. The Panel noted its ruling of no breach of Clause 7.10 above in that it considered that the email had encouraged the rational use of Remsima.

Point 4 The Panel noted that the email was headed with the phrase, in emboldened text, 'Don't get left behind – make the switch'. In the Panel's view, the heading implied that if the reader did not switch patients from Remicade to Remsima, they and their clinical practice were in some ways out-dated. The Panel considered that the phrase did not recognise the professional standing of the audience and their ability to make their own decisions and was likely to cause offence. A breach of Clause 9.2 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

Complaint received **17 November 2016**

Case completed **1 March 2017**

EX-EMPLOYEE v ASTRAZENECA

Websites

An ex-employee of AstraZeneca UK, complained about a number of AstraZeneca's websites.

The detailed response from AstraZeneca is given below.

With regard to a Brilique (ticagrelor) website, the complainant stated that choosing the option of being a health professional led to a website that did not have the prescribing information available. The link at the base of the page was only to the patient information leaflet.

The Brilique.co.uk website was aimed at patients who had already been prescribed Brilique. The Panel noted that when accessing the website the user was presented with a screen and asked to choose from a number of options in order to be directed to the appropriate page. The Panel noted that the first page of the site following confirmation of the reader as a health professional referred to the licensed indication of Brilique. In the Panel's view, health professionals directed to view the webpage should, from the same webpage, have access to the prescribing information. The Panel noted AstraZeneca's submission that the link to the Brilique prescribing information which appeared at the bottom of the webpage did not work and the patient information leaflet was provided instead. A breach of the Code was ruled. The Panel noted that although the link did not work there was a clear statement as to where the prescribing information should be found. The Panel therefore ruled no breach of the Code.

The complainant referred to AstraZeneca's simply4doctors website which encompassed many different products in different therapy areas. Given the number of concerns, the complainant addressed this website section by section.

In the cardiovascular section the complainant referred to a table of data comparing rosuvastatin (Crestor) with simvastatin and atorvastatin. The table was headed 'Unlike some statins, Crestor (rosuvastatin) has a low potential for interactions mediated via the cytochrome P450 3A4 pathway'. The complainant alleged that as pravastatin and fluvastatin were not included, the table was not a balanced comparison of statins in the UK. Pravastatin and fluvastatin were also omitted from another page headed 'Predicting statin related muscle ache'.

The complainant further noted that the page headed 'HCP [healthcare professional] information' had a link to a slide set entitled 'Acute Coronary Syndrome Disease [ACSD] & Diagnosis' which was dangerously misleading. This was probably because the slides had not been reviewed since being signed off in 2014. If the guidance was to be followed,

patients would cease treatment after 12 months when current evidence now displayed benefit to 3 years. The front of the document did not state where the prescribing information could be found and the prescribing information was from 2014 and several significant changes had happened since then. This, along with the inaccuracies in the clinical content appeared to indicate that the slides had not been updated.

The muscle symptom checklist, available via a link on the same page, was described as an item for doctors to give to patients which would be a medical or educational good or service, but had prescribing information on the final page which was out-of-date, as above.

The Panel noted AstraZeneca's submission that it had compared Crestor with simvastatin and atorvastatin as they were the most commonly prescribed statins in the UK. Whilst the Panel considered that this was a reasonable basis for selection, the data provided showed that more units of pravastatin were prescribed each month than Crestor.

The Panel noted that Crestor, which was neither an inhibitor nor an inducer of P450 isoenzymes, had been compared with two statins (simvastatin and atorvastatin) which did interact with P450 3A4. Pravastatin, however, was not metabolized to a clinically significant extent by the cytochrome P450 system. If pravastatin had been included in the table of data it would have shown a profile similar to that of Crestor and with less interactions than with either simvastatin or atorvastatin.

Given AstraZeneca's submission about the basis of the selection the Panel considered that it was disingenuous of AstraZeneca to omit pravastatin from the table at issue considering it was more commonly prescribed than Crestor. The Panel considered that the table together with the claim that 'Unlike some statins, Crestor (rosuvastatin) has a low potential for interactions mediated via the cytochrome P450 3A4 pathway' was unbalanced and misleading as alleged and a breach of the Code were ruled.

The Panel noted that Crestor, simvastatin and atorvastatin were also compared in a table on a separate page of the website with regard to the risk of statin related muscle ache beneath the claim 'choice of statin is relevant'. The table included the typical dose range and whether the statin was CYP3A4 metabolised or whether it was fat soluble. The Panel noted the reason for selecting the comparators as above. The Panel further noted that if pravastatin had been included in the table its profile would have been very similar to that of Crestor. The Panel considered that the claim 'Choice of statin is relevant', implied that the three statins listed were

the only ones to consider choosing which was not so; further the omission of pravastatin meant that the table was unbalanced and misleading. The Panel ruled breaches of the Code.

The Panel noted that the Brilique prescribing information included in the ACSD slide set was dated July 2014 and that the Brilique SPC was updated in February 2016 to include the 60mg dose. The Panel noted AstraZeneca's submission that the slide set was specific to the 90mg dose. The Code stated that at least one authorized indication for use had to be given and this had been done. The Panel considered that although the prescribing information in the slide set did not refer to the 60mg dose, prescribers had, nonetheless been provided with the appropriate prescribing information consistent with the content of the slides. No breach of the Code was ruled.

The Panel noted that the slide set was described as a therapy area presentation covering the diagnosis and treatment of ACS. The Panel noted that the first slide had a clear reference to the prescribing and adverse event reporting information and the Panel therefore ruled no breach of the Code.

The Panel noted the complainant's allegation that the slide set was dangerously misleading as it advised that patients should cease treatment after 12 months whereas current guidelines displayed benefit up to three years. The Panel noted that a slide entitled 'NICE Guidance' stated that [Brilique] in combination with low-dose aspirin was recommended for up to 12 months as a treatment option in adults with ACS. The Panel noted that the SPC stated that treatment with Brilique 90mg was recommended for 12 months in ACS patients unless discontinuation was clinically indicated which according to AstraZeneca's submission was referred to in the NICE guidelines which had not been updated since the slide set was certified; these guidelines had not been provided. The Panel noted AstraZeneca's submission that only Brilique 60mg was licensed for use for longer than 12 months and only in a sub-population of patients that was not referred to in the presentation. The Panel did not consider that the complainant had provided evidence to support his/her allegation that the slide set was misleading with regard to the recommended duration of treatment with Brilique and the Panel ruled no breach of the Code.

The Panel noted that the slides were reviewed and approved by AstraZeneca on 6 January 2015 which meant that as long as the content remained up-to-date, the slides did not need to be recertified until 5 January 2017. The Panel noted that the complaint was received in November 2016 and thus it ruled no breach of the Code.

The Panel noted its rulings above with regard to the slide set and did not consider that AstraZeneca had failed to maintain high standards. No breach of the Code was ruled.

The Panel noted the complainant's allegation that the Crestor prescribing information on the muscle

symptom checklist was out-of-date. The Panel noted AstraZeneca's submission that the prescribing information dated March 2015 was up-to-date as the last SPC change to Section 5.2 on 21 February 2016 did not affect it. The Panel ruled no breach of the Code.

The Panel noted the complainant's allegation that he/she could not access the Brilique prescribing information via the links provided on the support resources for health professional's webpage of the website. In the Panel's view, this part of the website was promotional and the prescribing information should have been provided by way of a clear and prominent, direct, single click link. The Panel noted AstraZeneca's submission that the link to the prescribing information which appeared on the webpage did not work. The Panel therefore ruled a breach of the Code.

The Panel noted that although the link did not work, it was clear as to where the prescribing information should be found. The Panel therefore ruled no breach of the Code.

The complainant noted that 'Focus' magazines available to download from the respiratory section of the simply4doctors website were intended to help nurses support treatment of patients and were separate, self-contained items. The complainant listed a number of concerns.

The Panel noted that the complainant was concerned that the Focus magazines were available to download from a promotional site and no prescribing information was provided and company specific items mentioned in certain issues were unfair and unbalanced. The complainant further alleged that the magazines dated back to 2012 and was concerned that they had not been appropriately recertified.

The Panel disagreed with AstraZeneca's submission that the magazines were non-promotional, given that they were provided to the sales force to distribute to health professionals; they mentioned AstraZeneca products and contained links to demonstrate the use of AstraZeneca inhalers which took the user to pages on the website where prescribing information was available. The magazines also directed readers to the promotional website if they had any queries on AstraZeneca products. In the Panel's view each copy of the magazine, where reference was made to an AstraZeneca medicine or device, had to stand alone as promotional material.

The Panel noted that Issue 9 (Winter 2015/2016) of the Focus magazine referred to Turbohaler and Genuair and in that regard AstraZeneca had submitted that links were provided to the Symbicort/Genuair promotional pages on the website where prescribing information was available. AstraZeneca provided a number of medicines in a Turbohaler – a device specific to the company. Noting its comments above, the Panel considered that prescribing information for at least one medicine to be used with the Turbohaler and for Genuair should have been included in the Winter 2015/2016 issue of the Focus magazine and a breach of the Code was ruled.

The Panel noted that the Code required that promotional material on the Internet must contain a clear prominent statement as to where the prescribing information could be found. The Panel noted that the Winter 2015/2016 Focus magazine did not include such a statement. The Panel therefore ruled a breach of the Code.

The Panel noted that the complainant had referred to company specific items in some of the magazines which failed to be fair and balanced. The complainant had not provided any evidence to support why the items he/she referred to were not fair or balanced. The Panel therefore ruled no breach of the Code.

The Panel noted AstraZeneca's submission that issues of the Focus magazine remained on the website indefinitely and were recertified within two years of their previous date of certification. The Panel noted AstraZeneca's submission that the signatories had signed in accordance with the Approval of Materials/Activities for Certification or Examination SOP which clearly stated that they 'confirm in their belief that the item is in accordance with the relevant advertising regulations and the ABPI Code of Practice, consistent with the marketing authorisation, the [SPC] and is a fair and truthful representation of the facts about the medicine', although the certificates themselves did not state this but merely included an approval date.

The Panel ruled no breaches of the Code in relation to Issues 3 and 4 of Focus magazine as they had been re-approved within two years.

The Panel noted the complainant's concern that the talking type 2 website was prepared in October 2014 and needed to be reviewed to ensure it had been recertified. The Panel noted AstraZeneca's submission that different sections of different websites were prepared and certified at different times; the earliest date of preparation being October 2014 for the above website. The earliest date of certification was however 14 January 2015. Thus no part of the website required recertification when it was taken down on 17 November 2016. The Panel therefore ruled no breach of the Code.

Overall, the complainant concluded that the number of errors and omissions, some of which could impact on patient safety, hardly gave health professionals confidence in the industry. However, the complainant stated it was not his/her place to judge, merely to raise concerns to the PMCPA.

The Panel noted its rulings above and considered that AstraZeneca had failed to maintain high standards with regard to the misleading statin comparison and the lack of prescribing information being provided when required in the Focus magazines. A breach of the Code was ruled. 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. No breach of Clause 2 was ruled.

The complainant, an ex-employee of AstraZeneca UK Limited, complained about a number of the company's websites. The case preparation manager printed the website pages referred to by the complainant and provided them to AstraZeneca.

A Brilique website

Brilique (ticagrelor), co-administered with acetylsalicylic acid, was indicated for the prevention of artherothrombotic events in at risk adults.

COMPLAINT

The complainant stated that choosing the option of being a health professional led to a website that did not have the prescribing information available. Clicking on the link at the base of the page only linked to a page with the patient information leaflet.

In writing to AstraZeneca, attention was drawn to the requirements of Clauses 4.1 and 4.6 of the Code.

RESPONSE

AstraZeneca submitted that the website was clearly designed for patients. To access the website, users had to declare whether they were a 'Patient Prescribed Brilique' or a 'Health Care Professional'. The website did not contain any promotional material for health professionals so if users clicked that they were a 'Health Care Professional' the only difference on the site was the offer of prescribing information both at the bottom of the screen and in a banner. That link however, did not work and instead the patient information leaflet was offered. AstraZeneca apologised for the confusion and had taken the website down until the issue could be rectified.

As the absence of promotional material did not therefore require the inclusion of a link to the prescribing information, AstraZeneca submitted that there was no breach of Clauses 4.1 or 4.6.

In response to a request for further information AstraZeneca provided a copy of the current Brilique summary of product characteristics (SPC).

PANEL RULING

The Panel noted AstraZeneca's submission that the Brilique website was aimed at patients who had already been prescribed it; in that regard prescribing information was not required. The Panel noted, however, that this was not the subject of the complaint. The Panel noted that when accessing the website the user was presented with a number of options in order to be directed to the appropriate page. The Panel noted that the first page of the site following confirmation of the identity of the reader as a UK health professional referred to the licensed indication of Brilique. The Panel noted that it had not been provided with a copy of the material provided on the rest of the website. In the Panel's view, health professionals directed to view this webpage should, from the same webpage, have access to the prescribing information. The Panel noted AstraZeneca's submission that the link to

the prescribing information which appeared at the bottom of the webpage did not work and the patient information leaflet was provided instead. The Panel therefore ruled a breach of Clause 4.1.

The Panel noted that Clause 4.6 required that promotional material on the Internet must contain a clear prominent statement as to where the prescribing information could be found. The Panel did not agree with AstraZeneca's submission that the webpage did not require the inclusion of a link to the prescribing information due to the absence of promotional material and noted its comments and ruling above in this regard. The Panel noted that although the link did not work as noted above, there was a clear statement as to where the prescribing information should be found. The Panel therefore ruled no breach of Clause 4.6.

B Simply4doctors website

The complainant stated that this was a rather large website encompassing many different products in different therapy areas. It appeared evident that different sections and pieces had been signed off at different times, possibly by different people. Given the number of concerns, the complainant addressed this website section by section.

1 Cardiovascular

COMPLAINT

The complainant referred to a table of data comparing rosuvastatin (Crestor, marketed by AstraZeneca) with simvastatin and atorvastatin. The table was headed 'Unlike some statins, Crestor (rosuvastatin) has a low potential for interactions mediated via the cytochrome P450 3A4 pathway'. The complainant alleged that as pravastatin and fluvastatin were not included, the table was not a balanced comparison of statin options in the UK. Pravastatin and fluvastatin were also omitted from another page headed 'Predicting statin related muscle ache'.

The complainant further noted that the page headed 'HCP [healthcare professional] information' had a link to a slide set entitled 'Acute Coronary Syndrome Disease [ACSD] & Diagnosis' which was dangerously misleading. This was probably because the slides had not been reviewed since being signed off in 2014. If the guidance was to be followed, patients would cease treatment before what was indicated by the current guidelines – discontinuing after 12 months when current evidence now displayed benefit to 3 years.

The front of the document did not state where the prescribing information could be found and the prescribing information was from 2014 when several significant changes had been undertaken in the [interceding] 2 years. This, along with the inaccuracies in the clinical content appeared to indicate that the slides had not been updated.

The muscle symptom checklist, also available via a link on the same page, was described as an item

for doctors to give to patients which would be a medical or educational good or service (MEGS), but had prescribing information on the final page. Most concerning of all was that this prescribing information was out-of-date, as above.

The complainant submitted that he/she was unable to review the prescribing information for Brilique as each time a link was provided the file was not found.

In writing to AstraZeneca attention was drawn to the requirements of Clauses 4.1, 4.6, 7.2, 7.3, 9.1, 14.5, 26.1 and 26.2.

RESPONSE

With regard to the comparison of statins, AstraZeneca stated that the website was intended for health professionals only and clear disclaimers were present. The cardiovascular section included a table of three statins (rosuvastatin, simvastatin and atorvastatin). Simvastatin and atorvastatin were chosen as comparators because they were the most commonly prescribed statins in the UK. The associated claim alongside this table stated 'Unlike some statins'. As there was no intent and no impression of a comparison with all available statins but only some statins, AstraZeneca submitted that this was neither a misleading claim nor misleading comparison and therefore there was no breach of Clauses 7.2 or 7.3.

With respect to the table that compared muscle ache, the associated claim alongside this table stated 'Choice of statin is relevant'. AstraZeneca accepted that whilst it was not the intent, some readers might assume that this referred to all available statins. AstraZeneca therefore accepted a breach of Clause 7.2 and 7.3.

AstraZeneca submitted that the presentation 'Acute Coronary Syndrome Disease & Diagnosis' in the health professional section was certified in December 2014 for use on the website from 2015. It was clear on the first slide as to where the prescribing information might be found and the prescribing information was available at the end of the presentation. AstraZeneca thus denied a breach of Clauses 4.1 or 4.6. The promotional slides did not need to be recertified until December 2016, therefore there was no breach of Clause 14.5. In response to a request for further information, including copies of the certificates approving all of the relevant material, AstraZeneca provided a table of the job bags at issue and the accompanying electronic approval forms. The 'Acute Coronary Syndrome Disease & Diagnosis' presentation approval form gave 6 January 2015 as the date reviewed. AstraZeneca stated that the signatories were signing in accordance with the Approval of Materials/Activities for Certification or Examination standard operating procedure (SOP) which clearly stated that they 'confirm in their belief that the item is in accordance with the relevant advertising regulations and the ABPI Code of Practice, consistent with the marketing authorisation, the SPC and is a fair and truthful representation of the facts about the medicine'.

AstraZeneca explained that the Brilique SPC was updated in February 2016 to include the 60mg dose. Other promotional material for Brilique was recalled when the prescribing information was updated but unfortunately this slide set was overlooked. However, the slides did not discuss the use of the 60mg dose and were specifically about the 90mg dose of Brilique. The complainant alleged that the slides were not accurate, in that patients might cease treatment before current timelines indicated. The National Institute for Health and Care Excellence (NICE) guidelines referred to within the slides were still current and had not been updated since this slide set was certified. These guidelines were clear that treatment with ticagrelor 90mg, clopidogrel or prasugrel should only be for 12 months which was consistent with their respective licences. Only ticagrelor 60mg was licensed for use longer than 12 months and this was only in a sub-population of patients, not all of those with acute coronary syndrome (ACS) which the slide set discussed. AstraZeneca thus denied breaches of Clauses 7.2 or 9.1.

AstraZeneca stated that the muscle symptom checklist was prepared in March 2015 and was distributed to health professionals to use with patients. The item clearly stated that: 'This is intended for Healthcare Professionals to give to Patients'. Guidance within the document stated 'The Muscle Symptom Checklist is short, self-explanatory and can be completed by the patient without your input. You could give a copy of the questionnaire when reviewing a patient on a statin to fill out before or during the consultation'. The page containing the checklist was visually separated from the other guidance pages in that its layout was separate, the format was different and the page was clearly headed 'Muscle Symptom Checklist'.

AstraZeneca submitted that it would be clear to a health professional that only a copy of the checklist page should be printed and given to patients.

AstraZeneca stated that the muscle symptom checklist was educational material for patients and the public and was certified as such. As only the tear-off checklists were handed to the patients, the prescribing information was never visible to them. AstraZeneca thus denied a breach of Clauses 26.1 or 26.2. The item might be viewed by health professionals who visited this website. As the checklist might be considered in the context of Crestor, AstraZeneca included prescribing information on the back page. This prescribing information (March 2015) was still accurate and up-to-date as the last SPC change (February 2016) did not affect the prescribing information. Therefore AstraZeneca submitted it was not a breach of Clause 4.1.

In response to a request for further information AstraZeneca stated that an approval for a revised Crestor SPC was granted on 21 February 2016 and the updates related to Section 5.2 Special populations, age and sex.

AstraZeneca stated that the link to Brilique prescribing information, referred to by the

complainant, had been unavailable since February 2016 when it was updated to include the 60mg dose. All of the other prescribing information links on this website were still correct. When the Brilique prescribing information was updated, the relevant SOP was followed and the updated prescribing information loaded into the sharepoint site 'Medical Repository for Marketing'. AstraZeneca was still trying to establish what led to the link being broken. The whole website had been taken down while this issue was resolved.

The Brilique pages had been down since February 2016 to allow them to be revised and updated. Therefore as the site did not contain any promotional material for Brilique, prescribing information did not need to be included. Therefore AstraZeneca submitted that there was no breach of Clauses 4.1 or 4.6.

PANEL RULING

Statin comparison: The Panel noted the complainant's concern that the table comparing AstraZeneca's medicine Crestor with simvastatin and atorvastatin with regard to interactions was not balanced as it omitted pravastatin and fluvastatin. The Panel noted AstraZeneca's submission that simvastatin and atorvastatin were chosen as they were the most commonly prescribed statins in the UK according to the data provided. The Panel considered that a reasonable basis for selection might be the most commonly prescribed statins compared with Crestor. In that regard, however the IMS data provided showed that more units of pravastatin were prescribed each month than Crestor.

The Panel noted that AstraZeneca had compared its product Crestor, which was neither an inhibitor nor an inducer of P450 isoenzymes, with two statins (simvastatin and atorvastatin) which did interact with P450 3A4. Pravastatin, however, was not metabolized to a clinically significant extent by the cytochrome P450 system. If pravastatin had been included in the table of data it would have shown a profile similar to that of Crestor and with less interactions than with either simvastatin or atorvastatin.

Given AstraZeneca's submission about the basis of the selection the Panel considered that it was disingenuous of AstraZeneca to omit pravastatin from the table at issue considering it was more commonly prescribed than Crestor. The Panel considered that the table together with the claim that 'Unlike some statins, Crestor (rosuvastatin) has a low potential for interactions mediated via the cytochrome P450 3A4 pathway' was unbalanced and misleading as alleged and a breach of Clauses 7.2 and 7.3 were ruled.

The Panel noted that Crestor, simvastatin and atorvastatin were also compared in a table on a separate page of the website with regard to the risk of statin related muscle ache beneath the claim 'choice of statin is relevant'. The table included the typical dose range and whether or not the statin was CYP3A4 metabolised or whether it was fat soluble. The Panel noted the reason for selecting

the comparators as above. The Panel further noted that if pravastatin had been included in the table its profile would have been very similar to that of Crestor. The Panel considered that the claim which appeared above the table 'Choice of statin is relevant' implied that the three statins listed were the only statins to consider choosing which was not so; further the omission of pravastatin meant that the table was unbalanced and misleading. The Panel ruled a breach of Clauses 7.2 and 7.3.

ACSD slides: The Panel noted that Clause 4.1 of the Code required the prescribing information listed in Clause 4.2 to be provided in a clear and legible manner. Clause 4.2 stated the prescribing information consisted of, *inter alia*, a succinct statement of the information in the SPC relating to the dosage and method of use relevant to the indications in the advertisement. The Panel noted that the Brilique prescribing information included in the slide presentation was dated July 2014.

The Panel noted AstraZeneca's submission that the Brilique SPC was updated in February 2016 to include the 60mg dose and whilst other promotional material was recalled and updated, the acute coronary syndrome slide set was overlooked. The Panel noted AstraZeneca's submission that the slides were specific to the 90mg dose. The Panel noted that the Brilique SPC stated that for acute coronary syndromes, the topic of the slide set and the prescribing information at issue, Brilique treatment should be initiated with a single 180mg loading dose (two tablets of 90mg) and then continued at 90mg twice daily. Brilique 60mg twice daily was the recommended dose when an extended treatment was required for patients with a history of myocardial infarction of at least one year and a high risk of an atherothrombotic event. The slide detailing relevant NICE guidance did refer to myocardial infarction in relation to clopidogrel and Brilique but not the relevant subset of patients for which Brilique 60mg twice daily was recommended. Clause 4.2 also stated that at least one authorized indication for use had to be given and this had been done. The Panel considered that although the prescribing information in the slide set did not refer to the 60mg dose, prescribers had, nonetheless been provided with the appropriate prescribing information consistent with the content of the slides. No breach of Clause 4.1 was thus ruled.

The Panel noted that Clause 4.6 required promotional material on the internet to contain a clear prominent statement as to where the prescribing information could be found. The Panel noted that the 'Acute Coronary Syndrome Disease & Diagnosis' slide set was available on the support section of AstraZeneca's simply4doctors website. The slide set was described as a therapy area presentation covering the diagnosis and treatment of ACS. The Panel noted that the first slide stated 'Prescribing and Adverse Event reporting information is available at the end of the presentation' and the prescribing information as discussed above was provided at the end of the presentation. The Panel therefore ruled no breach of Clause 4.6.

The Panel noted the complainant's concern that the prescribing information on the final page

of the presentation was from 2014 and had not been updated despite significant changes in the intervening two years, and that that together with the inaccurate clinical content, indicated that the presentation had not been updated. The Panel noted its ruling of no breach regarding the alleged failure to update the prescribing information above.

The Panel noted the complainant's allegation that the slide set was dangerously misleading as it advised that patients should cease treatment after 12 months whereas current guidelines displayed benefit up to three years. The Panel noted that a slide entitled 'NICE Guidance' stated that [Brilique] in combination with low-dose aspirin was recommended for up to 12 months as a treatment option in adults with ACS. The Panel noted that the SPC stated that treatment with Brilique 90mg was recommended for 12 months in ACS patients unless discontinuation was clinically indicated which according to AstraZeneca's submission was referred to in the NICE guidelines which had not been updated since the slide set was certified; these guidelines had not been provided. The Panel noted AstraZeneca's submission that only Brilique 60mg was licensed for use for longer than 12 months and only in a sub-population of patients that was not referred to in the presentation. The Panel did not consider that the complainant had provided evidence to support his/her allegation that the slide set was misleading with regard to the recommended duration of treatment with Brilique and the Panel ruled no breach of Clause 7.2.

The Panel further noted that Clause 14.5 required that material which was still in use be recertified at intervals of no more than two years to ensure that it continued to conform with the relevant regulations relating to advertising and the Code. The Panel noted AstraZeneca's submission that the slides were certified in December 2014 and did therefore not need to be recertified until December 2016. The certificate provided by AstraZeneca listed 6 January 2015 as the date the slides were reviewed and approved which meant that as long as the content remained up-to-date, the slides did not need to be recertified until 5 January 2017. The Panel noted that the complaint was received in November 2016 and thus it ruled no breach of Clause 14.5.

The Panel noted its rulings above with regard to the slide set and did not consider that AstraZeneca had failed to maintain high standards. No breach of Clause 9.1 was ruled.

Muscle symptom checklist: The Panel noted the complainant's narrow allegation that the muscle symptom checklist which was described as an item for doctors which would be a medical and educational goods and services (MEGS), contained prescribing information and that the prescribing information was out-of-date. The Panel noted that the case preparation manager had asked AstraZeneca to bear in mind the requirements of Clauses 26.1 and 26.2 in relation to this matter. The Panel did not consider that Clause 26.1 and 26.2 were relevant within the context of the narrow allegation and made no rulings in that regard.

The Panel noted the complainant's allegation that the Crestor prescribing information was out-of-date. The Panel noted AstraZeneca's submission that the prescribing information dated March 2015 was up-to-date as the last SPC change on 21 February 2016 did not affect it; the changes were to Section 5.2 with regard to special populations, age and sex. The complainant had provided no evidence that the prescribing information should have been updated since March 2015 and the Panel therefore ruled no breach of Clause 4.1.

Link to Brilique prescribing information: The Panel noted the complainant's allegation that he/she could not access the Brilique prescribing information via the links provided. The Panel noted that a link to the Brilique prescribing information appeared on the support resources for health professional's webpage of the website. This page included the 'Acute Coronary Syndrome Disease & Diagnosis' presentation which was described as a therapy area presentation covering the diagnosis and treatment of ACS. The presentation discussed Brilique, contained prescribing information and in the Panel's view was promotional. In the Panel's view, this part of the website was promotional and the prescribing information should have been provided by way of a clear and prominent, direct, single click link. The Panel noted AstraZeneca's submission that the link to the prescribing information which appeared on the webpage did not work. The Panel therefore ruled a breach of Clause 4.1.

The Panel noted that Clause 4.6 required that promotional material on the Internet must contain a clear prominent statement as to where the prescribing information could be found. The Panel did not agree with AstraZeneca's submission that the site did not require the inclusion of a link to the prescribing information due to the absence of promotional material. The Panel noted that although the link did not work as noted above, it was clear as to where the prescribing information should be found. The Panel therefore ruled no breach of Clause 4.6.

2 Respiratory

COMPLAINT

The complainant noted that 'Focus' magazines were available with a link to download them from the website. These were intended to help nurses support treatment of patients and were separate, self-contained items.

The complainant listed concerns with these items:

- a) Who were the items for? Were they for the nurses to read, or to be given to the patients themselves as support?
- b) The items were downloadable from a promotional site but had no prescribing information. Were they promotional items or not?
- c) There were company specific items in some of the magazines which failed to be fair and balanced.
- d) There was instruction to use both the Genuair and Turbohaler (issue 9, Winter 2015/16) and a leaflet on the Turbohaler was offered.

- e) In issue 10 Spring 2016, Turbohaler was again offered.
- f) In issue 11, Summer 2016, a video for Genuair was again mentioned and Symbicort was named by brand.
- g) Given the ambiguity relating to the physical items, who distributed them and to whom – patients on treatment or health professionals – and was this undertaken promotionally or to educate?
- h) The items dated back to 2012. Had they been re-examined/certified as appropriate – The complainant was not clear which category they had been placed in?

RESPONSE

AstraZeneca submitted that the Focus magazines could only be accessed after a user declared that they were a health professional; they were intended for nurses to help support the treatment of patients. The magazines sat on the 'support' section of the website and not in the branded sections. The content of the items was clearly directed to nurses to support them in their treatment of patients. Therefore these were non-promotional items and did not require prescribing information. AstraZeneca denied breaches of Clauses 4.1 and 4.6.

Issue 9 mentioned the Turbohaler, as noted by the complainant, but only in the context of how to use the devices. These items were also provided to the sales force to distribute to their customers with one copy per customer allowed; they were not intended to be given to patients.

The items contained links for patients to demonstrate to them how to use their inhalers. Clicking on these links took the user to the Symbicort/Genuair pages of the website where prescribing information was available. The user would have been clear that they were being directed from non-promotional material to a promotional website. Therefore AstraZeneca submitted there was no breach of Clause 7.2.

The first issue of Focus was in Autumn 2012 and the date of preparation for the website was November 2013. However, all the links within the digital issues linked to current pages within the website.

In response to a request for further information AstraZeneca provided details of Issues 3 and 4 of the Focus magazine together with their accompanying certificates. AstraZeneca stated that the signatories had signed in accordance with the Approval of Materials/Activities for Certification or Examination SOP which clearly stated that they 'confirm in their belief that the item is in accordance with the relevant advertising regulations and the ABPI Code of Practice, consistent with the marketing authorisation, the [SPC] and is a fair and truthful representation of the facts about the medicine'.

AstraZeneca submitted that Issue 3 was approved using an approval system that required separate and distinct approval identities for the two signatories ie one for the marketing signatory and one for the medical signatory. AstraZeneca explained that issues of the Focus magazine remained on the website indefinitely and were recertified within

two years of their previous date of certification in accordance with Clause 14.5.

PANEL RULING

The Panel noted the complainant's concerns regarding Focus magazines available on AstraZeneca's website. The complainant was concerned that the magazines were available to download from a promotional site and no prescribing information was provided and company specific items mentioned in certain issues were unfair and unbalanced. The complainant further alleged that the magazines dated back to 2012 and was concerned that they had not been appropriately recertified.

The Panel disagreed with AstraZeneca's submission that the magazines were non-promotional, given that they were provided to the sales force to distribute to health professionals, and mentioned AstraZeneca products and contained links to demonstrate the use of AstraZeneca inhalers which took the user to pages on the website where prescribing information was available. The magazines also directed readers to the promotional website if they had any queries on AstraZeneca products. In the Panel's view each copy of the magazine, where reference was made to an AstraZeneca medicine or device, had to stand alone as promotional material.

The Panel noted that Issue 9 (Winter 2015/2016) of the Focus magazine referred to Turbohaler and Genuair and in that regard AstraZeneca had submitted that links were provided to the Symbicort/Genuair promotional pages on the website where prescribing information was available. AstraZeneca provided a number of medicines in a Turbohaler – a device specific to the company. The Panel noted that the supplementary information to Clause 4.1, Advertisements for Devices, stated that where an advertisement related to the merits of a device used for administering medicines, such as an inhaler, which was supplied containing a variety of medicines, the prescribing information for one only need be given if the advertisement made no reference to any particular medicine. Full prescribing information must, however, be included in relation to each particular medicine referred to. Noting its comments above, the Panel considered that prescribing information for at least one medicine to be used with the Turbohaler and for Genuair should have been included in the Winter 2015/2016 issue of the Focus magazine and a breach of Clause 4.1 was ruled.

The Panel noted that Clause 4.6 required that promotional material on the Internet must contain a clear prominent statement as to where the prescribing information could be found. The Panel noted that the Winter 2015/2016 Focus magazine did not include such a statement. The Panel therefore ruled a breach of Clause 4.6.

The Panel noted that all complainants had the burden of proving their complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The Panel noted that in this case the complainant had referred to company specific items in some of the magazines which failed to be fair and balanced. The complainant had not provided any evidence to support why the items he/she referred to were not

fair or balanced. The Panel therefore ruled no breach of Clause 7.2.

The Panel noted AstraZeneca's submission that issues of the Focus magazine remained on the website indefinitely and were recertified within two years of their previous date of certification. The Panel noted AstraZeneca's submission that the signatories had signed in accordance with the Approval of Materials/Activities for Certification or Examination SOP which clearly stated that they 'confirm in their belief that the item is in accordance with the relevant advertising regulations and the ABPI Code of Practice, consistent with the marketing authorisation, the [SPC] and is a fair and truthful representation of the facts about the medicine', although the certificates themselves did not state this but merely included an approval date.

The Panel noted that it appeared from the certificates that Issue 3 of Focus magazine (Spring 2013) was first approved on 15 March 2013 and was then re-approved on 2 March 2015 which meant that re-approval was not required until 1 March 2017. The Panel noted the complaint was received in November 2016 and thus ruled no breach of Clause 14.5.

The Panel noted that it appeared from the certificates that Issue 4 of Focus magazine (Autumn 2013) was first approved on 16 September 2013 and was then re-approved on 11 August 2015 which meant that re-approval was not required until 10 August 2017. The Panel noted the complaint was received in November 2016 and thus ruled no breach of Clause 14.5.

C Talking type 2 website

COMPLAINT

The complainant noted that a page on this website stated it was prepared in October 2014. As with the above websites, this needed to be examined to ensure it had been reviewed and re-certified, given the many examples above where this had not occurred.

In writing to AstraZeneca attention was drawn to the requirements of Clause 14.5.

RESPONSE

AstraZeneca stated that the website was intended for patients and the public. It was taken down on 17 November (the day before the complaint was received) so that some of the pages in the patient section could be recertified. The public section referred to by the complainant was prepared in October 2014 and first certified in January 2015 and so was still current at the time of the complaint. In addition there was no product information on the public section. If a user was a declared health professional, they were redirected to the relevant pages within the simply4doctors website.

AstraZeneca submitted that the different sections of the website were certified at different times. The earliest date of preparation for any section was October 2014. The earliest date of certification, however, was 14 January 2015. AstraZeneca noted that Clause 14.5 stated that certification remained valid for a period of two years and was therefore

valid when the website was taken down on 17 November 2016. AstraZeneca denied a breach of Clause 14.5.

PANEL RULING

The Panel noted the complainant's concern that the website was prepared in October 2014 and needed to be reviewed to ensure it had been recertified. The Panel noted AstraZeneca's submission that different sections of different websites were prepared and certified at different times; the earliest being October 2014 for the above website. The earliest date of certification was however 14 January 2015. Thus no part of the website required recertification when it was taken down on 17 November 2016. The Panel therefore ruled no breach of Clause 14.5.

D Overall

COMPLAINT

The complainant concluded that the number of errors and omissions, some of which could impact on patient safety, hardly gave health professionals confidence in the industry. However, the complainant stated it was not his/her place to judge, merely to raise concerns to the PMCPA.

In writing to AstraZeneca attention was drawn to the requirements of Clauses 9.1 and 2.

RESPONSE

AstraZeneca did not consider that high standards had not been maintained and therefore submitted that there was no breach of Clauses 9.1 or 2.

PANEL RULING

The Panel noted its rulings above and considered that AstraZeneca had failed to maintain high standards with regard to the misleading statin comparison and the lack of prescribing information being provided when required in the Focus magazines. A breach of Clause 9.1 was ruled. 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. No breach of Clause 2 was ruled.

During the consideration of this case, the Panel were concerned to note that when asked for the copies of the certificates approving all of the materials listed in the table provided by AstraZeneca in its letter of 12 December, what was provided was electronic approval forms. The Panel noted AstraZeneca's submission that the reviewers listed on these forms were signing in accordance with the Approval of Materials/Activities for Certification or Examination SOP which clearly stated that they 'confirm in their belief that the item is in accordance with the relevant advertising regulations and the ABPI Code of Practice, consistent with the marketing authorisation, the [SPC] and is a fair and truthful representation of the facts about the medicine'. The Panel queried whether this satisfied the requirements of Clause 14.5 that the certificate itself must state the criteria against which the material had been approved. The Panel requested that AstraZeneca be advised of its concern in this regard.

Complaint received **18 November 2016**

Case completed **7 April 2017**

HEALTH PROFESSIONAL v NOVO NORDISK

Company website

A health professional who until recently worked in the pharmaceutical industry, complained about Novo Nordisk's company websites. One website was the corporate website and the other was a resource website for health professionals.

In relation to the corporate website the complainant was concerned that patients were identified by both their condition but also by a picture and their full name. This was inappropriate.

The complainant noted that there were more patients in the diabetes section regarding patient videos. These videos were on the same website as the many injectable treatments for diabetes and the patients' testimonies focussed mainly on injectable therapy with little time given to oral therapies, which even if the argument was made that this section on a promotional website was not product specific, this clearly indirectly focussed on Novo Nordisk products.

The complainant alleged that one patient, even stated 'Then three years ago, my doctor prescribed me a once-daily injection and it's utterly transformed my life' which was disturbing hyperbole. Although this was not directly related to a product, it was hosted on a website where several once daily injectable medicines were promoted and the complainant did not see what conclusion would be reached other than that those treatments provided those results.

The complainant was concerned that it was not clear whether any of the patient testimonies had been reviewed since 2014.

In a section of the website dealing with hormone replacement therapy (HRT), a booklet entitled 'After the Menopause' was available to download. The complainant stated that it was not clear who had final editorial control of the piece. It was stated that the booklet was written by one person but beneath his/her name it was stated that the booklet was produced by Novo Nordisk. The complainant noted that it was also unclear whether the booklet had been reviewed since 2014.

The detailed response from Novo Nordisk is given below.

The Panel noted that although the complainant had accessed the health professional section of the corporate website, the patient section had much the same information on it including the patient pictures and videos.

In the Panel's view there was no reason not to use the patients' names on the corporate website and noted Novo Nordisk's submission that patients had provided the appropriate consent. In that regard

the Panel considered that high standards had been maintained. No breach of the Code was ruled.

The Panel noted that the section of the website which dealt with diabetes included, *inter alia*, a link to Novo Nordisk products and a separate link to a patient video gallery. One of the patients featured in the video gallery had type 2 diabetes; he stated 'my doctor prescribed me a once-daily injection and it's utterly transformed my life. I can walk for miles with the dogs, play football with the grandkids, and I feel great'. The Panel noted Novo Nordisk's submission that the quotation had been taken out of context. At the start of the interview, the patient referred to going for long walks and eating healthily, both of which had a positive impact on his weight and hyperglycaemia. However, in the Panel's view the patient implied that despite this change 14 years ago, it was only three years ago when the once-daily injection was prescribed, that his life was 'utterly transformed'. One of the once-daily injections that the patient could have been prescribed was Novo Nordisk's product Victoza (liraglutide), information about which was available via the link to Novo Nordisk's products, although other once-daily injections for type 2 diabetes were available. Nonetheless, the Panel considered that it was exaggerated to state that a medicine 'utterly transformed' a life with the implication that it alone enabled the patient to walk miles and play football with children. The Panel noted that the Code required that information about prescription only medicines to the public must not raise unfounded hopes of successful treatment. Given that the patient video was available on the patient section of the website, the Panel ruled a breach of the Code. The Panel did not consider that the patient video constituted an advertisement for a prescription only medicine to the public and in that regard it ruled no breach of the Code.

The Panel noted Novo Nordisk's submission that the case studies were finally recertified more than two years after first being certified. In that regard the Panel ruled a breach of the Code.

The Panel noted that the front cover of the booklet entitled 'After the Menopause A personal guide for women' gave the independent author's details, below which was a statement that the booklet had been produced by Novo Nordisk. The Panel noted that Novo Nordisk had acknowledged that it was responsible for the content of the booklet. However, the statement 'Produced by Novo Nordisk' gave no indication as to the company's involvement, if any, in its content. The Panel ruled a breach of the Code.

The Panel noted that the booklet was re-certified within two years of the previous certification. The Panel thus ruled no breach of the Code.

The complainant noted that the resources available for health professionals to download from the professional resource website included several clinical papers. In the case of Victoza resources, this directed to a separate website to download the paper, whereas the Xultophy (insulin degludec/liraglutide) section did not. The complainant stated that although these papers were on a promotional website and were solely for the promoted products, there was no evidence that they had been reviewed to ensure that no material was off licence and there was no prescribing information on any of the items. It was therefore impossible to know when, and if, the articles were last reviewed.

The Panel noted that the website was for health professionals only; they were directed to it as a professional resource via representatives and/or promotional material. Health professionals were also directed to the site via the corporate website. The clinical papers reprints were, according to Novo Nordisk's submission, the references used in the current marketing campaigns for Victoza and Xultophy. The Panel considered that upon visiting the website and possibly downloading the reprints, relevant prescribing information should, at the same time, be available to the health professional and in that regard it noted that prescribing information could be accessed via a separate but prominent link in the same screenshot as the reprints. The link to the prescribing information was clear. No breaches of the Code were ruled.

A health professional who until recently worked in the pharmaceutical industry, complained about a number of matters on Novo Nordisk's company websites. One website was the corporate website and the other was a resource website which was only for health professionals.

When writing to Novo Nordisk, the Authority asked it to bear in mind the requirements of Clauses 4.1, 4.6, 9.10, 14.5, 26.1, 26.2 and 9.1 of the Code.

1 Corporate website

COMPLAINT

The complainant stated that he/she had the following concerns about Novo Nordisk's corporate website:

Throughout the website, patients were identified by both their condition but also by a picture and their full name. The complainant did not consider that this was appropriate. The complainant referred in particular to patients who were pictured and named in a section of the website which dealt with haemostasis.

The complainant noted that in the part of the website which dealt with diabetes there were more patients in the section regarding patient videos. These videos were on the same website as were the many injectable treatments for diabetes and the patients' testimonies focussed mainly on injectable therapy with little time given to oral therapies, which even if the argument was made that this section on a promotional website was not product specific, this clearly indirectly focussed on Novo Nordisk products.

The complainant noted that one named patient (ref UK/WB/1014/0036) even stated 'Then three years ago, my doctor prescribed me a once-daily injection and it's utterly transformed my life' which was disturbing hyperbole. Although this was not directly related to a product, it was hosted on a website where several once daily injectable medicines were promoted and the complainant did not see what conclusion would be reached other than that those treatments provided those results.

The complainant stated that it was not clear whether any of the patient testimonies had been reviewed since 2014 which was concerning.

In a section of the website dealing with hormone replacement therapy (HRT), a booklet entitled 'After the Menopause' (ref UK/HRT/0412/0001(1)) was available to download. The complainant stated that it was not clear who had final editorial control of the piece. It was stated that the booklet was written by one person but beneath his/her name it was stated that the booklet was produced by Novo Nordisk. The complainant queried who chose what to write. The complainant noted that it was also unclear whether the booklet had been reviewed since 2014.

RESPONSE

Novo Nordisk responded to the various points raised by the complainant:

Use of patient profiles

Novo Nordisk stated that its corporate website was a non-promotional resource. The use of patient profiles was intended to bring to life the conditions for which Novo Nordisk had therapies. The use of real life patients gave a more representative and realistic image of people living with these conditions than images of models who were, in reality, not actual patients. Appropriate consent and permissions had been gained in order for Novo Nordisk to use the images of the patients.

Patient quotation

Novo Nordisk had a consent form for patient interviews. The form was signed by a named patient in July 2014. It included the following statements:

'I fully understand that I am not able to mention or discuss specific diabetes treatments, including Novo Nordisk's treatments, at any point. Novo Nordisk is committed to maintaining high ethical standards and complying with industry and government regulatory requirements. Novo Nordisk is bound by the ABPI Code of Practice. As participant in the interview I understand that I must adhere to clause 22 [sic] of the ABPI Code of Practice which states: "statements must not be made for the purposes of encouraging members of the public to ask their health care professional to prescribe a specific prescription only medicine."

The named patient did not mention a specific product but a formulation of medicine (once-daily injection). There were once-daily injectable therapies for diabetes available from many manufacturers. In

Novo Nordisk's view, the complainant had taken the quotation out of context. At the start of his interview, the named patient referred to going for long walks and eating healthily, both of which had a positive impact on his weight and hyperglycaemia. Novo Nordisk considered that this was a balanced interview when read as a whole and did not breach Clauses 26.1 or 26.2 of the Code.

Certification of patient testimonies

Novo Nordisk stated that, in line with recertifying materials every two years, the patient testimonies were undergoing review within Zinc when it received the complaint. However, as part of the investigation into the complaint it was discovered that the testimonies had been uploaded for examination rather than recertification. They were now recertified. Novo Nordisk provided a copy of the roadmap of review and certification from Zinc for the patient testimonies which were in the diabetes section.

Additional training was being undertaken by the individual to ensure the processes as per the company's Certification of Materials standard operating procedure (SOP) and the Code were followed.

In response to a request for further information, Novo Nordisk stated that the patient videos for three named diabetes patients were first certified on 24 October 2014. The patient video for another named patient was first certified on 21 November 2014. The date which appeared on the video for the named patient who had given the quotation above referred to the date of preparation which was 1 October 2014. Novo Nordisk provided copies of the Zinc certificates for all the patient videos from that time.

On 17 November 2016 the videos were next uploaded onto Zinc for review by a third party agency, and forwarded within Zinc to the first approver. Initially they went through examination only, as explained above. They were then certified on 1 December 2016, once the error was discovered.

'After the Menopause' booklet

Novo Nordisk stated that the booklet was recertified on 14 September 2016. A copy of the certificate was provided. Novo Nordisk submitted that as it had funded the booklet, it was responsible for the content. It was clear that the website was funded and produced by Novo Nordisk UK, and there was a clear statement on the booklet that it was produced with support from the company. Novo Nordisk thus denied a breach of Clause 9.10.

In summary, Novo Nordisk stated that it had ensured that information on its website was balanced and appropriate for the audiences who might access it. The company submitted that it had maintained high standards.

PANEL RULING

The Panel noted that although the complainant had accessed the health professional section of the corporate website, the patient section had much the same information on it including the patient pictures and videos.

The Panel noted that it had previously issued guidance that companies could illustrate their promotional material with relevant patient case studies but that everything which the company stated, or the patient stated, about the disease or response to treatment would be subject to the Code. The Panel considered that the same advice would be applicable to non-promotional material. In the Panel's view there was no reason not to use the patients' names on the corporate website provided that the company had their permission to do so. The Panel noted Novo Nordisk's submission that patients had provided the appropriate consent and in that regard the Panel considered that high standards had been maintained. No breach of Clause 9.1 was ruled.

The Panel noted that the section of the website which dealt with diabetes included, *inter alia*, a link to Novo Nordisk products and a separate link to a patient video gallery. One of the patients featured in the video gallery had type 2 diabetes; he stated 'my doctor prescribed me a once-daily injection and it's utterly transformed my life. I can walk for miles with the dogs, play football with the grandkids, and I feel great'. The Panel noted Novo Nordisk's submission that the quotation had been taken out of context. At the start of the interview, the named patient referred to going for long walks and eating healthily, both of which had a positive impact on his weight and hyperglycaemia. However, in the Panel's view the named patient implied that despite this change 14 years ago, it was only three years ago when the once-daily injection was prescribed, that his life was 'utterly transformed'. One of the once-daily injections that the patient could have been prescribed was Novo Nordisk's product Victoza (liraglutide), information about which was available via the link to Novo Nordisk's products, although other once-daily injections for type 2 diabetes were available. Nonetheless, the Panel considered that it was exaggerated to state that a medicine 'utterly transformed' a life with the implication that it alone enabled the patient to walk miles and play football with children. The Panel noted that Clause 26.2 required, *inter alia*, that information about prescription only medicines to the public must not raise unfounded hopes of successful treatment. The Panel further noted that the supplementary information to Clause 26.2 stated that the requirements of Clause 7 relating to information also applied to information to the public. Clause 7.2 stated, *inter alia*, that information must not be misleading either directly or indirectly or by implication, by distortion, exaggeration or undue emphasis; any information, claim or comparison must be capable of substantiation. Given that the patient video was available on the patient section of the website, the Panel ruled a breach of Clause 26.2. The Panel did not consider that the patient video constituted an advertisement for a prescription only medicine to the public and in that regard it ruled no breach of Clause 26.1.

The Panel noted that the patient videos had originally been certified in October or November 2014. The Code required material to be recertified every two years if it was to remain in use. The Panel noted Novo Nordisk's submission that although the case studies had been entered into Zinc on 17 November 2016, they had, at first, only been examined, not certified. They were finally recertified on 1 December 2016 ie more than two years after first being certified.

In that regard the Panel ruled a breach of Clause 14.5.

The Panel noted that the corporate website also featured a section on HRT. Within that section, readers could download a copy of a booklet entitled 'After the Menopause A personal guide for women'. On the front cover of the booklet the independent author's details were stated, below which was a statement that the booklet had been produced by Novo Nordisk. The Panel noted that Clause 9.10 required companies to clearly indicate their sponsorship of, *inter alia*, information relating to human health and diseases. The supplementary information stated that the wording of the declaration must be unambiguous so that readers would immediately understand the extent of the company's involvement and influence over the material. The Panel noted that Novo Nordisk had acknowledged that it was responsible for the content of the booklet. However, in the Panel's view the statement that the booklet had been 'Produced by Novo Nordisk' gave no indication as to the company's involvement, if any, in its content. The Panel ruled a breach of Clause 9.10.

The Panel noted that the date of preparation stated on the last page of the booklet was October 2014. Novo Nordisk had provided a certificate to show that the booklet was last re-certified in September 2016 - within two years of the previous certification. The Panel thus ruled no breach of Clause 14.5.

2 Professional resource website

COMPLAINT

The complainant noted that the resources available for health professionals to download from this website included several clinical papers. In the case of Victoza resources, this directed to a separate website to download the paper, whereas in the Xultophy (insulin degludec/liraglutide) section it did not. The complainant stated that although these papers were on a promotional website and were solely for the promoted products, there was no evidence that they had been reviewed to ensure that no material was off licence and there was no prescribing information on any of the items. It was therefore impossible to know when, and if, the articles were last reviewed.

RESPONSE

The clinical papers referred to by the complainant were on a website that users could access only after they had confirmed that they were health professionals. It was approved for use by UK health professionals only and was clearly identified as such; Novo Nordisk provided a screen shot of the landing page.

Novo Nordisk noted that the complainant had specifically referred to clinical papers which were available on the Victoza professional resources page and the Xultophy professional resources page. A link to the summary of product characteristics (SPC), and also a link to the prescribing information was clearly available on these pages. Therefore Novo Nordisk disagreed with the complainant's assertion that there was no prescribing information for the items,

and that Novo Nordisk was in breach of Clauses 4.1 or 4.6. The papers would clearly be read within the context of those professional resource pages. They were not proactively supplied to a health professional, the health professional chose to click on them and read them.

The clinical papers were references used as part of the current marketing campaigns for both Victoza and Xultophy, therefore they were up-to-date and relevant, and did not cover unlicensed information.

In response to a request for further information, Novo Nordisk explained that health professionals were directed to the website via: the Novo Nordisk UK corporate website; promotional leavepieces given to health professionals to promote a brand, some of which included the website address for the health professional to visit if they wanted further information about the brand; promotional brand related e-mails. Promotional e-mails were sent as part of an e-mail campaign for different brands. If health professionals clicked for further information they were taken to the website and the diabetes representatives. The diabetes sales team was briefed with regard to videos in which health professionals discussed their experience with Xultophy. As part of that briefing they were told that one of the places the video could be accessed was the Novo Nordisk professional website. A copy of the briefing document was provided.

PANEL RULING

The Panel noted that the website was for health professionals only; they were directed to it as a professional resource via representatives and/or promotional material. Health professionals were also directed to the site via the corporate website. The complainant had drawn attention to clinical papers which, *inter alia*, were available to download from the website; the reprints were, according to Novo Nordisk's submission, the references used in the current marketing campaigns for Victoza and Xultophy. The Panel considered that upon visiting the website and possibly downloading the reprints, relevant prescribing information should, at the same time, be available to the health professional and in that regard it noted that prescribing information could be accessed via a separate but prominent link in the same screenshot as the reprints. No breach of Clause 4.1 was ruled. The link to the prescribing information was clear. No breach of Clause 4.6 was ruled.

During the consideration of this matter, the Panel noted that although the complainant had queried whether the clinical papers had been reviewed to ensure that no material was off licence, he/she had not made any specific complaint in that regard and Novo Nordisk had thus not been asked to consider the requirements of Clause 3.2. It was for the complainant to make out his/her case; he/she had the burden of proving his/her complaint on the balance of probabilities.

Complaint received **18 November 2016**

Case completed **4 April 2017**

ANONYMOUS NON-CONTACTABLE v GE HEALTHCARE

Promotion of Vizamyl

An anonymous, non-contactable complainant who stated that he/she had worked with positron emission tomography (PET) amyloid tracers for a number of years in clinical research complained about the promotion of ¹⁸F flutemetamol injection by GE Healthcare. Flutemetamol (¹⁸F) was a PET scanning radiopharmaceutical containing the radionuclide fluorine-18, used as a diagnostic tool for Alzheimer's disease.

The complainant alleged that GE Healthcare had actively approached some of his/her colleagues in PET centres to try and get them to use Vizamyl by supplying flutemetamol. GE Healthcare did not have a UK manufacturing site on its marketing authorisation for Vizamyl (¹⁸F flutemetamol injection), and so could not produce Vizamyl in the UK. The company had a special licence and could produce a variation chemical compound in the form of flutemetamol (¹⁸F) injection in the UK but this was not the same as the European licensed product, Vizamyl.

The complainant alleged that GE Healthcare was in breach of the Code with regard to disguised promotion and training of relevant staff, which demonstrated a lack of understanding of ABPI standards. Further, the complainant alleged that at the European Association of Nuclear Medicine (EANM) meeting in Barcelona in October, GE Healthcare had promoted Vizamyl to UK customers despite having no way of supplying the product in the UK. On the advertising booth, GE Healthcare informed everyone that GE Healthcare could supply flutemetamol while it sorted out its supply in the UK they just needed to ask for it.

The detailed response from GE Healthcare is given below.

The Panel noted that Vizamyl, which contained ¹⁸F flutemetamol, although licensed in the UK, was not available in the UK. None of the manufacturers listed in the marketing authorisation were UK based and so, as the medicine had a very short half-life, once made, it would not reach a UK patient in time to be used. GE Healthcare could instead manufacture ¹⁸F flutemetamol in the UK but as this was not a licensed medicine it could only be supplied for use in a clinical trial or on a named patient basis as a 'special'. To date it had not been supplied as a 'special'. The complainant stated, and was not contradicted by GE Healthcare, that Vizamyl and ¹⁸F flutemetamol were not the same and the two should not be confused.

The Panel noted that some of the material on the company stand at the EANM meeting included UK prescribing information which gave the cost of the product in pounds sterling, referred to the Medicines and Healthcare products Regulatory Agency (MHRA) and prominently displayed the UK company address.

The Panel considered that the use of such material misleadingly implied that Vizamyl was commercially available in the UK which was not so. A breach of the Code was ruled. The Panel further considered that as such material was bound to solicit questions from the UK delegates about the UK availability of the medicine, it would lead on to questions about ¹⁸F flutemetamol. The Panel considered that on the balance of probabilities, UK delegates at the EANM meeting would have been told about the unlicensed ¹⁸F flutemetamol. A breach of the Code was ruled. The Panel considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel noted that there was no evidence to show that, as alleged, GE Healthcare had actively approached PET centres to try to get them to use Vizamyl by supplying ¹⁸F flutemetamol. GE Healthcare submitted that all conversations with UK centres were as a result of an unsolicited enquiry. No ¹⁸F flutemetamol had been supplied to date on a named patient basis. The burden was on the complainant to prove his/her point. No breaches of the Code were ruled.

The Panel again noted that there was no evidence to show that on the balance of probabilities, GE Healthcare had disguised the promotion of Vizamyl or that relevant staff had not been appropriately trained. No breaches of the Code were ruled.

The Panel noted its comments and rulings above but did not consider that in the circumstances a ruling of a breach of Clause 2, a sign of particular censure, was warranted. No breach was ruled.

An anonymous, non-contactable complainant who stated that he/she had worked with positron emission tomography (PET) amyloid tracers for a number of years in clinical research and had had various dealings with all major manufacturers, complained about the promotion of ¹⁸F flutemetamol injection by GE Healthcare. Flutemetamol (¹⁸F) was a PET scanning radiopharmaceutical containing the radionuclide fluorine-18, used as a diagnostic tool for Alzheimer's disease.

COMPLAINT

The complainant was concerned that GE Healthcare had not fully engaged with the right authorities or followed correct procedures like other pharmaceutical companies. GE Healthcare did not have a UK manufacturing site on its marketing authorisation for Vizamyl (¹⁸F flutemetamol injection), and so could not produce Vizamyl in the UK. The company could produce a variation chemical compound in the form of flutemetamol (¹⁸F) injection at its head office in the UK but this was not the same as the European licensed product, and should be not be confused with Vizamyl.

The complainant alleged that GE Healthcare had actively approached some of his/her colleagues in PET centres to try and get them to use Vizamyl by supplying flutemetamol. This muddled the water as the two were completely different. Whilst the complainant understood that GE Healthcare had a specials licence, the company's approach was not in accordance with the Medicines and Healthcare Products Regulatory Agency (MHRA) Guidance Note 14 – The supply of unlicensed medicinal products (specials). The complainant stated that he/she would raise this separately with the MHRA.

The complainant particularly noted points 2.2 and 2.6 of the MHRA guidance. The complainant commented that there were equivalent licensed medicines available that could meet the patients' needs and that GE Healthcare had sent unsolicited emails asking clinicians to 'try' flutemetamol with their patients - indicating/promoting that GE Healthcare could supply on a specialist route or named patient basis. Named patient basis should not be confused with specialist supply – again no transparency.

The complainant stated that the GE Healthcare employee in question was in breach of Clause 12, Disguised Promotion and Clause 16, Training, which the complainant believed demonstrated a lack of understanding of ABPI standards. The complainant assumed that all GE Healthcare staff had accreditation from the ABPI. Further to this, at the European Association of Nuclear Medicine (EANM) meeting in Barcelona in October, GE Healthcare had promoted Vizamyl to UK customers despite having no way of supplying the product in the UK. On the advertising booth, GE Healthcare informed everyone that it could supply flutemetamol while it sorted out its supply in the UK; people were even informed that they just needed to ask for it. The complainant stated that the future of PET tracers in the UK rested heavily on funding and he/she sincerely believed that everyone needed to work in the highest standards of compliance with industry. The complainant requested anonymity as he/she did not want any of his/her research activities to be questioned, but considered that the GE Healthcare Vizamyl UK marketing team needed to be investigated.

When writing to GE Healthcare, the Authority asked it to consider the requirements of Clauses 2, 3.1, 3.2, 7.2, and 9.1 of the Code in addition to Clauses 12 and 16 cited by the complainant.

RESPONSE

GE Healthcare explained that Vizamyl (¹⁸F flutemetamol) was a radiopharmaceutical indicated for PET imaging of β -amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who were being evaluated for Alzheimer's disease and other causes of cognitive impairment. Vizamyl was granted a marketing authorisation from the European Medicines Agency (EMA) on 22 August 2014 via the centralised procedure.

GE Healthcare also supplied flutemetamol for investigator and pharmaceutical company

sponsored clinical trials only under an Investigational Medicinal Product Dossier (IMPD) as approved by the MHRA as part of the clinical trial applications submitted by trial sponsors.

Finally, GE Healthcare held a 'specials' licence for the supply of aseptically produced PET radiopharmaceuticals such as flutemetamol (¹⁸F) injection from its manufacturing site in Amersham. Whilst it had considered the feasibility of supplying ¹⁸F flutemetamol under the terms of the 'specials' licence, to date it had not done so.

GE Healthcare explained that the manufacturers listed in the Vizamyl summary of product characteristics (SPC) as being responsible for batch release, were all located outside the UK. Due to the short half-life (110 minutes) of the fluorine-18 radioactive isotope used for labelling Vizamyl, it was not logistically feasible to ship it from any of the currently licensed manufacturing sites to the UK. Flutemetamol (¹⁸F) injection was supplied in the UK under the authorisation of an investigational medical product dossier (IMPD) solely for the purposes of third party investigator sponsored studies. Flutemetamol was also theoretically available for supply under a specials licence, but GE Healthcare had not supplied any third party pursuant to any unsolicited request to date.

GE Healthcare stated that as the complainant had not provided any further information, it had assumed that the other licensed products he/she was likely to be referring to were Vizamyl, Neuraceq and Amyvid. GE Healthcare noted that these products were not equivalent and had different diagnostic characteristics.

As Vizamyl was not currently commercially available in the UK, there had been no formal product launch and product training for UK representatives. Such training was planned for when Vizamyl would be available in the UK. It would not be appropriate under the Code to conduct product training at the current time. GE Healthcare stated that all of its representatives were ABPI qualified. The company had specific employees which worked across Europe, with one based in the UK, including countries where Vizamyl was commercially available. Technical product training for this team had therefore been conducted using the Vizamyl Electronic Reader Training Programme. The programme was educational and had been approved by the MHRA in the UK, as required by the EMA before a planned launch of the product in any EU member state. The training programme was an EMA requirement for the correct usage of amyloid imaging agents. As such, GE Healthcare had provided the programme to investigators that used ¹⁸F flutemetamol in investigational studies.

¹⁸F flutemetamol was and had been used in the UK as an investigational product as well as being discussed at scientific congresses. As such, GE Healthcare occasionally received unsolicited requests from clinicians asking how they could access flutemetamol or Vizamyl in the UK. There might be a number of reasons for these requests, including

the clinician's preference for a particular tracer and image interpretation method and limitations in access to licensed amyloid imaging agents. In response to the case preparation manager's request for copies of emails sent by company staff asking clinicians to try flutemetamol, GE Healthcare explained that due to the absence of staff, it required any further information to help narrow down the search parameters as to where the alleged emails originated from, or from what date the alleged unsolicited requests to clinicians were made.

GE Healthcare noted that it was a key sponsor of the EANM meeting and as such had a booth at the meeting. PET amyloid imaging was promoted on the GE Healthcare booth. It was a European meeting with international attendees. Vizamyl was approved in all, and available in many, EU member states, including Spain, the host country of the EANM meeting. No materials were given to UK health professionals, although the following printed Vizamyl materials, which had been reviewed in accordance with Spanish requirements, were available at the booth:

- 1 Vizamyl technologist guide which outlined the technical aspects of conducting a Vizamyl scan (ref JB6680/PRT/OS UK); and
- 2 Vizamyl image interpretation guide which summarised the principles of image interpretation and was typically used as a summary for clinicians that had completed reader training (ref JB6772/PRT/OS UK).

The Vizamyl SPC was also available on the booth. A list of the promotional materials for Vizamyl as shown at the EANM meeting was provided.

GE Healthcare booth staff were from several European countries including the UK. The staff briefing for the meeting was provided. Those manning the booth were specifically reminded of the presence of medical affairs on the booth and how to direct questions. The relevant extracts of the EANM briefing, which also included a staff rota, were provided.

GE Healthcare stated that representatives were fully trained as to which products were available in their local markets. The company could not fully exclude that UK physicians might have sought information at its booth and it would be logistically impossible to exclude specific nationals from visiting the booth at an international meeting.

GE Healthcare conducted the following activities at the EANM meeting in relation to ¹⁸F flutemetamol:

- 1 A Vizamyl image reader training session (available by registration only) which was conducted by GE Healthcare's Medical Affairs team. No UK clinicians attended.
- 2 An ¹⁸F flutemetamol user group meeting conducted by GE Healthcare's medical affairs team. This was by invitation only for clinicians who had experience with flutemetamol, either in clinical routine or investigational use. No UK clinicians attended.

- 3 A lunchtime open symposium as part of the congress programme, open to any registered congress attendee. The symposium consisted of four presentations, each by a non-UK health professional. One of the four talks was about the clinical utility of ¹⁸F flutemetamol and the speaker was a doctor from Holland. GE Healthcare reviewed the content of the speaker's presentation, which was purely educational and non-promotional in content; a copy was provided. From the attendee list, GE Healthcare was aware that some UK health professionals had attended the symposium although it was not aware of that at the time.

GE Healthcare denied any breach of Clauses 2, 3.1, 3.2, 7.2, 9.1, 12 and 16 of the Code.

In response to a request for further information, GE Healthcare noted that it always encouraged responsible use of its products as patient safety was important. GE Healthcare submitted that it had a strong compliance culture and treated the anonymous complaint very seriously. The company strongly refuted all of the complainant's allegations and denied any breach of the Code. GE Healthcare submitted that in an abundance of caution, it would undertake additional internal training about unlicensed medicines, in particular the supply of Vizamyl.

GE Healthcare had interviewed the employee in question and gave brief details of his/her role. GE Healthcare explained that the employee and his/her colleagues supported customers with training and education on GE Healthcare's molecular imaging products and responded to customers' technical questions. GE Healthcare's account managers generally dealt with any commercial information about the products, however, due to the highly technical nature of the PET market, these employees were also typically the first point of contact for requests about named patient supply or interest in clinical studies. The employee did not proactively call on customers for promotional purposes; contact with customers regarding any product or issue was made at the request of the account manager or when the customer requested such information directly from the employee.

The employee in question confirmed that in his/her role he/she did not send unsolicited emails asking clinicians to try flutemetamol. The interactions with UK PET centres occurred in response to unsolicited requests for information and meetings about Vizamyl and/or flutemetamol. Specifically, he/she had had interactions with a number of named hospitals. In some cases, he/she said that it was not always clear which product a health professional wanted access to and why, since many requests referred to either the brand name or the international non-proprietary name. Also, health professionals who typically made these requests were often involved in clinical studies and/or made requests for individual patients. As already indicated, GE Healthcare manufactured various types of flutemetamol, including Vizamyl (although not for the UK market) and ¹⁸F flutemetamol for clinical

studies. GE Healthcare could also manufacture and supply flutemetamol on a named patient basis, and it considered each unsolicited request on a case-by-case basis. In any of these meetings the employee in question confirmed that he/she informed health professionals that VizamyI was not available in the UK. If physicians wanted access to flutemetamol, he/she would explain that GE Healthcare might be able to supply ¹⁸F flutemetamol on a so-called specialist route, ie on a named patient basis, or as part of a clinical trial. No product claims were made about flutemetamol and no encouragement was given to supply the product on this basis. In some instances, GE Healthcare had reached the stage of proposing a means of supply to include the necessary named patient supply agreement, dosing instructions, timings of delivery (all linked to manufacturing capacity) and price but to date had not supplied in this way.

GE Healthcare clarified the employment history of the employee in question which was such that there were no email exchanges between him/her and UK health professionals about VizamyI or flutemetamol before November 2016. The employee attended EANM 2016 and the autumn BNMS congress. GE Healthcare explained that such support was available at such meetings to give product presentations and technical training. The employee had attended the EANM congress to assist with the ongoing training of a new staff. UK health professionals approached the employee at these meetings about the supply of VizamyI and/or flutemetamol as detailed below, however, no specialist supplies of flutemetamol had been made to UK PET centres.

GE Healthcare interviewed another employee who covered the above employee's role during absences and who had interacted with two UK PET centres in response to unsolicited requests for information and meetings about flutemetamol. Due to this employee's technical knowledge of flutemetamol/VizamyI and knowledge about PET tracer supply, such requests were directed to him/her from time to time by the commercial teams or occasionally medical affairs in a situation where the product was not commercially available. The employee explained to the PET centres that 'while VizamyI has a European marketing authorisation, we currently do not have a production site on our marketing authorisation that is located in the UK and that we currently only produce flutemetamol for research purposes in the UK' and provided details of obtaining flutemetamol by special request when specifically asked.

GE Healthcare submitted that both employees had acted in accordance with GE Healthcare's global procedure on the Supply of Pharmaceuticals and Medical Devices as Unlicensed Product in relation to unlicensed flutemetamol. GE Healthcare provided a copy of the procedure (ref MDGP-0082) which reiterated that the company was forbidden to promote the use of unlicensed products but might, under certain conditions, supply unlicensed products to health professionals. This procedure was also consistent with the MHRA Specials Guide. GE Healthcare provided relevant emails

prior to 1 November 2016 and submitted that all email communication was reactive and factual in nature. The information provided did not contain any product claims or suggest that either of the GE Healthcare employees at issue had proactively reached out to health professionals to encourage the supply of unlicensed flutemetamol. Rather, the emails tended to provide logistical information about specialist supply of flutemetamol in response to requests for information from UK PET centres about the supply of VizamyI/flutemetamol, and also included information clarifying the licensing and supply status of VizamyI. This was entirely consistent with managing queries about named patient supply. It was necessary to discuss such logistical information before initiating the actual process for the specialist supply of flutemetamol due to the challengingly short half-life of the product, meaning it must be supplied on the correct day at the correct time to allow for a scan. Also, there were specific contractual and other safeguards that needed to be put in place before GE Healthcare could supply in this way.

GE Healthcare provided a detailed summary of specific interactions with a number of UK PET centres as supported by relevant email correspondence and interviews with relevant staff. These reactions were all reactive in response to unsolicited requests for information and meetings about VizamyI/flutemetamol.

GE Healthcare submitted that the UK sales team had not been trained on VizamyI or flutemetamol and had never been asked to talk to customers about it. However, the team the employee in question worked in was familiar with the Image Reader Training Package for VizamyI which was a required element of the risk management obligations associated with VizamyI's EMA marketing authorisation. The training was educational and contained relevant sections of the SPC as requested by the EMA (eg on indication, limitations, posology, safety information and pivotal clinical trials), but most of the programme was about how to read the images. The only other materials used in the reader training session were a set of PET amyloid scans displaying in 3 axis views for the training participants to practice/test reading scans to assess whether the scan was positive or negative. The Image Reader Training Package was consistent with the image reader training used in GE Healthcare's clinical trials and had been approved by the MHRA.

GE Healthcare submitted that in response to requests from UK PET centres for information about the supply of VizamyI/flutemetamol, its two employees in question provided logistical information about the specialist supply of flutemetamol. It was necessary to consider and discuss such logistical information before initiating the actual process for the specialist supply of flutemetamol given its very short half-life as it must be supplied on the correct day at the correct time to allow for a scan. The consideration was conducted on a case-by-case basis and in accordance with company policies, MHRA guidance and the law.

In accordance with GE Healthcare's global procedure on the Supply of Pharmaceuticals and Medical Devices as Unlicensed Product, when it received a request to supply an unlicensed product, the GE Healthcare contact must inform the local quality assurance/regulatory affairs (QA/RA) organization to verify the request and accompanying information. Therefore, the team in which one of the employees in question worked did not have any formal briefing material for such requests; he/she might have to liaise direct with the requestor in relation to issues not handled by medical affairs, such as questions about pricing, intellectual property license conditions and delivery times. Owing to the very short half-life of flutemetamol, the responses to the questions would vary on a case-by-case basis and a discussion of details such as delivery times were required before initiating the process.

In relation to international congresses, the internal certified briefing slides for EANM 2016 were provided. Slide 18 of the EANM 2016 staff briefing slides provided guidance on promotional conduct for those staffing the congress and included a reminder to refer 'all medical related questions to MA [medical affairs] via an introduction'. Slide 27 detailed the selected Vizamyl communications taking place at the congress and slide 28 went on to provide further details of how to handle referrals to medical affairs. Staff at the congress were therefore aware of their role and what requests should be referred to medical affairs colleagues.

Medical affairs conducted a session on the Vizamyl Reader Training Package (as described above) at BNMS 2016. GE Healthcare noted that the UK commercial team had promotional stand panels covering all of the company's molecular imaging products for use at the BNMS 2016 meeting, because at that time GE Healthcare planned to file a variation for a manufacturing site in the UK by the end of Q2 2016. Due to the on-going supply issues, the stands had subsequently been withdrawn from use.

GE Healthcare submitted that in accordance with GE Healthcare's global procedure on the Supply of Pharmaceuticals and Medical Devices as Unlicensed Product, when it received a request for the supply of an unlicensed product, the GE Healthcare contact must inform the local QA/RA organization to verify the request and accompanying information. Market access verified the request, for example asking whether the clinician asked for access to product for research purposes (in which case it would be directed the ISS route); was the clinician requesting access because he/she was engaging in a therapeutic trial (in this case it would be referred to the study clinical research organisation of the sponsor or answered by market access), or had the clinician requested access to the product for clinical use in patients not in a study.

In the latter scenario, market access discussed the legitimacy of this request and liaised with the systems owner of the global procedure on the Supply of Pharmaceuticals and Medical Devices as Unlicensed Product (or local equivalent). However, market access did not deal with questions such as pricing, delivery times so these queries might be

dealt with by one of the employee in question's team. In relation to flutemetamol in particular, the very short half-life of the product, meant that these logistical issues must be discussed before engaging in specialist supply of the product.

GE Healthcare did not sponsor UK health professionals to attend the EANM 2016 symposium. Since Vizamyl was not available for supply in the UK, a decision was taken not to invite the UK sales team or sponsor any UK customers.

The EANM booth displayed all GE Healthcare products. Approved information about the symposia and booth location was publicly available, including in the congress programme.

GE Healthcare concluded that, whilst it appreciated the concerns of the complainant, it denied breaches of Clauses 2, 3.1, 3.2, 7.2, 9.1, 12 and 16. GE Healthcare submitted that it treated any complaint very seriously and had ensured that relevant staff were fully aware of the company's position on unlicensed medicines and named patient supply. GE Healthcare would also organise additional internal training, in particular training on the company's global procedure on the Supply of Pharmaceuticals and Medical Devices as Unlicensed Product to reinforce the company's position on the issue. In particular, given the various different preparations of flutemetamol that GE could manufacture and supply on various different legal grounds (licensed, named patient, investigational medicinal product), it had reminded all of its technicians to be very clear going forward in terminology when responding to unsolicited requests since without clear wording it could appreciate that flutemetamol might become interchangeable with Vizamyl.

PANEL RULING

The Panel noted that the anonymous complainant was non-contactable and so could not be asked to provide further details. Anonymous complaints were accepted and like all complaints judged on the evidence provided by the parties. The complainant, who had the burden of proving his/her complaint on the balance of probabilities had not provided any evidence in support of his/her allegations.

The Panel noted that Vizamyl, which contained ¹⁸F flutemetamol, although licensed in the UK, was not available in the UK. None of the manufacturers listed in the marketing authorisation were UK based and so, as the medicine had a very short half-life, once made, it would not reach a UK patient in time to be used. GE Healthcare could instead manufacture ¹⁸F flutemetamol in the UK but as this was not a licensed medicine it could only be supplied for use in a clinical trial or on a named patient basis as a 'special'. To date it had not been supplied as a 'special'. The complainant had submitted, and it was not contradicted by GE Healthcare, that Vizamyl and ¹⁸F flutemetamol were not the same and the two should not be confused.

The Panel noted that the complainant had alleged that GE Healthcare had promoted ¹⁸F flutemetamol

to UK health professionals at the EANM meeting in Barcelona, October 2016. In that regard the Panel noted that some of the material on the company stand (A technologist's guide to imaging with Vizamyl and Vizamyl, A summary of image interpretation) both included UK prescribing information which gave the cost of the product in sterling, referred to the MHRA and prominently displayed the UK company address. The Panel considered that the use of such material misleadingly implied that Vizamyl was commercially available in the UK which was not so. A breach of Clause 7.2 was ruled. The Panel further considered that as such material was bound to solicit questions from the UK delegates about the UK availability of the medicine, it would lead on to questions about ¹⁸F flutemetamol. The Panel considered that on the balance of probabilities, UK delegates at the EANM meeting would have been told about the unlicensed ¹⁸F flutemetamol. 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.

The Panel noted that there was no evidence to show that, as alleged, GE Healthcare had actively

approached PET centres to try to get them to use Vizamyl by supplying ¹⁸F flutemetamol. GE Healthcare had submitted that all conversations with UK centres were as a result of an unsolicited enquiry. No ¹⁸F flutemetamol had been supplied to date on a named patient basis. The burden was on the complainant to prove his/her point. No breach of Clause 3.1 and 3.2 was ruled.

With regard to the complainant's allegations of breaches of Clauses 12 and 16, the Panel again noted that there was no evidence to show that on the balance of probabilities, GE Healthcare had disguised the promotion of Vizamyl or that the representatives had not been appropriately trained. No breach of Clause 12 and of Clause 16 was ruled.

The Panel noted its comments and rulings above but did not consider that in the circumstances a ruling of a breach of Clause 2, a sign of particular censure, was warranted. No breach was ruled.

Complaint received **29 November 2016**

Case completed **31 March 2017**

DIRECTOR v ROCHE

Clinical trial disclosure (Kadcyla and Perjeta)

A study published online in Current Medical Research & Opinion (CMRO) on 25 November 2016 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 2013'. The study authors were B R Deane, a freelance consultant in pharmaceutical marketing and research and Dr J Sivarajah, Head of Medical Affairs, ABPI. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2015. It covered 34 new medicines (except vaccines) from 24 companies that were approved by the European Medicines Agency (EMA) in 2013. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication 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 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 Roche 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 summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Kadcyla (trastuzumab emtansine) and Perjeta (pertuzumab).

The detailed response from Roche is given below.

General detailed comments from the Panel are given below.

With regard to Kadcyla, the Panel noted the CMRO publication in that one evaluable trial 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 91%. The disclosure percentage at 31 July 2015 was 91%.

Kadcyla was first approved and commercially available in February 2013.

With regard to Perjeta, the Panel noted the CMRO publication in that one evaluable trial had not been disclosed within the timeframe. The disclosure

percentage at 12 months was 95%. The disclosure percentage at 31 July 2015 was 100%.

Perjeta was first approved and commercially available in June 2012.

The Panel noted Roche's submission that the alleged undisclosed trial in each case related to one Phase Ib/IIa study which included both Kadcyla and Perjeta. The trial was conducted in multiple sites by Roche global and included one UK trial site and thus fell within the scope of the ABPI Code with regard to disclosure as acknowledged by Roche.

The Panel considered that the Second 2012 Code and the Joint Position 2009 applied based on the first commercialisation of Kadcyla.

The trial completed on 24 October 2013 which was after the date of commercialisation for both Kadcyla and Perjeta. The Panel noted that on the information before it the trial results should have been posted by 24 October 2014. The Panel noted Roche's submission that the trial at issue was registered on ClinicalTrials.gov on 6 July 2009 however due to an incorrect Phase I categorisation (rather than Phase I/II) within Roche, results were not posted to ClinicalTrials.gov. The trial had now been reclassified within Roche.

The Panel noted that data from the trial was published at the San Antonio Breast Cancer Symposium, in December 2012 (interim analysis) and December 2013, however the complete results had not been posted on a publicly accessible, internet based, clinical trials database within the required timeframe as acknowledged by Roche. 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 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 25 November 2016 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 2013'. The study authors were B R Deane, a freelance consultant in pharmaceutical marketing and research and Dr J Sivarajah, Head of Medical Affairs, ABPI. Publication support for the study was funded by the ABPI.

The study referred to the two previously reported studies which covered medicines approved in Europe in 2009, 2010 and 2011 (Rawal and Deane 2014) and in 2012 (Rawal and Deane 2015). The 2016 study surveyed various publicly available information sources for

clinical trial registration and disclosure of results searched between 1 May and 31 July 2015. It covered 34 new medicines (except vaccines) from 24 companies that were approved by the European Medicines Agency (EMA) in 2013. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication 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 Roche might have breached the Code and so she 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 or trial completion, or by 31 July 2015 (end of survey). Of the completed trials associated with 34 new medicines licensed to 24 different companies in 2013, results of 90% (484/539) had been disclosed within 12 months and results of 93% (500/539) had been disclosed by 31 July 2015.

Kadcyla

The supplemental information gave details of disclosure of clinical trial results for each product irrespective of sponsor. The data for Kadcyla (trastuzumab emtansine) were as follows:

Phase	Total	Un-evaluable	Evaluable	Disclosed in 12-month timeframe	Disclosure Percentage	Complete before 31 July 2015	Disclosed at 31 July 2015	Disclosure percentage at 31 July 2015
Phase I & II	11	2	9	8	89%	9	8	89%
Phase III	2	0	2	2	100%	2	2	100%
Phase IV	0	0	0	0		0	0	
Other	0	0	0	0		0	0	
Total	13	2	11	10	91%	11	10	91%

Footnote (company communication): Results of one phase I trial (originally put of scope of disclosure requirements) remained undisclosed. The results have been submitted for publication and will be posted on EudraCT.

Perjeta

The supplemental information gave details of disclosure of clinical trial results for each product irrespective of sponsor. The data for Perjeta (pertuzumab) were as follows:

Phase	Total	Un-evaluable	Evaluable	Disclosed in 12-month timeframe	Disclosure Percentage	Complete before 31 July 2015	Disclosed at 31 July 2015	Disclosure percentage at 31 July 2015
Phase I & II	20	0	20	19	95%	20	20	100%
Phase III	1	0	1	1	100%	1	1	100%
Phase IV	0	0	0	0		0	0	
Other	0	0	0	0		0	0	
Total	21	0	21	20	95%	21	21	100%

The explanation of terms given in the documentation was as follows:

Total	Total number of company sponsored trials identified which were completed by 31 July 2015
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
Results disclosed in 12 month timeframe	Evaluable trials which were disclosed within the target 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
Disclosure percentage	Proportion of evaluable trials which were disclosed within 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
Completed before 31 July 2015	Number of evaluable trials completed before 31 July 2015
Disclosed at 31 July 2015	Number of evaluable trials with results disclosed by 31 July 2015
Disclosure percentage at 31 July 2015	Proportion of evaluable trials which were disclosed by 31 July 2015

When writing to Roche 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

Roche submitted that it recognised the importance of accurate and timely disclosure and remained committed to broadening access to its clinical data.

Roche stated that it had a high degree of governance around data transparency for clinical trials. The company's policy and commitment was to ensure publication of clinical trial data in peer-reviewed journals and on publicly available clinical trial registries of the US National Institutes of Health (NIH) and the European Medicines Agency (EMA). As detailed in the Global Policy on Sharing of Clinical Trials Data, Roche also granted requests for access to full clinical study reports, periodic safety reports and summary reports of clinical data across multiple trials, upon request. The company's standard operating procedure (SOP) relating to Global Clinical trials disclosures and the Global Publication Policy described the process that underpinned its data sharing policy. The UK affiliate was within the scope of all of these documents.

Roche stated that Kadcylla as a single agent was indicated for the treatment of adults with human epidermal growth factor receptor (HER2)-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for locally advanced or metastatic disease; or developed disease recurrence during or within six months of completing adjuvant therapy. Kadcylla was first licensed and commercialised in the US on 22 February 2013 and subsequently approved in the EU on 15 November 2013.

Roche stated that Perjeta was indicated for use in combination with trastuzumab and docetaxel in adults with HER2-positive metastatic or locally recurrent unresectable breast cancer, who had not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. It was also indicated for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adults with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence. It was first licensed and commercialised in the US on 8 June 2012, with first approval in the EU on 4 March 2013.

Roche noted that one trial each for Kadcylla and Perjeta was not disclosed within the required 12 month timeframe nor disclosed by 31 July 2015 (the end of the CMRO study). Roche submitted that in both of these instances, the alleged undisclosed study related to the same Phase Ib/IIa study (BP22572) which included both Kadcylla and Perjeta.

The trial in question was predominantly a Phase Ib, multi-centre, open-label study to assess the feasibility of Kadcylla plus docetaxel in patients with HER2-positive metastatic breast cancer, and Kadcylla plus docetaxel with or without Perjeta, in patients with HER2-positive locally advanced breast cancer. There was also a Phase IIa component to obtain further safety and efficacy data from the maximum tolerated dose from each patient cohort. The trial was initiated, led and conducted through Roche's global organisation. It was conducted in multiple sites globally and there was one UK trial site. Accordingly, Roche stated that the study fell within the scope of the Code with regard to disclosure.

The trial was completed (last patient, last visit) on 24 October 2013, after the date of commercialisation for both Kadcylla and Perjeta. As a result, having considered the Joint Positions 2008 and 2009, Roche stated that this date should be the reference point for disclosure timeframes thereafter.

From the Decision Tree developed in the context of previous complaints Roche submitted that as Perjeta was first licensed in June 2012 it should be considered within the scope of the 2012 Code which referred solely to the Joint Position 2008. As Kadcylla was first licensed in February 2013 it should be considered within the scope of the Second 2012 Edition of the Code which referred to the Joint Position 2009.

Roche stated that as the BP22572 trial completed on 24 October 2013, after the first approval dates for both Kadcylla and Perjeta, the timelines for posting the trial results on Clinicaltrials.gov should have been one year after study completion, ie by 24 October 2014.

BP22572 was registered on clinicaltrials.gov on 6 July 2009 (NCT00934856) however due to an incorrect Phase I categorisation (rather than Phase I/II) within Roche, results were not posted to Clinicaltrials.gov. (Phase I trials were excluded from the registration and results submission requirements of FDAAA 801). The trial had now been reclassified within Roche and the Clinicaltrials.gov posting of results was in progress.

Although trials could be registered on EudraCT, the results section was not launched until 21 July 2014. For any interventional clinical trials that ended on or after 21 July 2014, it was compulsory for sponsors to post results within six or twelve months following the end of the trial, depending on the type of trial concerned. For other trials (where regulated by Directive 2001/20/EC) that ended <1 year prior to the finalisation of the programming (21 July 2014) the 'Trial results: modalities and timing of posting', document on the EudraCT website stated that results should be posted ≤12 months after finalisation of the programming.

As BP22572 completed on 24 Oct 2013, the results were due to be posted on EudraCT by 21 July 2015. Roche initiated the process of posting this information in March 2015 however due to issues with the third party vendor supporting the submission and review/approval delays, the deadline of 21 July 2015 was missed.

The EudraCT system was then withdrawn from 31 July 2015 until 13 January 2016 as stated in the release notes on the EudraCT website. Results for BP22572 were posted by Roche on 17 February 2016 and following validation by the EMA they were finalised on the system on 4 March 2016. The results publication on EudraCT was removed for a period of time in 2016 stating that 'the results have been removed from public view whilst they are reviewed and may need to be corrected before being returned to public view'. Roche was not made aware of this by the EMA and the results were returned to public view following an enquiry from Roche to the EMA.

Disclosure in the scientific literature

Roche stated that the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010 was first referenced within the Second 2012 Edition of the Code. Strictly speaking therefore it only applied to Kadcylla in the context of this complaint however Roche recognised the need for adherence to the Joint Position for Perjeta also regardless of when the ABPI Code applied to it.

The requirement in this Joint Position stated that results of completed industry-sponsored clinical 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 medicinal products) (therefore in this case, by April 2015). A primary manuscript was submitted to The Journal of Clinical Oncology on 15 May 2015. This manuscript was rejected and re-submitted to Annals of Oncology and after two rounds of time consuming peer-reviewed comments it was subsequently published on 6 April 2016.

Data from the BP22572 trial was published at the San Antonio Breast Cancer Symposium, in December 2012 (interim analysis) and December 2013 (data from locally advanced breast cancer (LABC) patients treated at the maximum tolerated dose).

Summary

Roche submitted that the requirement in the ABPI Code was based around the disclosure of clinical trials rather than by product. Roche appreciated that the PMCPA did not have the full detail regarding the trials associated with each product and thus raised two separate complaints. It submitted that as both complaints related to the same trial they should be combined and assessed as one complaint rather than two.

Roche stated that with regard to trial BP22572, it accepted that it did not disclose details of this trial in accordance with the requirements of Clause 13.1 set out in the relevant ABPI Code detailed above. In failing to disclose details of this trial in line with disclosure requirements, Roche also accepted its failure to maintain high standards at all times.

Roche stated that whilst it was unfortunate that this trial was not disclosed within the required timeframes, it had since been published both on the EudraCT platform and within the scientific literature ensuring full disclosure. Furthermore Roche did not believe that the delay in disclosure of this trial would have impacted patient safety and/or public health.

Roche stated that it took its commitment to disclosure very seriously and strove to operate within clearly documented processes and procedures. In addition, Roche had recently implemented a new clinical trial disclosure internal review platform which would be used to manage the process of clinical trial protocol and results disclosure to public registries. This would improve its oversight of the trials to be processed, with timelines and deliverables built and automated within the system.

Roche regretted that the trial at issue was not disclosed within the required timeframes however Roche submitted that a breach of Clause 2, a sign of particular censure, was not warranted in this case.

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 34 new medicines licensed to 24 different companies in 2013, results of 90% had been disclosed within 12 months and results of 93% had been disclosed by 31 July 2015.

The Panel noted that the CMRO publication in question was an extension of previously reported data from two studies, one 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 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 25 November 2016.

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 (for example Case AUTH/2654/11/13 *et al*) which had been updated in 2015 and published in Case AUTH/2763/5/15. The Panel updated the 2015 decision tree to include the 2016 Code.

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.

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 2013 and searched for the data between 1 May and 31 July 2015. The study was published online on 25 November 2016. 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 approval.

PANEL RULING

The Panel noted the CMRO publication in that one evaluable trial had not been disclosed within the timeframe for Kadcylla. The disclosure percentage at 12 months measured from the later of the first date of regulatory approval or trial completion date was 91%. The disclosure percentage at 31 July 2015 was 91%.

The Panel noted Roche's submission that Kadcylla was first approved and commercially available in in the US on 22 February 2013.

The Panel noted the CMRO publication in that one evaluable trial for Perjeta had not been disclosed within the timeframe. The disclosure percentage at 12 months was 95%. The disclosure percentage at 31 July 2015 was 100%.

The Panel noted Roche's submission that Perjeta was first approved and commercially available in the US on 8 June 2012.

The Panel noted Roche's submission that in both of the instances above, the single alleged undisclosed trial related to the same Phase Ib/Ila study (BP22572) which included both Kadcylla and Perjeta. The trial was initiated, led and conducted through Roche's global organisation; it was conducted in multiple sites globally and included one UK trial site and thus fell within the scope of the ABPI Code with regard to disclosure as acknowledged by Roche.

In the circumstances, the Panel considered that the most recent applicable Code and Joint Position would apply ie the Second 2012 Code and the Joint Position 2009 based on the first commercialisation of Kadcylla.

The trial was completed (last patient, last visit) on 24 October 2013. This completion date was after the date of commercialisation for both Kadcylla and Perjeta. The Panel noted that on the information before it the trial results should have been posted on a publicly accessible, internet-based clinical trials database by 24 October 2014. The Panel noted Roche's submission that the trial at issue was registered on ClinicalTrials.gov on 6 July 2009 (NCT00934856) however due to an incorrect Phase I categorisation (rather than Phase I/II) within Roche, results were not posted to ClinicalTrials.gov. (Phase I trials were excluded from the registration and results submission requirements of FDAAA 801). The trial had now been reclassified within Roche.

The Panel noted that data from the BP22572 trial was published at the San Antonio Breast Cancer Symposium, in December 2012 (interim analysis) and December 2013 (data from LABC patients treated at the maximum tolerated dose), however the complete results had not been posted on a publicly accessible, internet based, clinical trials database within the required timeframe as acknowledged by Roche. The Panel thus ruled a breach of Clause 13.1. The delay in disclosure meant that high standards had not been maintained and a breach of Clause 9.1 was ruled.

As the data had now been disclosed the Panel considered that there was no breach of Clause 2 and ruled accordingly.

Complaint received	29 November 2016
Cases completed	13 March 2017

DIRECTOR v NOVO NORDISK

Clinical trial disclosure (Tresiba)

A study published online in Current Medical Research & Opinion (CMRO) on 25 November 2016 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 2013'. The study authors were B R Deane, a freelance consultant in pharmaceutical marketing and research and Dr J Sivarajah, Head of Medical Affairs, ABPI. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2015. It covered 34 new medicines (except vaccines) from 24 companies that were approved by the European Medicines Agency (EMA) in 2013. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication 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 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 Novo Nordisk 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 summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Tresiba (insulin degludec).

The detailed response from Novo Nordisk is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that 18 evaluable trials (10 Phase I and II studies and 8 Phase III) 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 63%. The disclosure percentage at 31 July 2015 was 69%.

Tresiba was first approved and commercially available in January 2013. The Second 2012 Code and thus the Joint Position 2009 were relevant. The Panel noted that on the information before it, the trials completed before 21 January 2013 should have been published by 20 January 2014.

The Panel noted Novo Nordisk's submission that the 10 Phase I and II trials had no UK involvement including no UK patients, investigators or UK funding and none of the trials were conducted on behalf of Novo Nordisk Ltd (the UK legal entity). The Panel considered that as there was no UK involvement in any of the ten Phase I or II trials that they did not come within the scope of the UK Code and no breach of the Code was ruled. The Panel noted Novo Nordisk's submission that full clinical trial reports were available from novonordisk-trials.com.

The Panel noted that according to the CMRO publication there were eight Phase III trials that had not been disclosed within the timeframe; five had still not been disclosed by 31 July 2015. The Panel noted Novo Nordisk's submission regarding EudraCT submission deadlines and IT issues but considered that the applicable Joint Position 2009 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. Publication in any free, publicly accessible internet-based clinical trials database would achieve the intended objectives.

The Panel noted Novo Nordisk's submission that ten Phase III trials had UK involvement (UK sites and patients). The Panel was not aware which eight of these trials corresponded to the eight Phase III trials highlighted in the CMRO publication. The Panel examined the table provided by Novo Nordisk which included the ten completed Phase III studies with UK involvement.

The results for trials NN1250-3583 and NN1250-3644 had been published within the timeframe. Thus the Panel ruled no breaches of the Code including no breach of Clause 2.

The Panel noted that on the information before it both trials NN1250-3585 and NN1250-3725 completed before 21 January 2013 and therefore should have been published by 21 January 2014. Novo Nordisk had however received an extension to delay the results. Thus the Panel ruled no breaches of the Code including no breach of Clause 2.

The Panel noted that on the information before it that trial NN1250-3944 completed after 21 January 2013 and therefore should have been published by 31 December 2014. Although Novo Nordisk had received approval to delay publication of the results, full publication occurred on 1 September 2014 which was within the appropriate timeframe. Thus the Panel ruled no breaches of the Code including no breach of Clause 2.

The Panel noted that on the information before it trials NN1250-3770, NN1250-3668, NN1250-3672

and NN1250-3724 all completed before 21 January 2013 and therefore should have been published by 20 January 2014. All four trials had been disclosed within the appropriate timeframe. Thus the Panel ruled no breaches of the Code including no breach of Clause 2.

Trial NN1250-3561 completed on 30 July 2013, first results were available on Novonordisk-trials.com on 15 October 2014, an oral presentation of the abstract took place in September 2014 and full publication on 12 February 2015. The Panel noted that on the information before it the trial completed after 21 January 2013 and therefore should have been published by 29 July 2014. The results had not been disclosed in the timeframe. The Panel 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 results had been disclosed, the Panel considered there was no breach of Clause 2 and ruled accordingly.

The Panel noted that Novo Nordisk provided details of fifteen additional Phase III trials. The Panel noted Novo Nordisk’s submission that the additional fifteen Phase III trials had no UK involvement including no UK patients, investigators or UK funding and none of the trials were conducted on behalf of Novo Nordisk Ltd (the UK legal entity). The Panel considered that as there was no UK involvement in any of the fifteen Phase III trials that they did not come within the scope of the UK Code and no breach of the Code was ruled.

A study published online in Current Medical Research & Opinion (CMRO) on 25 November 2016 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 2013’. The study authors were B R Deane, a freelance consultant in pharmaceutical marketing and research and Dr J Sivarajah, Head of

Medical Affairs, ABPI. Publication support for the study was funded by the ABPI.

The study referred to the two previously reported studies which covered medicines approved in Europe in 2009, 2010 and 2011 (Rawal and Deane 2014) and in 2012 (Rawal and Deane 2015). The 2016 study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2015. It covered 34 new medicines (except vaccines) from 24 companies that were approved by the European Medicines Agency (EMA) in 2013. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication 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 Novo Nordisk might have breached the Code and so she 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 or trial completion, or by 31 July 2015 (end of survey). Of the completed trials associated with 34 new medicines licensed to 24 different companies in 2013, results of 90% (484/539) had been disclosed within 12 months and results of 93% (500/539) had been disclosed by 31 July 2015.

Tresiba

The supplemental information gave details of disclosure of clinical trial results for each product irrespective of sponsor. The data for Tresiba (insulin degludec) were as follows:

Phase	Total	Un-evaluable	Evaluable	Disclosed in 12-month timeframe	Disclosure Percentage	Complete before 31 July 2015	Disclosed at 31 July 2015	Disclosure percentage at 31 July 2015
Phase I & II	24	1	23	13	57%	23	13	57%
Phase III	25	0	25	17	68%	25	20	80%
Phase IV	0	0	0	0		0	0	
Other	0	0	0	0		0	0	
Total	49	1	48	30	63%	48	33	69%

Footnote (company communication): Results of the 15 remaining undisclosed trials (10 phase I trials, originally out of scope of disclosure requirements, of which four also pre-dated disclosure requirements, and five phase III trials) have since been posted on ClinicalTrials.gov and/or the company’s own registry in October 2015, following the approval of the product in US in September 2015, in compliance with Food and Drug Administration Amendments Act (FDAAA) 801 (2007) requirements for results disclosure at ClinicalTrials.gov.

The explanation of terms given in the documentation was as follows:

Total	Total number of company sponsored trials identified which were completed by 31 July 2015
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
Results disclosed in 12 month timeframe	Evaluable trials which were disclosed within the target 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
Disclosure percentage	Proportion of evaluable trials which were disclosed within 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
Completed before 31 July 2015	Number of evaluable trials completed before 31 July 2015
Disclosed at 31 July 2015	Number of evaluable trials with results disclosed by 31 July 2015
Disclosure percentage at 31 July 2015	Proportion of evaluable trials which were disclosed by 31 July 2015

When writing to Novo Nordisk 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

Novo Nordisk submitted that it was committed to transparency of its clinical trials and took this matter very seriously. It followed international and national laws on clinical trial disclosure.

Novo Nordisk provided result tables to clinicaltrials.gov following the US FDAAA legal requirements and to the EudraCT database for public disclosure at the EU ClinicalTrials Register by EMA according to the EU ClinicalTrials Directive, the Paediatric Regulation and other requirements governing the use of EudraCT. It adhered to the timelines below, as outlined in the company's policy 'Principles for the registration of clinical study information in external registries'.

The company submitted that a summary of results was provided to www.ClinicalTrials.gov at FDA product approval plus 30 days, or last patient last visit plus 12 months whichever came last. A summary of results for clinical trials, Phase I-IV in adults, was provided to EU ClinicalTrials Register at the date of last patient last visit plus 12 months. Only results for Phase II-IV trials would be disclosed. It provided a summary of results for paediatric clinical trials, Phase I-IV, to EU ClinicalTrials Register at last patient last visit plus 6 months.

Novo Nordisk stated that it posted a redacted clinical study report (CSR) for clinical trials, Phase I-IV, and non-interventional study (NIS) on www.novonordisk-trials.com 30 days after approval of product and indication in both EU and the US, or at last patient last visit plus 12 months whichever came last.

Results for non-interventional studies classified as post-authorisation safety studies (NI PASS) in the EU PAS Register were posted preferably within two weeks after the finalisation of the study report in the format of a redacted study report.

Novo Nordisk posted a CSR for clinical trials, Phase I-IV on www.novonordisk-trials.com 12 months after public announcement of discontinuation of project, or at last patient last visit plus 12 months whichever came last.

The company posted references to scientific publications for clinical trials, Phase I-IV, and NIS on www.novonordisk-trials.com and/or www.ClinicalTrials.gov within one year from publication. Links were provided as they became available.

Novo Nordisk released clinical trial reports (CTRs) (redacted for private personal data and company confidential information) on its portal www.novonordisk-trials.com within 30 days after the latest of the EU and US approvals.

Novo Nordisk stated that Tresiba was first licensed and commercially available in the UK on 21 January 2013. Tresiba was approved in the US by the FDA on 25 September 2015.

With regard to the evaluable trials highlighted in the CMRO study supplemental information Novo Nordisk Ltd (the UK legal entity) had no involvement and there were no UK patients in the Phase I and Phase II studies; therefore these were not addressed below. However, it emphasised that all trials had full clinical trial reports available for download from novonordisk-trials.com. This also included the Phase I and II trials with no UK involvement. There were ten Phase III trials with UK involvement (UK sites and patients). Details were provided.

Relevant trials in scope for results disclosure via the EudraCT database were submitted by the deadlines

specified by EMA for the EudraCT results disclosure implementation in the period July 2014 - July 2015. For older trials completed prior to implementation the first of these deadlines was 21 July 2015, to which Novo Nordisk adhered.

Unfortunately EMA faced information technology issues with the release of results from EudraCT to the public register and had to close down the access to the public site and for further entry into the EudraCT system for approximately half a year from July 2015 – January 2016. The results submitted to EudraCT were therefore not available to the ABPI for its audit. The EU Clinical Trials Register and the EudraCT results database was back in operation as of 13 January 2016 and EMA had defined new deadlines for the trials that were due during the period when the system was inaccessible. All trials in scope for EudraCT had been submitted by Novo Nordisk and old ones re-released after the EMA requested quality control according to EMA's specifications.

Trials in scope for ClinicalTrials.gov were submitted within the deadline of 30 days after approval by the FDA and were all publicly available.

The results of study NN1250-3561 were presented at the International Society for Paediatrics and Adolescent Diabetes (ISPAD) meeting, 3-6 September 2014. The trial completion date was 30 July 2013. It was submitted at the earliest possible time according to EudraCT requirements and availability. The trial had a positive outcome and formed the basis of the licence extension for paediatric use. All other trials had been publically disclosed within the timeframe. Therefore Novo Nordisk submitted that it had upheld high standards (Clause 9.1) and had not brought the industry into disrepute (Clause 2).

In response to a request for further information Novo Nordisk confirmed that Novo Nordisk Ltd (the UK legal entity) had no involvement in the Phase I and II trials and that there were no UK investigators involved in the trials, nor were any of the trials conducted on behalf of Novo Nordisk Ltd. There was no UK funding nor any other UK involvement.

Novo Nordisk confirmed that that was also the situation for 15 of the 25 studies listed in the table provided titled 'Overview of trials with UK involvement (Tresiba)'. There were no UK investigators involved in the trials and none of the trials were conducted on behalf of Novo Nordisk Ltd. There was no UK funding or any other UK involvement. Novo Nordisk submitted that only the ten trials highlighted had any UK involvement.

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 34 new medicines licensed to 24 different companies in 2013, results of 90% had been

disclosed within 12 months and results of 93% had been disclosed by 31 July 2015.

The Panel noted that the CMRO publication in question was an extension of previously reported data from two studies, one 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 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 25 November 2016.

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 (for example Case AUTH/2654/11/13 *et al*) which had been updated in 2015 and published in Case AUTH/2763/5/15. The Panel updated the 2015 decision tree to include the 2016 Code.

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.

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 2013 and searched for the data between 1 May and 31 July 2015. The study was published online on 25 November 2016. 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 approval.

PANEL RULING

The Panel noted the CMRO publication in that 18 evaluable trials (10 Phase I and II studies and 8 Phase III) 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 63%. The disclosure percentage at 31 July 2015 was 69%.

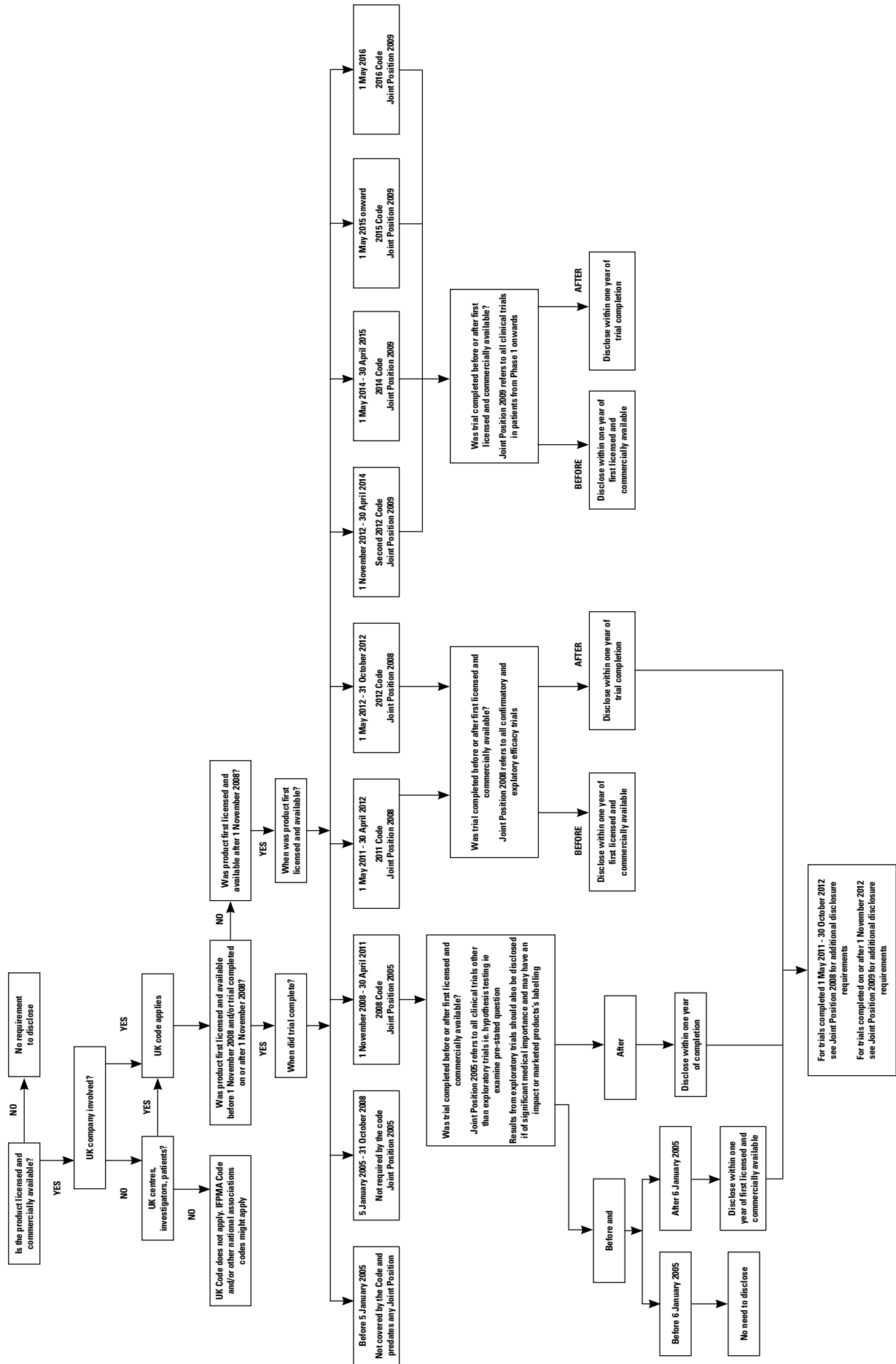
The Panel noted Novo Nordisk's submission that Tresiba was first approved and commercially available in the UK on 21 January 2013. The Second 2012 Code and thus the Joint Position 2009 were relevant. The Panel noted that on the information before it, the trials completed before 21 January 2013 should have been published by 20 January 2014.

The Panel noted Novo Nordisk's submission that the 10 Phase I and II trials had no UK involvement including no UK patients, investigators or UK funding and none of the trials were conducted on behalf of Novo Nordisk Ltd (the UK legal entity). The Panel considered that as there was no UK involvement in any of the ten Phase I or II trials that they did not come within the scope of the UK Code and no breach of the Code was ruled. The Panel noted Novo Nordisk's submission that they had full clinical trial reports available for download from novonordisk-trials.com.

The Panel noted that according to the CMRO publication there were eight Phase III trials that had not been disclosed within the timeframe; five had still not been disclosed by 31 July 2015. The Panel noted Novo Nordisk's submission regarding EudraCT submission deadlines and IT issues but considered that the applicable Joint Position required relevant

Decision Tree

Updated Decision tree developed by the Panel



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. Publication in any free, publicly accessible internet-based clinical trials database would achieve the intended objectives.

The Panel noted Novo Nordisk's submission that ten Phase III trials in the table it provided had UK involvement (UK sites and patients). The Panel was not aware which eight of these trials corresponded to the eight Phase III trials highlighted in the CMRO publication. The Panel examined the information provided by Novo Nordisk which included the ten completed Phase III studies with UK involvement.

Trial NN1250-3583 completed on 8 November 2011. First results were available on Novonordisk-trials.com on 3 January 2014 and full publication on 21 April 2012. Trial NN1250-3644 was an extension of the above study which completed on 15 November 2011; the first full publication of results occurred on 17 June 2013. The results for both NN1250-3583 and NN1250-3644 had been published within the timeframe. Thus the Panel ruled no breach of Clause 13.1 of the Code and consequently no breach of Clauses 9.1 and 2.

Trial NN1250-3585 completed on 16 June 2011; a request for an extension to delay the results was received on 25 February 2011. The first results were available on Novonordisk-trials.com on 25 June 2014 and full publication on 8 May 2014. Similarly, Trial NN1250-3725 was an extension of NN1250-3585 and completed on 16 June 2011, first results were available on Novonordisk-trials.com on 25 June 2014 and full publication on 7 September 2015. The Panel noted that on the information before it both trials completed before 21 January 2013 and therefore should have been published by 21 January 2014. Novo Nordisk had however received an extension to delay the results. Thus the Panel ruled no breach of Clause 13.1 of the Code and consequently no breach of Clauses 9.1 and 2.

Trial NN1250-3944 completed on 31 December 2013, the first results were available on Novonordisk-trials.com on 4 March 2015 and full publication on 1 September 2014. The Panel noted that on the information before it the trial completed after 21 January 2013 and therefore should have been published by 31 December 2014. Although Novo Nordisk had received approval to delay publication of the results, full publication occurred on 1

September 2014 which was within the appropriate timeframe. Thus the Panel ruled no breach of Clause 13.1 of the Code and consequently no breach of Clauses 9.1 and 2.

Trial NN1250-3770 completed on 1 May 2011, first results were available on Novonordisk-trials.com on 26 November 2013 and full publication on 7 February 2013. Trial NN1250-3668 completed on 6 September 2010, first results were available on Novonordisk-trials.com on 26 November 2013 and full publication on 22 January 2013. Trial NN1250-3672 completed on 26 November 2010, first results were available on Novonordisk-trials.com on 26 November 2013 and full publication on 28 May 2013. Trial NN1250-3724 completed on 18 November 2010, first results were available on Novonordisk-trials.com on 26 November 2013 and full publication on 9 July 2013. The Panel noted that on the information before it the above four trials all completed before 21 January 2013 and therefore should have been published by 20 January 2014. All four trials had been disclosed within the appropriate timeframe. Thus the Panel ruled no breach of Clause 13.1 of the Code and consequently no breach of Clauses 9.1 and 2.

Trial NN1250-3561 completed on 30 July 2013, first results were available on Novonordisk-trials.com on 15 October 2014, an oral presentation of the abstract took place in September 2014 and full publication on 12 February 2015. The Panel noted that on the information before it the trial completed after 21 January 2013 and therefore should have been published by 29 July 2014. The results had not been disclosed in the timeframe. The Panel ruled a breach of Clause 13.1. 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 been disclosed, the Panel considered there was no breach of Clause 2 and ruled accordingly.

The Panel noted that Novo Nordisk provided details of fifteen additional Phase III trials. The Panel noted Novo Nordisk's submission that the additional fifteen Phase III trials had no UK involvement including no UK patients, investigators or UK funding and none of the trials were conducted on behalf of Novo Nordisk Ltd (the UK legal entity). The Panel considered that as there was no UK involvement in any of the fifteen Phase III trials that they did not come within the scope of the UK Code and no breach of the Code was ruled.

Complaint received **29 November 2016**

Cases completed **14 March 2017**

DIRECTOR v BAYER

Clinical trial disclosure (Xofigo)

A study published online in Current Medical Research & Opinion (CMRO) on 25 November 2016 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 2013'. The study authors were B R Deane, a freelance consultant in pharmaceutical marketing and research and Dr J Sivarajah, Head of Medical Affairs, ABPI. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2015. It covered 34 new medicines (except vaccines) from 24 companies that were approved by the European Medicines Agency (EMA) in 2013. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication 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 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 Bayer 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 summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Xofigo (radium-223 dichloride).

The detailed response from Bayer is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that one evaluable Phase I trial had not been disclosed within the 12 month timeframe. The disclosure percentage at 12 months measured from the later of the first date of regulatory approval or trial completion date was 88%. The disclosure percentage at 31 July 2015 of trials completed by the end of July 2015 was 88

The Panel noted Bayer's submission that the trial in question was conducted in the UK on 6 patients to explore the bio-distribution, pharmacokinetics, and dosimetry of radium 223; it was neither a confirmatory clinical trial nor an exploratory efficacy trial and it completed on 3 December 2008.

The Panel noted Bayer's interpretation of the 2009 Joint Position that trials '...initiated 6 months after the publication date of this Joint Position should be included in a public clinical trial registry'. It was Bayer's understanding that the trial in question qualified as an 'additional trial' under the 2009 Joint Position as it was not required to be disclosed under the 2008 Joint Position. In the Panel's view, Bayer had mixed up requirements regarding clinical trial registries with those of clinical trial results databases. The 2009 Joint Position clearly stated that the posting of clinical trial results should occur in compliance with the timelines and conditions defined in that Joint Position.

The Panel noted that Xofigo was first licensed and commercially available in May 2013 and this, as stated in the Panel's general comments above, was the trigger date for disclosure. The Second 2012 Code and thus the Joint Position 2009 applied which meant that for all licensed and commercially available medicines, all clinical trials from Phase I onward needed to be disclosed regardless of their completion date. Disclosure had to be within 1 year of the product first being licensed and commercially available or within one year of the trial's completion whichever was later.

The Panel noted on the information before it results from the trial should have been posted on a publicly accessible, internet-based clinical trials database by May 2014. As this had not happened the Panel 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.

The Panel noted Bayer's submission that there had been four clinical publications drawn from the results of the trial from 2011 to 2015. Details were provided and all four clinical papers had also been linked to disclosure on clinicaltrials.gov and were publicly accessible with full trial results published online in July 2015 and in print in September 2015. In addition Bayer added the results synopsis to the EudraCT database in May 2016. As the data had been disclosed the Panel considered there was no breach of Clause 2 and ruled accordingly.

A study published online in Current Medical Research & Opinion (CMRO) on 25 November 2016 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 2013'. The study authors were B R Deane, a freelance consultant in pharmaceutical marketing and research and Dr J Sivarajah, Head of Medical Affairs, ABPI. Publication support for the study was funded by the ABPI.

The study referred to the two previously reported studies which covered medicines approved in

Europe in 2009, 2010 and 2011 (Rawal and Deane 2014) and in 2012 (Rawal and Deane 2015). The 2016 study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2015. It covered 34 new medicines (except vaccines) from 24 companies that were approved by the European Medicines Agency (EMA) in 2013. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication 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 Bayer might have breached the Code and so she 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 or trial completion, or by 31 July 2015 (end of survey). Of the completed trials associated with 34 new medicines licensed to 24 different companies in 2013, results of 90% (484/539) had been disclosed within 12 months and results of 93% (500/539) had been disclosed by 31 July 2015.

Tresiba

The supplemental information gave details of disclosure of clinical trial results for each product irrespective of sponsor. The data for Xofigo (radium-223 dichloride) were as follows:

Phase	Total	Un-evaluable	Evaluable	Disclosed in 12-month timeframe	Disclosure Percentage	Complete before 31 July 2015	Disclosed at 31 July 2015	Disclosure percentage at 31 July 2015
Phase I & II	8	1	7	6	86%	7	6	86%
Phase III	1	0	1	1	100%	1	1	100%
Phase IV	0	0	0	0		0	0	
Other	0	0	0	0		0	0	
Total	9	1	8	7	88%	8	7	88%

Footnote (company communication): The one remaining undisclosed phase I trial was originally out of scope of disclosure requirements; results will be posted on EudraCT.

The explanation of terms given in the documentation was as follows:

Total	Total number of company sponsored trials identified which were completed by 31 July 2015
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
Results disclosed in 12 month timeframe	Evaluable trials which were disclosed within the target 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
Disclosure percentage	Proportion of evaluable trials which were disclosed within 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
Completed before 31 July 2015	Number of evaluable trials completed before 31 July 2015
Disclosed at 31 July 2015	Number of evaluable trials with results disclosed by 31 July 2015
Disclosure percentage at 31 July 2015	Proportion of evaluable trials which were disclosed by 31 July 2015

When writing to Bayer 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

Bayer stated that Radium 223's first licence was granted in the US on 15 May 2013 for the treatment of patients with symptomatic bone metastatic, castrate-resistant prostate cancer; and within Europe on 13 November 2013 for the same indication. The date of first commercialisation was May 2013 in the US and January 2014 in the UK. Therefore the company submitted that the Second 2012 Edition of the Code was relevant.

With regard to the one trial which had not been disclosed Bayer noted the footnote which read 'The one remaining undisclosed Phase I trial was originally out of scope of disclosure requirements; results will be posted on EudraCT'. Details of the trials, UK involvement and disclosure parameters in relation to the publication were provided. The trial in question was Trial #15302 (NCT00667537), a Phase I, open-label, dosimetry, bio-distribution and pharmacokinetic trial of alpharadin in patients with hormone refractory prostate cancer and skeletal metastases. The trial completed on 3 December 2008 and was conducted in the UK on 6 patients to explore the bio-distribution, pharmacokinetics, and dosimetry of radium 223. It was neither a confirmatory clinical trial nor an exploratory efficacy trial.

Bayer considered clinical trial disclosure obligations at a global level; the Global Headquarters based in Germany, provided overarching determinations in such matters. As such, Bayer Plc had no involvement in the analysis and decision-making process regarding the company's overarching determination on whether a clinical trial's results should be disclosed under the relevant Joint Position. Notwithstanding global management of this decision-making process, Bayer Plc acknowledged that as the UK affiliate of a global organisation it was bound to comply with the ABPI Code and the various Joint Positions.

Bayer submitted that the results of Trial #15302 had not been disclosed because globally, the disclosure decision was made with only the Joint Positions without sight of the Decision Tree cited in numerous PMCPA cases from early 2014 onwards.

The company stated that the Joint Position 2008, published one month before Trial #15302 completed, identified which clinical trials were required to be listed and results disclosed. These footnotes could be summarised as stating that disclosure obligations detailed in the Joint Position 2008 were relevant only to confirmatory clinical trials and exploratory efficacy trials, with Phase I clinical trials expressly excluded from the definition of disclosable studies. Bayer submitted that as Trial #15302 was a Phase I clinical trial it fell into this exemption for disclosure purposes; under the Joint Position 2008, Trial #15302 was not required to be disclosed within one year of licensing and commercialisation of Xofigo. However, within 12 months of the publication of the Joint Position 2008 it was updated by the Joint Position 2009 and Bayer looked again to see if its evaluation of non-disclosure of Trial #15302 remained appropriate.

The Joint Position 2009 expanded the disclosure obligations to include Phase I trials, and as such all interventional trials involving human subjects from Phase I and beyond were required to be disclosed. For Trial #15302 this expanded definition of disclosable clinical trial results was considered by Bayer Global to determine if disclosure was now required within one year of licensing.

Bayer referred to the 'Implementation dates' and the section:

'Additional trials that fall within the scope of this revised Joint Position and are initiated 6 months after the publication date of this Joint Position should be included in a public clinical trial registry.'

Bayer submitted that Trial #15302 qualified as an 'additional trial' under the Joint Position 2009 as it had not been the subject of disclosure requirements under the Joint Position 2008, but as a Phase I study now fell within the scope of Joint Position 2009. Bayer understood that such Phase I trials were only subject to disclosure requirements if the trial was initiated 6 months after the publication of the Joint Position 2009. Trial #15302 completed on 3 December 2008 and therefore, under Bayer's construction of the above text, it did not fall within the category of 'additional trials' requiring disclosure under the Joint Position 2009. The company submitted that there was no posting obligation for Trial # 15302 under the Joint Position 2009.

Previous Case Guidance

Bayer highlighted the complexity when looking at previous cases, particularly in relation to the correct interpretation on which Joint Position was relevant and whether a Phase I trial which completed prior to 2009, came within scope of disclosure (ie Joint Position 2008 or earlier) even when the date of commercialisation followed thereafter.

The ambiguity surrounding this came from the decision tree used during a number of cases in 2014 all cited in the August 2014 Code of Practice review:

Bayer appreciated that the updated decision tree of June 2015 provided greater clarity around this, however it was not available to Bayer nor, from its understanding, was it in the public domain prior to being provided to the company in December 2016.

Bayer drew attention to a box in the 2014 decision tree which stated:

'Was product first licensed and available before 1 November 2008 and/or trial completed on or after 1 November 2008?'

This box contained an and/or which allowed the trial to be considered in variance to the date of commercialisation (this had been removed in the updated decision tree dated June 2015). If the 2014 decision tree was followed in relation to this case then:

Was the product first licensed and available before 1 November 2008 – NO and/OR trial completed on or after 1 November 2008 – Yes. (This created variance from date of licence to the date of trial completion)

The next question on the 2014 decision tree was when did the trial complete, the answer to which in relation to this case would be considered in the box '1 November 2008 - 30 April 2011' and consideration of the trial in this case under the 2008 Code and the Joint Position 2005.

It was not Bayer's position that this case should be considered under the Joint Position 2005 or the 2008 Code. However Bayer would like to highlight the large degree of ambiguity under which Joint Position Trial #15302 should be considered. Had Bayer Plc sought confirmation regarding its disclosure obligations at the time of licensing and commercialisation of Xofigo and reviewed previous Code cases and particularly the 2014 decision tree, this would have contributed to rather than eliminated the ambiguity surrounding disclosure requirements. The company submitted that this should be taken into consideration by the Panel when reviewing this case.

Disclosure of Trial #15302

Bayer stated it was committed to the principles and obligations placed upon it for disclosure of clinical trial results as set out in both the Joint Position and the Code. Bayer did not consider that Trial #15302 was subject to disclosure, however it was still committed to disclosing the results and there had been 4 clinical publications drawn from the results of this trial from 2011 to 2015. Details were provided and all 4 clinical papers had also been linked to disclosure on clinicaltrials.gov and were publically accessible with full trial results published online in July 2015 and in print in September 2015. In addition Bayer added the results synopsis to the EudraCT database in May 2016. (Result posting on the EU Clinical Trial Database EudraCT was only required since 21 July 2014 with studies with EudraCT number and end of study before 21 July 2013: result synopsis submission to EudraCT was required by 21 Dec 2016).

Bayer therefore submitted that Trial #15302 was not within the scope of disclosure according to the requirements of the Joint Position. As such, Bayer disagreed that any breach of Clause 21.3 of the Second 2012 Edition of the Code had occurred. In addition, Bayer had demonstrated full disclosure of the trial results for Trial #15302 and as such there was no breach of Clause 9.1 or Clause 2 of the Second 2012 Edition.

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 34 new medicines licensed to 24 different companies in 2013, results of 90% had been

disclosed within 12 months and results of 93% had been disclosed by 31 July 2015.

The Panel noted that the CMRO publication in question was an extension of previously reported data from two studies, one 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 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 25 November 2016.

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 (for example Case AUTH/2654/11/13 *et al*) which had been updated in 2015 and published in Case AUTH/2763/5/15. The Panel updated the 2015 decision tree to include the 2016 Code.

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.

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 2013 and searched for the data between 1 May and 31 July 2015. The study was published online on 25 November 2016. 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 approval.

PANEL RULING

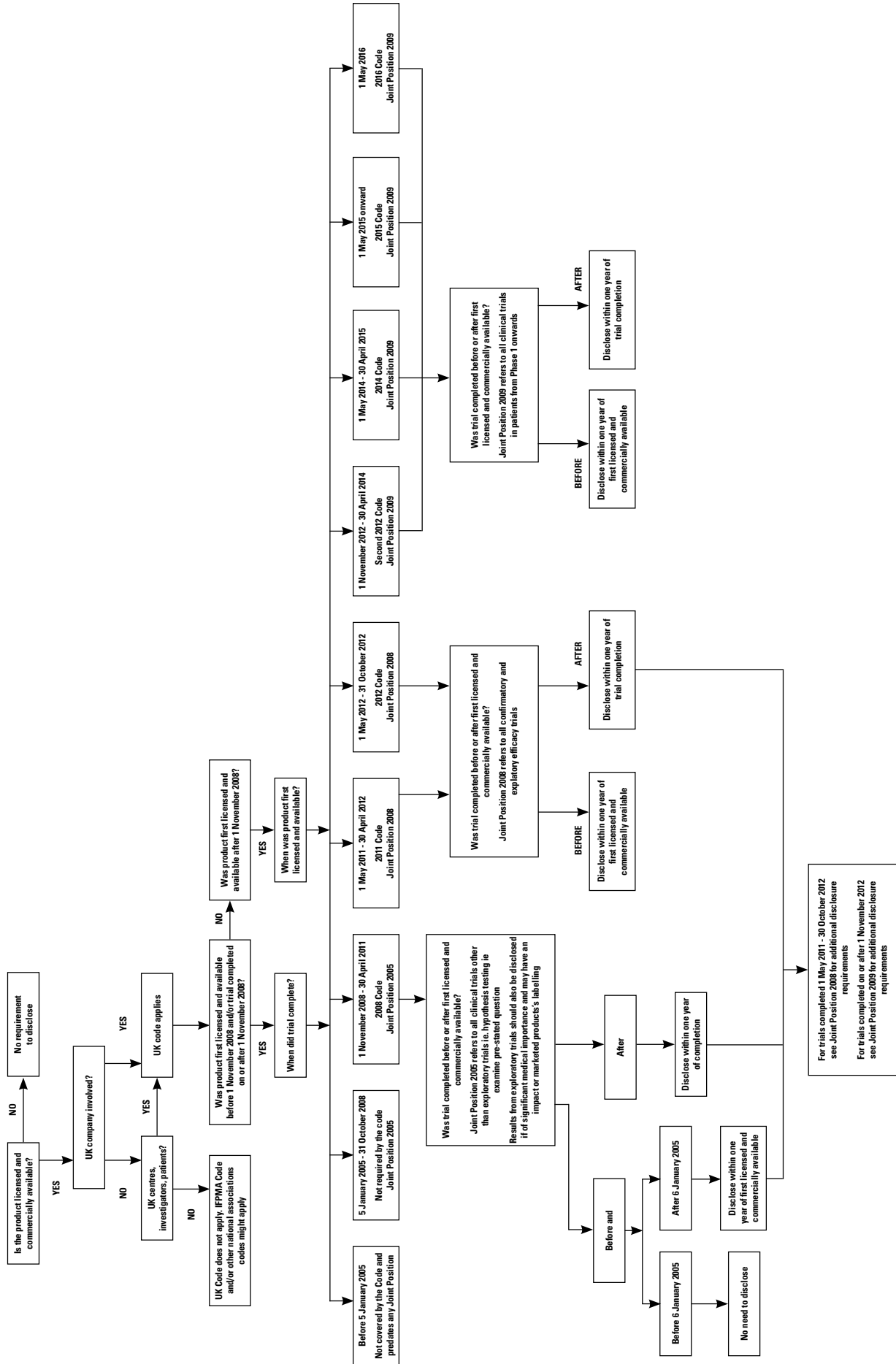
The Panel noted the CMRO publication in that one evaluable Phase I trial had not been disclosed within the 12 month timeframe. The disclosure percentage at 12 months measured from the later of the first date of regulatory approval or trial completion date was 88%. The disclosure percentage at 31 July 2015 of trials completed by the end of July 2015 was 88%. A footnote (company communication) stated that the undisclosed phase I trial was originally out of scope of disclosure requirements and results would be posted on EudraCT.

The Panel noted Bayer's submission that the trial in question (NCT00667537) was conducted in the UK on 6 patients to explore the bio-distribution, pharmacokinetics, and dosimetry of radium 223; it was neither a confirmatory clinical trial nor an exploratory efficacy trial and it completed on 3 December 2008.

The Panel noted Bayer's interpretation of the 2009 Joint Position which stated 'Additional trials that fall within the scope of this revised Joint Position and are initiated 6 months after the publication date of this Joint Position should be included in a public clinical trial registry'. It was Bayer's understanding that the trial in question (NCT00667537) qualified as an 'additional trial' under the 2009 Joint Position as it was not required to be disclosed under the 2008 Joint Position and that 'additional trials' were only subject to disclosure requirements if the trial was initiated [emphasis added] 6 months after the publication of the 2009 Joint Position. In the Panel's view, Bayer had mixed up requirements regarding clinical trial registries with those of clinical trial results databases. The complaint related to the disclosure of clinical trial results. The 2009 Joint Position clearly stated that the posting

Decision Tree

Updated Decision tree developed by the Panel



of clinical trial results should occur in compliance with the timelines and conditions defined in that Joint Position.

The Panel noted that Xofigo was first licensed and commercially available in May 2013 and this, as stated in the Panel's general comments above, was the trigger date for disclosure. In May 2013, the Second 2012 Code and thus the Joint Position 2009 applied which meant that for all licensed and commercially available medicines, all clinical trials from Phase I onward needed to be disclosed regardless of their completion date. Disclosure had to be within 1 year of the product first being licensed and commercially available or within one year of the trial's completion whichever was later.

The Panel noted on the information before it results from the trial should have been posted on a publicly accessible, internet-based clinical trials database

by May 2014. As this had not happened the Panel ruled a breach of Clause 13.1. The delay in disclosure meant that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted Bayer's submission that there had been four clinical publications drawn from the results of the trial from 2011 to 2015. Details were provided and all four clinical papers had also been linked to disclosure on clinicaltrials.gov and were publicly accessible with full trial results published online in July 2015 and in print in September 2015. In addition Bayer added the results synopsis to the EudraCT database in May 2016. As the data had been disclosed the Panel considered there was no breach of Clause 2 and ruled accordingly.

Complaint received **29 November 2016**

Cases completed **14 March 2017**

VOLUNTARY ADMISSION BY ASTELLAS EUROPE

Promotion of Betmiga to the public via social media and the Internet

Astellas Pharma Europe voluntarily admitted breaches of the Code in that three Betmiga (mirabegron) videos had been posted online by third parties. The videos included a number of product claims and thus Betmiga, a prescription only medicine, had been promoted to the public.

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 Astellas.

Astellas Pharma Europe explained that a member of staff received alerts relating to Betmiga content changes on the web when certain key words were detected. From an alert (1 November 2016) accessed on 2 November it appeared that two videos which contained multiple references to Betmiga and various product claims were available on the social media site, Vimeo. Medical colleagues and other staff were informed.

A third video, of an internal Astellas launch event, was then identified via a UK events awards website by the Astellas Pharma Europe compliance team on 14 November 2016.

Astellas Pharma Europe explained that videos 1 and 2 were initially created by a UK based agency contracted to provide support for the launch of Betmiga.

The objective of video 1 was to motivate and grow the interest of Betmiga for brand teams involved in the product launch. The video was for internal use only and at that time, could only be viewed on a secure, internal intranet. This secure site was password protected and only the brand manager/medical managers for Betmiga in EMEA affiliates had access to it.

The objective of video 2 was to demonstrate the quality of the Betmiga launch campaign for a pharmaceutical industry advertising awards submission. The agency submitted the video on its own behalf but received permission from Astellas Pharma Europe to do so. This video was intended to be viewed by the competition judges only.

Video 3 contained excerpts of an internal Betmiga launch event filmed by another third party agency which created video 3 specifically for another award.

Neither Astellas Pharma Europe nor the agency knew that videos 1 and 2 had been posted by an ex-employee of the agency to demonstrate past work experience for future employment opportunities.

Video 3 was found on an awards website where it appeared that it was linked to YouTube which hosted the video in an area that could only be accessed via a secure link rather than by searching YouTube or the wider internet. The secure link had

now been deleted. Astellas Pharma Europe could not confirm if the video was taken down at source as the agency no longer existed.

Given the above, Astellas Pharma Europe fully accepted that it had breached the Code as prescription only medicines were advertised to the public. In addition, it might have encouraged members of the public to ask their health professional to prescribe a specific prescription only product. Given that promotion of a prescription only medicine to the public was a serious matter, Astellas understood that the Panel might wish to consider whether high standards had been maintained and the requirements of Clause 2.

Detailed information from Astellas Pharma Europe appears below.

The Panel noted that Vimeo was an open access website and was not limited to professional use. The Panel considered that there was a difference between putting examples of pharmaceutical promotional material on an advertising agency's website, in a section clearly labelled in that regard and putting the same on Vimeo. The Panel considered that placing videos 1 and 2 on Vimeo promoted a prescription only medicine to the public and statements had thus been made in a public forum which would encourage members of the public to ask their health professional to prescribe Betmiga. Breaches of the Code were ruled including that high standards had not been maintained. The Panel noted that Astellas Pharma Europe had taken immediate steps to ensure removal of the material from the websites as soon as it was discovered. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such.

The Panel noted that video 3, which also contained claims for Betmiga, was filmed by a second agency, specifically for entry into an awards event in 2013 and contained excerpts of an internal Betmiga launch event. The agency had ceased trading. Astellas Pharma Europe knew of no correspondence requesting permission to create and use video 3 in the way described.

The Panel acknowledged that creative agencies would want to enter their work for awards and that as a result, examples of such work might appear, *inter alia*, on open access websites. The website in this case was directed specifically at the creative media and although anyone could access it, it was not aimed at the general public. In addition it appeared that whilst the video could be viewed from the event awards website, the video could only be accessed on YouTube via a secure link rather than by searching YouTube or the wider internet.

The Panel considered that in the particular circumstances of this case, Betmiga had not been promoted to the public. No breaches of the Code were ruled including no breach of Clause 2.

Astellas Pharma Europe Ltd (Astellas Pharma Europe) voluntarily admitted breaches of the Code in that three Betmiga (mirabegron) videos had been posted online by two third parties.

The videos included a number of product claims. The company considered that Betmiga, a prescription only medicine, had thus been promoted to the public. Betmiga was indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as might occur in adults with overactive bladder (OAB) syndrome.

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 Astellas.

VOLUNTARY ADMISSION

Astellas Pharma Europe explained that a member of staff received alerts relating to Betmiga when content changes on the web in relation to certain key words were detected. From an alert delivered on 1 November and accessed on 2 November 2016 it appeared that two videos which contained multiple references to Betmiga and various product claims were available on the social media site, Vimeo. Medical colleagues and other staff were informed.

The videos were entitled Manifesto (video 1) and an International launch campaign by a named third party (video 2). A third video, of an internal Astellas launch event, was then identified by Astellas Pharma Europe compliance team on 14 November 2016 via a UK event awards website. Video 3 was entitled Astellas Betmiga launch. All three videos and the transcript for video 1 were provided.

Background

Astellas Pharma Europe explained that videos 1 and 2 were initially created by a UK based agency contracted by Astellas Pharma Europe to provide support for the launch of Betmiga.

The objective of video 1 was to motivate and grow the interest of Betmiga for brand teams involved in the product launch. The video was for internal use only and was presented to internal marketing staff during a meeting of Astellas Europe, Middle East & Africa (EMEA) affiliate companies. At the time, it could only be viewed on a secure, internal only Betmiga intranet hub which was a repository of Betmiga material for EMEA affiliates. This secure site was password protected and only the brand manager/medical managers for Betmiga in EMEA affiliates had access. This video was not approved in Zinc as it was for internal use only. It was not for use with representatives or for training of any kind and was not intended to be used externally with health professionals or other relevant decision makers.

The objective of video 2 was to demonstrate the quality of the Betmiga launch campaign for a pharmaceutical industry advertising awards submission. The agency submitted the video on its own behalf but received permission from Astellas Pharma Europe to do so. This video was intended to be viewed by the competition judges only. The video was not approved in Zinc.

Video 3 contained excerpts of an internal Betmiga launch event. The launch event was filmed by a second third party agency which created video 3 specifically for entry into an event awards in 2013. However, the agency had ceased trading and Astellas Pharma Europe could not confirm its objective. Astellas Pharma Europe staff were unaware of any correspondence requesting permission from Astellas Pharma Europe to create and use video 3 in the ways described.

A brief description of the videos which included medicine related text/voiceover script only was provided as follows:

a) Video 1 (1 minute 53 seconds)

A male actor displays multiple images for the majority of video. Towards the end of the video the following voiceover and imagery was presented:

'We make more than just medicines. We make change happen for patients whose needs aren't being met ... all around the world ... and soon when we launch Betmiga ... we will be making a bit of history too... this is an entirely new approach to Overactive Bladder the first in 30 years ...'

A screen shot follows which contained the Betmiga brand and text which said; 'countdown to launch'.

b) Video 2 (2 minutes 9 seconds)

Opening screenshot with text: it's time to think of Betmiga- international launch by [agency name]'. There then followed screen shots of Betmiga marketing materials, shots of booths, congress and shots of an evening dinner. Much of the material stated that Betmiga was a new product – as it was at the time of launch in 2013.

c) Video 3 (35 seconds)

This video included snapshots of the internal Astellas audience, and a large cinematic screen could be seen in full view. The screen displays the following text at a specific timepoint in the video:

'Betmiga has a unique product profile which makes a real difference to patient's lives'

The following text appeared on the events awards website page in the same setting as the video but was not present in the video:

'Betmiga has redefined the competitive landscape in OAB'.

Astellas Pharma Europe submitted that it appeared that videos 1 and 2 were available on Vimeo, a video-sharing website (similar to YouTube) on which users could upload, share and view videos. The website was freely available for the public to use.

When it discovered videos 1 and 2 on Vimeo, Astellas Pharma Europe contacted its agency as part of its investigation. Neither Astellas Pharma Europe nor the agency knew that these videos had been posted. Upon further investigation it was noted that the video uploader was an ex-employee of the agency who when contacted confirmed his/her responsibility for the postings. The videos appeared to have been posted in order to demonstrate past work experience for future employment opportunities and access was not password protected. On learning of the error, the ex-employee apologised and immediately removed the videos. Astellas Pharma Europe confirmed that the videos were no longer available on Vimeo from 2 November 2016. Neither Astellas Pharma Europe nor its agency had received any request or correspondence from the ex-employee regarding the placing of these videos on the internet.

By taking the videos with him/her when he/she left the agency, the ex-employee had breached the terms of his/her employment contract and the agency had asked its ex-employee to destroy all copies of videos 1 and 2.

The exact dates that videos 1 and 2 were first posted to Vimeo were unknown. However, on 2 November 2016, Vimeo generated text stated that it was posted '3 years ago'. The agency confirmed that the individual had already left its employ when the videos appeared to have been first posted to Vimeo.

The agency was disappointed and assured Astellas Pharma Europe that as soon as rare situations such as this came to its attention, it acted swiftly to resolve them.

Video 3 was found on a UK event awards website. It appeared that the awards website did not receive or host the video itself but rather linked to YouTube which hosted the video in a secure section of that site ie an area of the site that could only be accessed via a secure link rather than by searching YouTube or the wider internet. The video itself could be viewed from the awards website.

Following the discovery of video 3, the awards body confirmed that the second agency had sent the link to the video. Astellas Pharma Europe noted that the agency no longer existed so it could not verify any further information. According to YouTube generated text, the video was posted in September 2013. Video 3 was removed from the awards website in November 2016 following a request from Astellas Pharma Europe.

As noted above, Astellas Pharma Europe could not access the video directly via YouTube as it was only available via a secure link that had now been deleted. Astellas Pharma Europe could not confirm if the video was taken down at source as the agency no longer existed.

Agency Oversight

As part of the investigation in to these issues, Astellas Pharma Europe reviewed:

- The terms of engagement between Astellas Pharma Europe and the two agencies
- The compliance of the agency to terms of engagement (including training procedures)
- Astellas internal supplier vetting procedures.

Contract

Agency responsible for videos 1 and 2

Astellas Pharma Europe had a current master services agreement (MSA) with the agency, effective from January 2015. The previous MSA was effective between January 2012 and January 2014.

Both MSAs stipulated that:

- The agency complied with all applicable laws and codes including the ABPI Code
- The agency ensured its staff had the proper skills, expertise, knowledge, training and background necessary to accomplish the services required of them
- Astellas Pharma Europe did not expect or intend the agency to recommend or promote Astellas' pharmaceutical products.

In addition, the agency advised on 3 November 2016 that the standard agency employee contract contained two clauses relating to client confidentiality and intellectual property rights. These included sub-clauses which forbade the disclosure of client confidential information both during and post-employment at the agency. On the same date, the agency also advised that in their exit interviews, employees leaving the company were reminded of these clauses and specifically that their responsibilities continued after termination of their employment. The agency noted that, although it had appropriate protocols and training procedures in place, human error could occur as demonstrated in this case.

Agency training

The agency advised Astellas Pharma Europe on 7 November 2016 that it was standard practice that all new employees were required to complete the e-learning module provided by the PMCPA, regardless of prior experience or discipline. This formed part of their induction and must be completed within the first month of employment. Internal training might also be provided for major changes to the Code. All training was logged in individual employee continuing professional development (CPD) diaries on the Institute of Practitioners in Advertising (IPA) website. It did not have a record of the specific training received by the ex-employee. The agency itself held the Platinum Award for CPD for the last three years; in 2015 it recorded 3061 hours of training and 96% of employees did more than the industry average. A total of 48% of employees logged over 100 hours of training.

Agency vetting and monitoring

Astellas Pharma Europe submitted that it now had a process whereby third party suppliers were vetted in accordance with the Astellas Pharma Europe standard operating procedure (SOP) Working with suppliers (SOP-1479). This SOP required that a summary of key Astellas Pharma Europe SOPs (Rules of Engagement) was sent to all suppliers providing services that fell within the scope of the Code, and certain suppliers were also required to complete a supplier questionnaire designed to elicit information about Astellas Pharma Europe key compliance requirements. If this questionnaire was not satisfactorily completed, then further action was taken. Such actions might include training, audits of the supplier or removal from the list of approved suppliers to Astellas. This SOP was put in place in August 2016, the agency received a copy of the Rules of Engagement and recently completed the supplier questionnaire. Further clarification was being sought from the agency about its answers to the questionnaire.

Agency responsible for video 3

Agency Contract

Astellas Pharma Europe had an MSA with the agency from December 2012 to December 2015. The MSA stipulated that:

- The agency agreed to perform the due services in compliance with the applicable law, the Codes and good business ethics
- the agency ensured that any personnel assigned to provide the services or to create or deliver the project material would have the proper skills, expertise, knowledge, training and background necessary to accomplish the services
- Astellas Pharma Europe did not expect or intend the agency to recommend or promote Astellas' products.

However, as this agency no longer traded, additional information, including that about its training and procedures, was not available.

Given the above, Astellas Pharma Europe fully accepted that it had breached Clause 26.1 as prescription only medicines were advertised to the public in all three situations.

In addition, Astellas Pharma Europe submitted that as the promotional material was accessible to the public it might have encouraged members of the public to ask their health professional to prescribe a specific prescription only product. Astellas therefore acknowledged a breach of Clause 26.2.

Given that promotion of a prescription only medicine to the public was a serious matter, Astellas Pharma Europe understood that the Panel might wish to consider the requirements of Clauses 9.1 and 2.

Astellas Pharma Europe confirmed that it did not provide permission for videos 1 and 2 to be placed on the internet. Available Astellas Pharma Europe

staff who had worked on Betmiga, did not know about video 3 and so could not confirm whether Astellas Pharma Europe had given permission for video 3 to be placed on the internet.

Astellas Pharma Europe took immediate steps to ensure removal of the material from the websites as soon as it was discovered. Whilst Astellas Pharma Europe did not consider there was any attempt or intention on its part to advertise to the public it fully recognised that under the Code it was responsible for any acts or omissions of its third party suppliers.

When writing to Astellas Pharma Europe, the Authority asked it to respond in relation to Clauses 26.1, 26.2, 9.1 and 2.

RESPONSE

Astellas Pharma Europe submitted that it had no further comments in relation to the requirements of Clauses 26.1, 26.2, 9.1 or 2 but provided USB sticks with the electronic versions of all enclosures including the three videos at issue.

PANEL RULING

The Panel noted Astellas Pharma Europe's submission that three videos relating to Betmiga had appeared on the internet. Videos 1 and 2 had been created for Astellas Pharma Europe by a UK based agency and both made claims about Betmiga. Video 1 was a motivational piece for internal use only and video 2 had been created to demonstrate the quality of the Betmiga launch campaign in an advertising awards submission. Both videos had been posted on Vimeo, a video-sharing website, similar to YouTube and available for the public to use. It appeared that neither Astellas nor the agency knew that either video had been posted on Vimeo; investigation showed that both had been posted by an ex-employee of the agency in order to demonstrate past work experience for future employment opportunities. Taking the videos when leaving the agency was a breach of his/her employment contract with the agency. Astellas Pharma Europe had taken immediate steps to ensure removal of the material from the website as soon as it was discovered.

The Panel understood that individuals might want to be able to show examples of their work. The Panel noted that both versions of the MSA between Astellas Pharma Europe and its agency stipulated that the agency must comply with all applicable laws and codes including the ABPI Code; ensure that staff members had the proper skills, expertise, knowledge, training and background necessary to accomplish the services required of them and that Astellas Pharma Europe did not expect or intend the agency to recommend or promote Astellas' pharmaceutical products. In addition, the Panel noted Astellas Pharma Europe's submission that the standard agency employee contract contained two clauses relating to client confidentiality and intellectual property rights. These included sub-clauses which forbade the disclosure of client confidential information both during and post-employment at the agency. The agency also

advised that in its exit interviews, employees leaving the company were reminded of these clauses specifically their responsibilities which continued after termination of their employment. Nonetheless, it was an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf. Pharmaceutical companies had to ensure that prescription only medicines were not advertised to the public. The Panel considered that Astellas Pharma Europe had been let down by an ex-employee of the third party working on its behalf.

The Panel noted that Vimeo was an open access website and was not limited to professional use. The Panel considered that there was a difference between putting examples of pharmaceutical promotional material on an advertising agency's website, in a section clearly labelled in that regard and putting the same on Vimeo. The Panel considered that placing videos 1 and 2 on Vimeo promoted a prescription only medicine to the public. A breach of Clause 26.1 was ruled. The Panel considered that statements had thus been made in a public forum which would encourage members of the public to ask their health professional to prescribe Betmiga. A breach of Clause 26.2 was ruled. The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel noted that Astellas Pharma Europe had taken immediate steps to ensure removal of the material from the websites as soon as it was discovered. The Panel noted its rulings and comments above and did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

The Panel noted that video 3, which also contained claims for Betmiga, was filmed by a second agency specifically for entry into an awards event in 2013 and contained excerpts of an internal Betmiga launch event. The Panel noted Astellas Pharma Europe's

submission that the agency had ceased trading and so it could not be asked to confirm its objective. Astellas Pharma Europe staff members knew of no correspondence requesting permission from Astellas Pharma Europe to create and use video 3 in the way described. The Panel noted that the MSA between Astellas Pharma Europe and its second agency imposed closely similar requirements to those imposed between it and the first agency.

The Panel acknowledged that creative agencies would want to enter their work for awards and that as a result, examples of such work might appear, *inter alia*, on open access websites. The website in this case was directed specifically at the creative media and although anyone could access it, it was not aimed at the general public. In addition it appeared that whilst the video could be viewed from the event awards website, the video itself was hosted in a secure section of YouTube which could only be accessed via a secure link rather than by searching YouTube or the wider internet. The Panel noted that the secure link had now been deleted but Astellas Pharma Europe could not confirm if the video was taken down at the source as the agency no longer existed.

The Panel noted that the organisation was a network for marketing agencies and the annual event awards allowed event organisers, promoters, etc to showcase events they had organised. The Panel further noted that the video could only be viewed on a secure part of YouTube and considered that in the particular circumstances of this case, Betmiga had not been promoted to the public. No breach of Clause 26.1 and 26.2 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled. The Panel noted its rulings above and consequently ruled no breach of Clause 2.

Voluntary admission received	5 December 2016
Case completed	3 April 2017

EX-EMPLOYEE v GLAXOSMITHKLINE

Material on internal hosting server

A former GlaxoSmithKline employee who no longer worked in the pharmaceutical industry, complained about an online cost calculator prepared for Relvar Ellipta (fluticasone furoate/vilanterol) by GlaxoSmithKline UK, which the complainant found using the search term 'GSK cost calculator'. The complainant alleged breaches of the Code as the page at issue did not include prescribing information, the non-proprietary name, an adverse event reporting statement or a black triangle to denote that additional monitoring was required. He/she alleged that the material promoted prescription only medicines to the public and that high standards had not been maintained.

The page at issue promoted Relvar Ellipta 92/22mcg and claimed it was the cheapest.

The detailed response from GlaxoSmithKline is given below.

The Panel noted GlaxoSmithKline's explanation that in August 2016 that search engines were searching the company's internal hosting servers and that this was quickly resolved. On receipt of this complaint GlaxoSmithKline became aware that the fix put in place in August 2016 no longer prevented such searches. This appeared to be due to the continuous evolution of search engine technology; search engines were not obliged to share publicly when updates were made.

The Panel noted GlaxoSmithKline's submission that if the page of the website was accessed in the manner intended ie not via the internal hosting server but via the health professional site (hcp.gsk.co.uk) be that directly, via links from other materials or by searching for 'Relvar costs', 'Relvar cost calculator', 'GSK medicines' or similar, then all the obligatory information was available. It was clear to visitors that the site was for health professionals rather than the public which had its own site.

The Panel was sympathetic to the company's submission and considered that it had taken reasonable steps to ensure that its internal hosting server was not accessed by search engines. It also noted the submission regarding search engines tailoring search results to the individual user and that the complainant was an ex-employee with specialist knowledge. Although the Panel was concerned that material that did not appear to meet the requirements of the Code could be accessed, it seemed reasonable in this case to consider it as material on an internal company hosting server rather than that which was intended for UK health professionals. The Panel decided that the lack of obligatory information when searching on the internal company hosting server did not amount to breaches of the Code as alleged. It considered that health professionals would be supplied with

the requisite information including the prescribing information, the non-proprietary name, the adverse event statement and the black triangle when using the websites for external use. It did not consider that the circumstances amounted to advertising a prescription only medicine to the public or that the company had failed to maintain high standards. No breaches of the Code were ruled.

A former GlaxoSmithKline employee who no longer worked in the pharmaceutical industry, complained about an online cost calculator (ref UK/FFT/0232/15(1), date of preparation, April 2016) for Relvar Ellipta (fluticasone furoate/vilanterol) prepared by GlaxoSmithKline UK Limited. Relvar Ellipta was a combined inhaled corticosteroid (ICS) and long-acting beta agonist (LABA) indicated for the treatment of chronic obstructive pulmonary disease (COPD).

COMPLAINT

The complainant stated that a search using the term 'GSK Cost calculator' on two search engines produced results top and second top hits to a page (address provided).

This page promoted Relvar Ellipta 92/22mcg and claimed it was the cheapest ICS/LABA for COPD patients. The complainant alleged breaches of the following:

Clause 4.1 – There was no prescribing information.

Clause 4.3 – The non-proprietary name must appear immediately adjacent to the first or most prominent display of the brand name.

Clause 4.9 – There was no prominent adverse event statement.

Clause 4.10 – There was no black triangle to denote that additional monitoring was required.

Clause 9.1 – Promotion of medicines direct to the public was a failure to maintain high standards.

Clause 26.1 – Promoting directly to the public. There was no request, as was normal for readers to confirm they were health professionals or other relevant decision makers. There was also a link from this page to contact GlaxoSmithKline representatives to discuss the financial impact of the wider Ellipta portfolio.

RESPONSE

GlaxoSmithKline stated that the Relvar Ellipta Cost Calculator was developed to provide health professionals treating COPD patients with a simple calculator to explore the savings opportunity with Relvar Ellipta 92/22 compared with other ICS/LABA options. Health professionals could input the number of COPD patients being treated by an ICS/LABA within their practices or areas and then select what their alternative ICS/LABA option would be. The potential monthly budget impact with Relvar 92/22 was then

calculated on the website. If customers wanted to explore savings opportunities with Ellipta in more detail then there was a link below the calculator to build on this by contacting a GlaxoSmithKline health outcomes consultant. Appropriate disclaimers were also provided around costs and savings figures being for illustrative purposes only and were subject to assumptions outlined.

Representatives had not been briefed to use the Relvar Ellipta Cost Calculator with customers or to direct customers to it on the website; instead they had a similar but separately approved cost calculator on their iPads which they were trained and accredited to use. A Relvar price reduction email notification had previously been sent to all customers who subscribed to receive emails through third party providers on 14 July 2016. This notification contained a link to the Relvar Ellipta Cost Calculator on the GlaxoSmithKline website.

Background to the health professional website

GlaxoSmithKline stated that it had two websites: one for UK health professionals (hcp.gsk.co.uk) and one for members of the public (public.gsk.co.uk). The objective of the health professional website was to support the appropriate and rational use of GlaxoSmithKline prescription only medicines and vaccines through the provision of high-quality, up-to-date information aligned to customer needs and GlaxoSmithKline business. All content on the health professional site was certified as promotional. The health professional website provided up-to-date GlaxoSmithKline product and therapeutic information, patient and professional resources and options to contact GlaxoSmithKline medical information teams. It also allowed health professionals to register for emails, sign up for webinars, order samples and patient materials and have a virtual chat with a GlaxoSmithKline medical information team member.

Metadata was data that described other data. In the case of a website, the metadata associated with a particular webpage provided information to search engines about the content on that webpage. Metadata for all webpages on the health professional website was approved and certified with the content before any content went live. GlaxoSmithKline used a standard format to create compliant metadata. Page title always included product and generic name, therapy area, company name (GlaxoSmithKline UK Pharma) and intended audience (health professionals). Meta description was a simple paragraph that outlined the content available on the page. Meta keywords were the search phrases/ words that users might enter in a search engine to obtain the information they were looking for.

Background to the certification process for website content

The certification process in Zinc and 'build' process for webpages on the GlaxoSmithKline website was as follows:

Step 1: A job bag was created in Zinc for the webpage.

Step 2: A pdf of the webpage and the metadata for the webpage were approved by the nominated medical signatory.

Step 3: The webpage was then built on a staging website that was password protected.

Step 4: The certification round was then started for the job bag in Zinc. The job bag item, screen shot of the webpage on the staging website and a link to the staging website were sent to the nominated medical signatory. The medical signatory checked that all 3 (job bag item, screenshot of staging website and the webpage on the staging website) were the same in both content and format, checked the metadata, checked that the 'pop-up' appeared requesting visitors to confirm they were health professionals, checked that all links on the webpage in the staging website were correct and that all necessary disclaimers appeared.

Step 5: The medical signatory certified the final form of the webpage if all the above checks were correct.

Step 6: The certified webpage was published to live on the website with its metadata.

There were limited instances where interactive content appeared on the health professional website. The way in which this interactive content was designed was such that the content was uploaded to the GlaxoSmithKline internal hosting server and this content was pulled into the relevant page on the website through an 'I-frame'. The webpage on the website containing the I-frame also contained all the mandatory regulatory and compliance information.

In this specific example relating to the Relvar Cost Calculator, when the item was accessed in the way it was intended (on the health professional website) the following information was displayed on the webpage and fulfilled Code requirements: a link to the most up-to-date prescribing information; the non-proprietary name appeared immediately adjacent to the first mention of the brand name; a prominent adverse event statement and a black triangle at the first mention of the brand name. Moreover visitors to this website were immediately asked to confirm by way of a pop-up that they were health professionals, at the top of the webpage the intended audience was clearly stated 'For UK Healthcare Professionals' as well as the following statement 'Not a healthcare professional? Visit our public site [link to the public site]'. The certified metadata for the health professional website webpage on which the Relvar Cost Calculator was provided.

The internal hosting server was maintained by GlaxoSmithKline's global digital platforms department. This server was intended and used solely as a content storage repository for any interactive content that appeared on the website. It was not promoted by GlaxoSmithKline and contained no metadata. GlaxoSmithKline understood that search engines could not search or 'crawl' and therefore display content that sat on GlaxoSmithKline's internal hosting server.

Sequence of events and actions taken

In August 2016 GlaxoSmithKline's digital team searched for 'Relvar Cost Calculator' in Google and discovered that results from the internal hosting server were being displayed. This was the first time that the company realised that search engines could crawl GlaxoSmithKline's internal hosting server. The GlaxoSmithKline global digital platforms department was contacted immediately and the next day reported that the issue had been resolved. GlaxoSmithKline UK checked this by searching for 'Relvar Cost Calculator' and confirmed on 17 August 2016 that the internal hosting server no longer appeared in the search results.

When GlaxoSmithKline received this complaint it became aware the issue had reoccurred and that the fix put in place in August 2016 would not prevent search engines from being able to re-crawl its internal hosting server. After further technical investigation by GlaxoSmithKline's global digital platforms department it had now resolved the issue again and to ensure that it would not reoccur it had:

- Blocked all content that sat on GlaxoSmithKline's internal hosting server from appearing in search engine results through the search engine's 'webmaster tool'. This involved instructing the search engines not to display historical search results that previously appeared related to this URL.
- Proactively inserted a line of code into both the content source code and search engine's webmaster tool which would block search engines from being able to crawl any new content hosted on this URL in the future.

Following the completion of the above, GlaxoSmithKline checked to ensure the Relvar cost calculator and any other content hosted on the internal hosting server no longer appeared in search results. This was confirmed the day after receiving the complaint. GlaxoSmithKline had now also included a new check into its regular quality control monitoring for the health professional website to ensure that any content on the internal hosting server could not be found in search engine results.

GlaxoSmithKline had always used the most up-to-date technical measures to prevent its internal hosting server from being crawled by search engines. However, search engines were continuously evolving their search technology and search algorithms. As they were not obliged to share publicly when and how they updated their search technology and search algorithms, it was theoretically possible that in the future GlaxoSmithKline might not know about a new search engine generated issue as soon as it happened. This was out of GlaxoSmithKline's control. However, as demonstrated by the sequence of events above, as soon as it became aware of such an issue it fulfilled its responsibilities as the website owner by taking immediate, remedial actions. Furthermore, GlaxoSmithKline now had a search engine results monitoring plan in place so when it became aware of such an issue in the future it would work to resolve it immediately.

Consideration for potential breaches of Clauses 4.1, 4.3, 4.9, 4.10, 9.1 and 26.1

GlaxoSmithKline submitted that the 'GlaxoSmithKline Cost Calculator' was a very specific search term that would not usually be used by a health professional or member of the public seeking general information on Relvar. Furthermore, searches for 'Relvar costs', 'Relvar Cost Calculator', 'GSK medicines' or similar would direct the searcher to the appropriate webpages on the professional or public websites. To find content on the internal hosting server took specialist knowledge which the complainant might have as a former GlaxoSmithKline employee.

GlaxoSmithKline noted that search results could differ for individuals as explained by Google itself:

'Google search results are different on different computers. There are many factors that affect the Google search results you see. Google seeks to provide the best results for individual users. This means that they want and expect search results to be different from person to person and that people searching in the same office may see different search results.'

When accessing the document in the manner in which it was intended, all obligatory information was available (Clauses 4.1, 4.3, 4.9, 4.10). In addition, this information was only available to health professionals; the public was redirected to an appropriate website (Clause 26.1). As such, GlaxoSmithKline maintained high standards at all times for all digital content within its control (Clause 9.1). GlaxoSmithKline therefore refuted any breaches of the Code.

In view of the above, GlaxoSmithKline submitted this anomalous and temporary, technical issue had now been resolved and that the Relvar Cost Calculator content, when accessed as intended on the health professional website, had always complied with the Code and had not prejudiced patient safety.

PANEL RULING

The Panel noted the explanation from GlaxoSmithKline regarding search engines. The company used an internal hosting server and in August 2016 it became aware that search engines were searching the company's internal hosting servers. This was quickly resolved. On receipt of the complaint GlaxoSmithKline became aware that the fix put in place in August 2016 no longer prevented search engines from searching the company's internal hosting server. This appeared to be due to the continuous evolution of search engine technology and that search engines were not obliged to share publicly when updates were made to technology and algorithms. In these circumstances it could be considered unreasonable to expect companies to continuously monitor search engines as some search engine activities appeared to be outside the company's control. The Panel noted that GlaxoSmithKline now had a monitoring plan to ensure that content on the internal hosting server could not be found in search engine results.

The Panel noted GlaxoSmithKline's submission that if the page of the website was accessed in the manner intended ie not via the internal hosting server but via the health professional site (hcp.gsk.co.uk) be that directly or via links from other materials or by searching for 'Relvar costs', 'Relvar cost calculator', 'GSK medicines' or similar, all the obligatory information was available. It was clear to visitors that the site was for health professionals rather than the public which had its own site.

The Panel was sympathetic to the company's submission and considered that taking all the circumstances into account the company had taken reasonable steps to ensure that its internal hosting server was not accessed by search engines. It also noted the submission regarding Google's position in tailoring search results to the individual user and that the complainant was an ex-employee. Although the Panel was concerned that material that did not appear to meet the requirements of the Code could be accessed, it seemed reasonable in this case

to consider it as material on an internal company hosting server rather than that which was intended for UK health professionals. The Panel decided that the lack of obligatory information when searching on the internal company hosting server did not amount to breaches of the Code as alleged. It considered that health professionals would be supplied with the requisite information including the prescribing information, the non-proprietary name, the adverse event statement and the black triangle when using the websites for external use. It therefore ruled no breach of Clauses 4.1, 4.3, 4.9 and 4.10. It did not consider that the circumstances amounted to advertising a prescription only medicine to the public and therefore ruled no breach of Clause 26.1. Given its rulings and the specific circumstances of this case the Panel did not consider that the company had failed to maintain high standards. No breach of Clause 9.1 was ruled.

Complaint received **19 December 2016**

Case completed **3 February 2017**

ANONYMOUS, NON-CONTACTABLE EX-REPRESENTATIVE v UCB

Promotion of Naloxone Minijet

An anonymous, non-contactable ex-representative of UCB Pharma alleged that he/she was asked to promote Naloxone Minijet Injection off licence.

The complainant explained that naloxone was a generic product and many other companies marketed it. UCB's naloxone had a narrow indication mainly for the treatment of respiratory depression induced by natural and synthetic opioids. The complainant submitted, however, that naloxone marketed by Martindale had a broader indication in that it was licensed for complete and partial reversal of opioid depression and not only the respiratory depression associated with it.

The complainant submitted that in 2012 the Advisory Council on the Misuse of Drugs recommended that take-home naloxone should be made more widely available. Public Health England also produced guidance on promoting the wider availability of naloxone to reduce overdose deaths from heroin and the like.

Under this guidance, naloxone could be supplied to anyone who: currently used illicit opiates such as heroin; received opioid substitution therapy; left prison with a history of drug use or previously used opiates (to protect in the event of relapse). Under this guidance, with the agreement of someone to whom naloxone could be supplied, it could also be provided to their family members, carers, peers and friends. Other UK nations also came up with similar guidelines.

The complainant stated that UCB representatives were asked to promote take-home naloxone Minijets to prescribers, pharmacists and budget holders. Representatives were told by their line manager that by doing this the sales of UCB's product would increase which would easily help to achieve targets. The complainant also referred to a poster which was produced for a company sales meeting by one of his/her colleagues in the Minijets team.

The complainant was concerned that although government agencies published clear guidelines on naloxone take-home, UCB's naloxone was not licensed for this indication but representatives were asked to actively promote it in this indication for financial gains. The company asked representatives to pursue a course of action which was in breach of the Code. The complainant alleged that the company and senior managers did not maintain high standards because the poster was presented and commended at a national sales conference and no one picked it up. There were also patient safety issues in keeping and properly administering an injectable as the complainant did not remember any training support for the same. The complainant

alleged that UCB acted in a highly unprofessional way and that this activity was known to many senior managers and had happened for a long time; if unchecked these types of activities could bring discredit to the whole industry.

The complainant noted that UCB had recently sold the entire Minijets product portfolio to a third party but in his/her view a company could be reprimanded for its historical wrong doings.

The detailed response from UCB is given below.

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 the parties' interpretation of the licensed indication for naloxone Minijet differed.

The Panel noted that naloxone Minijet 400mcg/ml was indicated for the treatment of respiratory depression induced by natural or synthetic opioids. The medicine was presented as prefilled syringes of 1 or 2mls (400 or 800mcg). The usual initial adult dose was 400 - 2000mcg every 2 to 3 minutes if necessary. If no response was observed after the administration of 10mg then the depressive condition might be caused by a medicine or a disease process not responsive to naloxone. Treatment of overdose might thus require the use of a number of Minijet syringes. Use of naloxone Minijet in the non-medical setting was not referred to in the SPC and in that regard it did not appear that the product was specifically intended or packaged for such use and so non-medical responders might find it more difficult to use than other forms of naloxone, particularly Martindale's Prenoxad. Nonetheless, the Panel did not consider that take-home use of naloxone Minijet was off licence *per se* as alleged. No breach of the Code was ruled.

The Panel disagreed with UCB's submission that the poster was not briefing material for the representatives; it had been presented at an internal UCB conference with the purpose of sharing best practice. The Panel assumed that as the poster had been developed by a representative, it mirrored what he/she considered was acceptable to claim about naloxone Minijet. The Panel noted that the poster did refer to training family friends, however it was extremely concerned that the title of the poster stated, without qualification, 'Minijet team Naloxone: How a Take Away Can Save

Hundreds of Lives’. There was no reference cited in support of the statement and no indication as to the time period over which hundreds of lives would be saved by naloxone Minijet. Additional text stated that an overdose could now be referred to in the present tense: ‘I have a friend who [overdosed] last week. Naloxone did that’ which implied that naloxone saved the lives of everyone who overdosed. The poster also stated that naloxone Minijet provided the ideal offering, and in that regard the Panel noted its comments above about Prenoxad. The poster also stated that naloxone Minijet had the potential to dominate the market and that the dose of the competitor was too high. The Panel considered that the content of the poster was such that it advocated claims for take-home naloxone Minijet, or the competitor, which were likely to be in breach of the Code. A breach of the Code was ruled. Overall the Panel considered that, given its content, the production of the poster showed poor judgement and in that regard it ruled a breach of the Code as it considered that high standards had not been maintained.

The Panel noted its rulings and comments above and although it had some concerns, it did not consider that the circumstances were such as to rule a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

A non-contactable, ex-representative complained about the promotion of Naloxone Minijet injection by UCB Pharma Ltd alleging that he/she was asked to promote the medicine off licence.

COMPLAINT

The complainant stated that he/she joined UCB relatively new to the industry and not very well versed on the Code. Since leaving the company and after working in the industry for a few years now, he/she had a much broader understanding of the Code. With his/her current knowledge, the complainant was horrified about what UCB asked its representatives to do and being a conscientious person, he/she was now complaining.

The complainant explained that he/she joined UCB as a representative in the mature products business unit which had a product range called IMS, consisting of several injectable products for emergency use. One of the products, naloxone, was indicated for:

‘the treatment of respiratory depression induced by natural and synthetic opioids, such as codeine, diamorphine, levorphanol, methadone, morphine, concentrated opium alkaloid hydrochlorides and propoxyphene. It is also useful for the treatment of respiratory depression caused by opioid agonist/antagonists nalbuphine and pentazocine. Naloxone is also used for the diagnosis of suspected acute opioid overdose.’ (emphasis added).

UCB’s naloxone was indicated mainly for the treatment of respiratory depression induced by various agents. Naloxone, however, was a generic

product and many other companies marketed it, including Martindale whose product was indicated for:

‘the complete or partial reversal of opioid depression, including mild to severe respiratory depression induced by natural and synthetic opioids, including dextropropoxyphene, methadone and certain mixed agonist/antagonist analgesics: nalbuphine and pentazocine. It may also be used for the diagnosis of suspected acute opioid overdosage. Naloxone may also be used to counteract respiratory and other CNS depression in the new-born resulting from the administration of analgesics to the mother during childbirth.’(emphasis added).

The complainant submitted that the Martindale indication was broader than UCB’s naloxone and was for complete and partial reversal of opioid depression and not only the respiratory depression associated with it, which was the narrow indication for UCB’s naloxone.

Besides indications, there were other differences in the qualitative and quantitative composition of the various naloxones available in the market.

The complainant submitted that in 2012 the Advisory Council on the Misuse of Drugs recommended that take-home naloxone should be made more widely available. Public Health England also produced guidance for local authorities and local partners on promoting the wider availability of naloxone to reduce overdose deaths from heroin and the like.

Under this guidance, naloxone could be supplied to anyone who: currently used illicit opiates such as heroin; received opioid substitution therapy; left prison with a history of drug use or previously used opiates (to protect in the event of relapse).

Under this guidance, with the agreement of someone to whom naloxone could be supplied, it could also be provided to their family members, carers, peers and friends. Other UK nations also came up with similar guidelines.

The complainant stated that UCB representatives who promoted the Minijets Naloxone range were asked to promote take-home naloxone to prescribers, pharmacists and budget holders. Representatives were told by their line manager that by doing this the sales of UCB’s product would increase and that take-home naloxone would easily help to achieve targets. This was mentioned at team meetings and via emails. The complainant also referred to a poster which was produced for a company sales meeting by one of his/her colleagues in the Minijets team; the poster was highly commended.

The complainant stated that his/her concerns were that although government agencies published clear guidelines on naloxone take-home, UCB’s naloxone was not licensed for this indication but representatives were asked to actively promote it in this indication for financial gains, in breach of Clause 3. The company asked representatives to pursue a course of action which was in breach of Clause

15.9. The complainant alleged that the company and senior managers did not maintain high standards because the poster was presented and commended at a national sales conference and no one picked it up. There were also patient safety issues in keeping and properly administering an injectable as the complainant did not remember any training support for the same. The complainant alleged that UCB acted in a highly unprofessional way and that this activity was known to many senior managers and had happened for a long time; if unchecked these types of activities could bring discredit to the whole industry.

The complainant heard that recently UCB sold the entire Minijets product portfolio to a third party but in his/her view a company could be reprimanded for its historical wrong doings.

In writing to UCB, the Authority asked it to bear in mind Clauses 9.1 and 2 in addition to Clauses 3 and 15.9 as cited by the complainant.

RESPONSE

UCB noted that there was nothing specific in the complaint regarding the time period but the dating of the poster referred to by the complainant allowed it to assume early 2012.

Relevant chronology of events and licensed indications

UCB stated that naloxone was an opioid antagonist used to counteract opiate respiratory depression induced by natural and synthetic opioids. Naloxone Hydrochloride Minijet 400mcg/ml was commercialised by UCB as part of a portfolio of critical care sterile injectable products. As of June 2016, the complete Minijet portfolio was divested along with the company to International Medications System Ltd which was the registered marketing authorisation holder for the products.

The complainant referred to the indications from the summaries of product characteristics (SPCs) for two naloxone products, the UCB Minijet 400mcg/ml and the product licensed by Martindale Pharma (1mg/ml).

UCB stated that the naloxone Minijet was first licensed in 1986 and since then had always been indicated for:

‘the treatment of respiratory depression induced by natural and synthetic opioids, such as codeine, diamorphine, levorphanol, methadone, morphine, concentrated opium alkaloid hydrochlorides and propoxyphene. It is also useful for the treatment of respiratory depression caused by opioid agonist/antagonists nalbuphine and pentazocine. Naloxone is also used for the diagnosis of suspected acute opioid overdose’.

The Martindale naloxone, according to its SPC:

‘may be used for the complete or partial reversal of opioid depression, including mild to severe respiratory depression induced by natural and synthetic opioids, including dextropropoxyphene,

methadone and certain mixed agonist/antagonist analgesics: nalbuphine and pentazocine. It may also be used for the diagnosis of suspected acute opioid overdose. Naloxone may also be used to counteract respiratory and other CNS depression in the new-born resulting from administration of analgesics to the mother during childbirth’.

The two products had different concentrations of naloxone but both were indicated for the treatment of respiratory depression induced by natural and synthetic opioids, and in essence the indications could be considered as having core similarities both in wording and clinical use.

Well before 2012, the take-home concept was well accepted and established in practice. In 2005, in light of the clear potential of naloxone to save life and the need for naloxone-based overdose prevention programmes, naloxone was added to the list of medicines that could be given parentally (intramuscularly, intravenously or subcutaneously) by any member of the public for the purpose of saving a life (Medicines and Healthcare products Regulatory Agency (MHRA) 2005). A prescription was still needed for the opiate user at risk but the medicine could then be kept for them by other people, like family members, partners or other carers, who could legally use it in an emergency.

From 2007 onwards, pilot take-home naloxone programmes aimed at preventing overdose-related deaths started at local and national level as clinically driven and evidence-based initiatives. Many important guidelines, like the ‘Drug Misuse and Dependence: UK Guidelines on Clinical Management’ supported this course of action. Naloxone Minijet was one of the choices of medicine available then for clinicians to use in such a setting, and was considered licensed for such use.

UCB noted that up until mid-2012, all naloxone products to be used in the take-home setting had to be re-packaged, often by the healthcare service, to be distributed through emergency kits. In June 2012, Martindale’s Prenoxad (naloxone) was introduced, with use in the community setting specifically detailed. The product composition was the same as Martindale’s naloxone hydrochloride injection 1mg/ml, with the addition of two suitable needles in order to minimize the need of any secondary re-packaging and the patient information leaflet was updated accordingly. The clinical indication of Prenoxad was the same as other naloxone products (‘complete or partial reversal of respiratory depression induced by natural and synthetic opioids’, from the Prenoxad SPC) with additional information regarding the use setting (‘intended for emergency use in the home or other non-medical setting by appropriate individuals or in a health facility setting’, from the Prenoxad SPC).

The addition of the needles and of a brand name differentiated the product from Martindale’s existing naloxone injection, and enabled prescribers to select a package designed specifically for community use. However, the additional wording of the Prenoxad licence did not exclude other naloxone products from use in the community setting.

UCB stated that UK Medicines Information (UKMi), a well-established and reputed body that reviewed the practical use of products in relevant clinical settings, supported this concept in its recent document 'In use product safety assessment report: naloxone products for emergency opiate reversal in non-medical settings', March 2016. The review assessed the four UK licensed naloxone products available in a prefilled syringe, among which naloxone Minijet 400mcg/ml based on clinical experience since before 2012.

In particular, on page 2 under 'Licensing status' the review reported that 'All naloxone prefilled syringe products were licensed for the reversal/treatment of opioid induced respiratory depression. Prenoxad was specifically developed for use in community and as such the product licence specified it can be used in the home, non-medical setting or in a health facility setting ... The product licences for the three non-proprietary products do not indicate use for a specific setting or user'. The review concluded on page 4 with two considerations on which product to choose to safely deliver naloxone dosing in a non-medical setting:

- It is vital that naloxone products supplied are suitable for the non-medical setting; in our view prefilled syringes are the preferred formulation choice compared to vials or ampoules.
- Each of the four prefilled syringe products are presented differently and thus features of each should be considered carefully [...].'

For the reasons above, UCB submitted that naloxone Minijet had the same clinical indication in treating respiratory depression induced by natural and synthetic opioid as Martindale's products. The medicine treatment services choice of which product to use in a take-home setting, as suggested by the UKMi review, was based on many factors including, *inter alia*, dose, product packaging and facility of administration. Therefore, there was no out-of-licence promotion of naloxone Minijet.

Poster and alleged out-of-licence promotion

UCB provided a copy of the non-promotional poster, dated March 2012; it was for internal use only and was not a sales briefing on how to promote the product.

The poster was created by a key account manager in the Minijet team and highlighted the fact that naloxone (programmes) saved lives. UCB supported naloxone training programmes for families and carers run across England and initiated by local drug treatment services with the purpose of distributing and educating on the use of naloxone in an overdose emergency situation to save lives.

The service model developed by one of the local drug and alcohol teams cited in the poster and serviced by UCB, included supply of the product through a commercial pricing agreement.

The poster was presented as part of an internal UCB conference in the 'Power of Partnership' initiative, an internal award to recognise patient/NHS centred initiatives that showed collaboration across UCB, the

NHS and patients with beneficial outcomes for all parties. Other posters were produced for the same award session by representatives operating in other therapeutic areas within UCB with the only purpose of sharing best practices that delivered patient benefit.

UCB sales and promotional activities

In 2012 take-home programmes were acknowledged in UK clinical practice and recommended as a measure to prevent opiate overdose-related deaths. UCB submitted that it supplied product in response to demand from this type of initiative.

UCB sales targets were based on the whole Minijet portfolio and there was no specific drive from the company to increase Naloxone Minijet use in the take-home setting. The incentive scheme at the time related to the full Minijet portfolio and not to naloxone particularly (UCB provided a copy of the incentive scheme document); this involved a national target with no specific sales targets at either key account manager or product level.

In the NHS, customer engagement was focussed on supply to meet demand with commercial pricing arrangements based on the full range of Minijet products. There was no interest in UCB product differentiation and UCB had not produced any material with this purpose. These products were clinically important generics, with a significant proportion of the engagement with customers in the procurement and purchasing pharmacy arenas, rather than clinical discussions.

In summary, UCB submitted that based on all the considerations above, there was no ground in the complainant's allegations for Clause 3 as naloxone Minijet had always been promoted within the terms of its licence. UCB therefore refuted a breach of Clause 9.1 as high standards had been maintained.

UCB submitted that the complainant had portrayed the use of the poster in a completely different way from both intention and actual use therefore UCB denied a breach of Clause 15.9.

Collectively in relation to all of the above, UCB submitted that it had never pursued a course of action that could bring discredit upon the pharmaceutical industry or harm patient safety and/or public health; therefore, it denied a breach of Clause 2.

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 the parties' interpretation of the licensed indication for naloxone Minijet differed.

The Panel noted that naloxone Minijet 400mcg/ml was indicated for the treatment of respiratory depression induced by natural or synthetic opioids. The medicine was presented as prefilled syringes of 1 or 2mls (400 or 800mcg). The usual initial adult dose was 400 - 2000mcg every 2 to 3 minutes if necessary. If no response was observed after the administration of 10mg then the depressive condition might be caused by a medicine or a disease process not responsive to naloxone. Treatment of overdose might thus require the use of a number of Minijet syringes. Use of naloxone Minijet in the non-medical setting was not referred to in the SPC and in that regard it did not appear that the product was specifically intended or packaged for such use and so non-medical responders might find it more difficult to use than other forms of naloxone, particularly Martindale's Prenoxad. Nonetheless, the Panel did not consider that take-home use of naloxone Minijet was off licence *per se* as alleged. No breach of Clause 3.2 was ruled.

The Panel disagreed with UCB's submission that the poster was not briefing material for the representatives; it had been presented at an internal UCB conference with the purpose of sharing best practice. The Panel assumed that as the poster had been developed by a representative, it mirrored what he/she considered was acceptable to claim about naloxone Minijet. The Panel noted that the poster did refer to training family friends, however it was extremely concerned that the title of the poster stated, without qualification, 'Minijet team Naloxone: How a Take Away Can Save Hundreds of Lives'. There

was no reference cited in support of the statement and no indication as to the time period over which hundreds of lives would be saved by naloxone Minijet. Additional text stated that an overdose could now be referred to in the present tense: 'I have a friend who [overdosed] last week. Naloxone did that' which implied that naloxone saved the lives of everyone who overdosed. The poster also stated that naloxone Minijet provided the ideal offering, and in that regard the Panel noted its comments above about Prenoxad. The poster also stated that naloxone Minijet had the potential to dominate the market and that the dose of the competitor was too high. The Panel considered that the content of the poster was such that it advocated claims for take-home naloxone Minijet, or the competitor, which were likely to be in breach of the Code. A breach of Clause 15.9 was ruled. Overall the Panel considered that, given its content, the production of the poster showed poor judgement and in that regard it ruled a breach of Clause 9.1 as it considered that high standards had not been maintained.

The Panel noted its rulings and comments above and although it had some concerns, it did not consider that the circumstances were such as to rule a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

Complaint received	20 December 2017
Case completed	27 March 2017

ASSISTANT DIRECTOR MEDICINES MANAGEMENT v MEDA

Conduct of representative

An assistant director, medicines management, complained about the activities of a representative from Meda Pharmaceuticals at a GP meeting. The complainant stated that the representative distributed leaflets about Dymista (fluticasone/azelastine for perennial and seasonal allergic rhinitis) and stated that local consultants recommended the product. However, the local area prescribing committee had reviewed the product and recommended that it should be grey listed and thus not be prescribed by either primary care or secondary care (not on any hospital formulary in the area). The complainant pointed out the grey recommendation to the representative and how he/she was promoting against the local NHS guidance.

The complainant stated that from there the representative became very combative and arrogant. He/she shouted the complainant down and stated in front of the audience of GPs and practice managers that it was just guidance and GPs could prescribe anything they wished. The representative then stated that he/she would put the complainant in touch with the formulary pharmacist of the local area trust who would, in his/her words, 'set you right'. The complainant stated that she had known the local formulary pharmacist and on speaking to him after this event, he was particularly disturbed that his name was brought up by the representative when they had had no contact in over two years.

The detailed response from Meda is given below.

The Panel noted that the parties' accounts differed; it was difficult in such cases to know exactly what had transpired. The complainant had consistently alleged that the representative had not proactively referred to the local formulary status of Dymista. The complainant had also consistently described the representative's conduct as combative even if that was not the representative's view of his/her behaviour. A judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually necessary on the part of an individual before he or she was moved to actually submit a complaint. The Panel further noted that the complainant bore the burden of proof and had to establish his/her case on the balance of probabilities.

The Panel noted that the issue which had led to the disagreement between the parties centred around the status of Dymista on the local prescribing formulary. In March 2014 the local area prescribing committee had deemed Dymista as a 'grey' product ie it was not recommended for use. It appeared that this decision had been appealed and committee minutes from October 2014 stated that the Dymista appeal had helped to clarify the appeals process and that any appeal must be process-driven and that the

committee could make recommendations but the individual prescriber made the clinical decision on whether or not to prescribe. It thus appeared to the Panel that in October 2014, although Dymista was still grey listed the committee's recommendation not to use it was just that – a recommendation, not a mandate. Nonetheless, the Panel noted that the representative in question clearly knew that history of Dymista locally but chose not to proactively inform the audience of its status. The representative stated that he/she did not clarify the Dymista formulary status before he/she detailed the product. In the Panel's view, to detail a product without reference to its local prescribing status at the outset was unhelpful and misleading. The Panel ruled a breach of the Code. Whilst the Panel did not know exactly what the representative had stated regarding the local prescribing of Dymista, it considered that on the balance of probabilities he/she created an impression which could not be substantiated. On balance, the Panel ruled a breach of the Code. In the Panel's view, the representative had not maintained a high standard of ethical conduct and a breach of the Code was ruled.

The Panel did not consider that the complainant had demonstrated that, on the balance of probabilities, the representative was combative and so in that regard it ruled no breach of the Code.

The Panel noted its rulings above and although it was concerned that the representative had not proactively referred to the local formulary status of Dymista, it nonetheless did not consider that this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure. No breach of Clause 2 was ruled.

An assistant director, medicines management complained about the activities of a representative from Meda Pharmaceuticals Limited at a GP meeting held in December 2016. The representative provided sandwiches and was given ten minutes at the start of the evening to talk about Meda's products.

COMPLAINT

The complainant stated that the representative distributed leaflets about Dymista (fluticasone/azelastine for perennial and seasonal allergic rhinitis) and stated that local consultants recommended this product. However, the local area prescribing committee had reviewed this product and recommended that it should be grey listed and thus not be prescribed by either primary care or secondary care (not on any hospital formulary in the local area). The complainant pointed out the grey recommendation to the representative and how GPs and local consultants were recommended not to

prescribe Dymista and that he/she was promoting against the local NHS guidance.

The complainant stated that from there the representative became very combative and arrogant. He/she shouted the complainant down and stated in front of the audience of GPs and practice managers that it was just guidance and GPs could prescribe anything they wished. The representative then stated that he/she would put the complainant in touch with the formulary pharmacist of the local area trust, who would, in his/her words, 'set you right'. The complainant stated that she had known the local formulary pharmacist for many years and on speaking to him after this event, he confirmed that he had not spoken to the representative in over two years and he also found him/her combative and ignorant. The local formulary pharmacist was also particularly disturbed that his name was brought up by the representative when they had had no contact in over two years.

The complainant was concerned about the combative and ignorant attitude of the representative and the fact that Meda had actively promoted a product against the local guidance, and if questioned, then asked GPs to ignore that guidance.

In writing to Meda, the Authority asked it to respond in relation to the requirements of Clauses 2, 7.2, 7.4, 9.1 and 15.2.

RESPONSE

Meda stated that it did not believe that it had breached Clause 2. The representative in question was interviewed and he/she detailed the sequence of events and considered that he/she had acted properly and in accordance with the expected behaviour of a Meda representative and of the pharmaceutical industry on the whole, in line with the Code.

Meda submitted that it was legitimate for the industry to highlight available clinical evidence, both randomised clinical trials and real life and local and national specialist clinical consensus and practice (the British Society for Allergy and Clinical Immunology (BSACI) conference/local trust). It was necessary to discuss identifiable NHS system inefficiencies (specialist outpatient prescriptions being challenged following referral when appropriately prescribed within licence based on specialist clinical assessment and history). It was essential that there was an open environment to have this discussion, especially, when local prescribing guidance was different to other large and highly regarded health economies.

The repeated applications from leading national specialist consultants in the local area trust with real-life clinical experience was highly relevant. As was the clinical usage of Dymista locally – it highlighted reasonable clinical usage above IPR level and aligned to research suggested unmet need with conventional standards of care and position for Dymista in sequential pathways as a step-up option.

Meda referred to the interview transcript whereby the representative confirmed that the local formulary

pharmacist was mentioned but disagreed that the words 'set you right' were used. The representative clarified that he/she had referred to the local formulary pharmacist only to highlight that he had supported another customer applying for formulary application for Dymista. Meda had also been able to verify email correspondence between the local formulary pharmacist and that customer.

Meda stated it had no reason to doubt the representative's account and concluded that there had been a misunderstanding between the representative and the complainant. The representative did not intend to contradict the complainant, but to direct her to differences of opinion relating to the guidelines.

Meda submitted that it had not breached Clauses 7.2 and 7.4; the complainant had not objected to promotional materials. The Dymista leavepiece was provided which had been produced in line with requirements of the Code and approved following internal Meda processes.

Meda submitted that there was no breach of Clause 9.1. All Meda representatives were regularly trained and the representative in question was fully aware of the importance of maintaining high standards. He/she had been in the industry for a long time, and had not been previously involved in any complaints from health professionals in relation to his/her conduct and behaviour in his/her time with Meda.

Meda submitted that there was no breach of Clause 15.2. Like all Meda representatives, the representative in question had been trained on the Code on an annual basis. He/she had been trained and examined on the promoted medicines to ensure that he/she was able to provide full and accurate information. He/she was aware that Meda representatives must at all times maintain ethical conduct in the discharge of their duties and must comply with all relevant requirements of the Code.

Furthermore, Meda had an in-house voluntary e-training system, which sent daily random questions on the Code and promoted products, to reinforce the employees' knowledge. Meda invested time and resources on employee education and training.

Whilst Meda noted that this was the first complaint against the representative, he/she was reminded during the interviews of the high standards expected for interactions with customers and of Meda's obligations under the Code and would be retrained in that regard.

Meda would welcome an opportunity to reach out to the complainant in order to establish a dialogue if that would be beneficial. The company took the views of health professionals seriously.

From the interview transcripts, the representative stated that there was a ten minute presentation on three products. The leavepieces for Dymista, Elleste (oestradiol) and Treclin (clindamycin/tretanoin) were left on the seats. The representative used his/her iPad to present the Dymista and Treclin e-details.

According to the representative, some said that Dymista was grey listed and not to be prescribed but some used it according to prescribing committee minutes. Some clinical commissioning groups (CCGs) were happy to prescribe Dymista and others, especially the complainant's CCG, were not. According to the representative, the complainant's CCG followed the prescribing committee minutes which stated not to prescribe in primary and secondary care. According to the representative, he/she noted that there was an update in October which the complainant was reluctant to accept but checked her laptop and read out the update. The complainant then suggested another formulary application was submitted. The representative said that the consultant had applied and the local area formulary pharmacist was very supportive to this customer.

The representative denied there was any sort of an argument.

When asked by the Panel if it could send its response to the complainant for comment, given that the parties' accounts were so different, Meda stated that it had tried to contact those who had attended the meeting but that those who were contactable were unwilling to provide an account of the events.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant noted Meda's submission that it had carried out a thorough investigation and tried to contact those who were at the meeting but unfortunately those contactable were unwilling to provide an official account of the event. As far as the complainant knew, the only person Meda had contacted was one of the practice managers at the meeting; that person was also mentioned in the interview transcript.

The complainant had spoken to the practice manager and she was willing to provide an official account of the event; contact details were provided.

The complainant queried who from the attendance list of the meeting Meda had tried to contact that were unwilling to provide accounts of the event as they also might be happier to provide an account to the PMCPA rather than to Meda.

The complainant noted Meda's submission that she had taken the view that Dymista had been grey listed. The complainant noted that as previously pointed out to the representative it was not just her view, this was the current position of the area prescribing committee. The complainant provided a link to the published guidance. The complainant noted that the recommendations on the local area prescribing committee website were kept up-to-date and if this recommendation had been withdrawn it would be stated so in both the title and the link.

The complainant submitted that the current Dymista recommendation had been published on the website since March 2014 when this was decided. The complainant noted that in January 2017 there was a further application to change the status of this recommendation and so this recommendation

would be updated once agreed by the area prescribing committee.

The complainant noted Meda's submission that it was 'legitimate for the industry to highlight available clinical evidence, both randomised clinical trials and real life, local and national specialist clinical consensus' and that 'it was essential that there was an open environment to have this discussion especially when local prescribing guidance was different to other large and highly regarded health economies'. However in this case the Meda representative did not highlight all available information to those at the meeting in question; he/she chose to knowingly not mention the grey listing published on the website of the local area prescribing committee when he/she promoted Dymista to the clinicians present. The complainant stated that once she pointed out that piece of information the representative became aggressive and combative.

The complainant noted that Meda had stated that she had taken the view that there could be no discussion or promotion of Dymista. The minutes of the interview mentioned a meeting that she had had last year with the representative and one of his/her colleagues. The complainant confirmed that she and a colleague met with the two Meda employees. At that meeting they noted the grey status of Dymista locally and that they did not want to go through any clinical trial data until the status had been changed. At that meeting the representative knew about the grey status of Dymista and did not point out at that stage that he/she had used the minutes of the area prescribing committee meeting rather than the official published recommendation to promote Dymista. If he/she had, they could have clarified the situation at that point. The representative also did not ask for a written letter from the CCG asking him/her not to promote, the complainant would have thought a publicly available grey listing would have been sufficient to be aware of the CCG's position on the medicine, which she considered it was from the comment in the transcript 'Some CCGs are happy to prescribe and some aren't especially [the complainant's] CCG'.

The complainant stated that at the meeting in December, the representative mentioned where he/she had taken a few of the local GPs out to dinner to discuss Dymista and that they had thought it acceptable to prescribe Dymista. The complainant submitted however, that a decision at a meal sponsored by Meda with local GPs did not constitute a CCG decision that its GPs prescribe. Any decision would need to follow local procedures. At this point one of the GPs who was at the meal joined the meeting and gave a different recollection of the evening meal meeting and stated that he was aware of the grey status of Dymista.

The complainant noted that in an interview transcript the representative stated 'I would never do this to anyone else'. On reading that it made the complainant feel as if the representative knew that he/she had not treated her with respect at the meeting.

On the last page of the transcript when asked did anyone else at the meeting get involved, the representative stated 'No'. The complainant stated that this was incorrect because the chair of a local medicines management committee commented that he knew about the grey status of Dymista.

The complainant noted that at various points in the transcript it mentioned an argument. The complainant agreed there was no argument, just a differing of opinion; she would not let the situation become an argument in an open meeting. It was the combative and arrogant attitude of the representative that was inappropriate.

The complainant agreed that she did not object to the promotional materials; her only concern was the representative's inappropriate behaviour. The complainant considered that the interview transcript showed the representative's arrogance to accept when he/she was wrong, even when she pointed out the official grey status publication, and it looked like the representative was still unwilling to accept he/she was wrong.

FURTHER COMMENTS FROM MEDA

Meda stated that it would very much appreciate the recollection of accounts by other meeting attendees, given the only accounts of the events that were available thus far were from the complainant and the representative. Meda asked that the additional accounts be made available for review.

Meda stated that in a third interview with the representative, the complainant's comments that he/she had knowingly chosen not to mention the grey listing for Dymista when promoting to the clinicians in the room was highlighted. The representative agreed that he did not actively raise this but when this was highlighted, he/she acknowledged and respectfully agreed with the Dymista grey listing.

Meda stated that the representative was mortified to read that he/she had shown disrespect to the complainant. He/she stated unequivocally that he/she would never knowingly show a lack of respect or speak out of turn with any health professional. He/she asked to note his/her sincere and humble apology for having given the complainant the impression that he/she was not being respectful.

The representative confirmed that the chair of the local medicines management committee entered the meeting room, however he/she did not recall talking with him; it was possible that the chair, as part of the round table discussion, might have mentioned the grey listing status, but if that was the case he/she did not hear the comment.

Meda also agreed that there was no argument. Due to 'cultural differences' (English was the representative's second language), and personalities between the complainant and the representative, there could potentially have been a disconnect and misunderstanding. For this the representative was profoundly apologetic for showing any unintended disrespect towards the complainant.

Meda reiterated that all representatives conducted themselves in line with Code expectations. In addition, Meda provided emotional intelligence awareness training to ensure that the representatives understood the need to engage with their clients on an individual basis and flex their personality styles accordingly.

Meda renewed its offer to engage with the complainant and for the representative to personally apologise for the misunderstanding.

Following the additional interview, Meda still considered that the representative did not breach the Code, however, as stated above, he/she apologised for any perceived disrespect or offence caused.

PANEL RULING

The Panel noted that the parties' accounts differed; it was difficult in such cases to know exactly what had transpired. The complainant had consistently alleged that the representative had not proactively referred to the local formulary status of Dymista. The complainant had also consistently described the representative's conduct as combative even if that was not the representative's view of his/her behaviour. A judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually necessary on the part of an individual before he or she was moved to actually submit a complaint. The Panel further noted that the complainant bore the burden of proof and had to establish his/her case on the balance of probabilities.

The Panel noted that the issue which had led to the disagreement between the parties centred around the status of Dymista on the local prescribing formulary. In early 2014 the local area prescribing committee had deemed Dymista as a 'grey' product ie it was not recommended for use. It appeared that this decision had been appealed and committee minutes from later in 2014 stated that the Dymista appeal had helped to clarify the appeals process and confirmed that any appeal must be process-driven and that the committee could make recommendations but the individual prescriber made the clinical decision on whether or not to prescribe. It thus appeared to the Panel that in October 2014, although Dymista was still grey listed the committee's recommendation not to use it was just that – a recommendation, not a mandate. Nonetheless, the Panel noted that the representative in question clearly knew that history of Dymista locally but chose not to proactively inform the audience of its status. The representative stated that he/she did not clarify the Dymista formulary status before he/she detailed the product. In the Panel's view, to detail a product without reference to its local prescribing status at the outset was unhelpful and misleading. The Panel ruled a breach of Clause 7.2. Whilst the Panel did not know exactly what the representative had stated regarding the local prescribing of Dymista, it considered that on the balance of probabilities he/she created an impression which could not be substantiated. On balance, the Panel ruled a breach of Clause 7.4. In the Panel's view, to mislead a local audience in that regard

meant that the representative had not maintained a high standard of ethical conduct and a breach of Clause 15.2 was ruled. The Panel considered that this ruling covered any consideration of the requirements of Clause 9.1 and so it made no additional ruling in that regard.

The Panel did not consider that the complainant had demonstrated that, on the balance of probabilities, the representative was combative and so in that regard it ruled no breach of Clause 15.2.

The Panel noted its rulings above and although it was concerned that the representative had not proactively referred to the local formulary status of Dymista, it nonetheless did not consider that this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure. No breach of Clause 2 was ruled.

Complaint received **19 December 2016**

Case completed **24 March 2017**

HEALTH PROFESSIONAL v PFIZER

Websites

A health professional who until recently worked in the pharmaceutical industry complained about Pfizer's websites.

The complainant alleged that the prescribing information on a number of materials on the websites was out of date. The materials at issue were a Vfend (voriconazole) leavepiece, a Tygacil (tigecycline) leavepiece, an Ecalta (anidulafungin IV) leavepiece, and documents headed 'Prescribing Information' for Depo-Provera (medroxyprogesterone acetate) and Sayana Press (medroxyprogesterone acetate).

In response to a request for more information from the case preparation manager, the complainant explained that he/she had reviewed the date of creation of the prescribing information on the items compared with the latest versions on the electronic medicines compendium (eMC). The complainant focussed on when the information in Section 4.4 [Special warnings and precautions for use] had been updated, since it was highly likely to be of direct clinical impact.

The complainant referred to the prescribing information for Depo-Provera on the Pfizer website which was dated July 2015 whereas the eMC for Depo-Provera had been updated twice with the latest change stipulating an update to the adverse drug reaction (ADR) frequency. The date of the prescribing information for Sayana Press on the Pfizer website was May 2015 whereas the eMC had been updated once or twice since then. The complainant also referred to changes on the eMC for Ecalta and Tygacil.

The detailed response from Pfizer is given below.

The Panel noted that despite the prescribing information being updated in November 2015 and a new version of the Vfend leavepiece with the updated prescribing information being certified in January 2016, the previous version of the leavepiece with out-of-date prescribing information remained on the website when viewed by the complainant in January 2017. The out-of-date prescribing information did not inform the reader of a number of side effects. A breach of the Code was ruled.

The Panel noted Pfizer's submission that although there had been four revisions of the Tygacil SPC since the current prescribing information was approved in May 2015, none of those revisions had necessitated a change to the prescribing information. The May 2015 prescribing information thus remained up-to-date. The Tygacil leavepiece referred to by the complainant was certified in September 2015 and contained the current and up-to-date prescribing information that had been effective since May 2015. The Panel therefore ruled no breach of the Code.

The Panel noted Pfizer's submission that the Ecalta leavepiece at issue was certified in January 2016 and that it contained the current prescribing information that had been effective since July 2014. The only intervening change to the Ecalta SPC did not impact on the prescribing information. The Panel thus considered that the leavepiece contained the up-to-date prescribing information and so it ruled no breach of the Code.

The Panel noted Pfizer's submission that the prescribing information on the Sayana-Press website which was last updated in May 2016, and not May 2015 as referred to by the complainant, was current and up-to-date. The only revision to the SPC since that date involved Section 5.1 which did not necessitate a change to the prescribing information. The Panel therefore ruled no breach of the Code.

The Panel noted Pfizer's submission that the Depo-Provera SPC was updated in December 2016 such that three clinically non-serious side effects were moved to the 'Very Common' category from the 'Common' (and 'Other') categories. The Panel noted Pfizer's submission that the prescribing information had since been updated and that a new version was now effective on all materials but that at the time of the complaint the previous prescribing information was effective. The Panel noted Pfizer's submission that regulatory approval for the type II variation was received on 8 December 2016 and the SPC was updated the same day. The Panel further noted that according to the eMC, the updated SPC was displayed on Wednesday, 14 December 2016. The Panel noted that the general principle was that the prescribing information must be up-to-date, must comply with the Code and must not be inconsistent with the particulars given in the SPC. The Panel considered that the prescribing information seen by the complainant on 2 January when the complaint was received was not up-to-date and a breach of the Code.

The complainant stated that each instance might be technically following the requirements of the Code if the sections that had been updated had not altered the prescribing information but together pointed to a concerning picture when all four were out-of-date. The complainant queried whether the processes were sufficiently rigorous.

The Panel noted its rulings above and considered that high standards had not been maintained. Up-to-date prescribing information had not been provided in the case of the Vfend leavepiece available on the Pfizer website. The out-of-date prescribing information did not refer to dermatological adverse events and higher frequency of liver enzyme elevations in the paediatric population in the Warnings and Precautions Section. It also did not include the addition of new very

common and common side effects. Further, out-of-date Depo-Provera prescribing information was provided at the time of the complaint such that three clinically non-serious side effects were not listed as ‘Very Common’.

The Panel considered that Pfizer had failed to maintain high standards. A breach of the Code was ruled.

The complainant referred to a page on Pfizer’s Champix (varenicline) website from which a copy of a new landmark study, EAGLES, the largest comparative randomised controlled trial of approved smoking cessation medicines could be downloaded. The complainant stated that although it was clear that the document was held on a different site, as health professionals were proactively encouraged to use the link, the complainant queried whether it was an independent item or whether it was promotional in nature.

The Panel noted Pfizer’s submission that health professionals had, in effect, been invited to access the publication and that Pfizer had certified the e-print for promotional use. The Panel considered that upon visiting the website and possibly downloading the publication, relevant prescribing information should, at the same time, be available to the health professional and in that regard it noted that prescribing information could be accessed via a separate but prominent link in the same screenshot as the link to the publication. No breach of the Code was ruled.

A health professional, who until recently worked in the pharmaceutical industry complained about Pfizer Limited’s websites. The complainant was concerned about a number of issues.

1 Prescribing information

COMPLAINT

The complainant alleged that the prescribing information on a number of materials on the websites was out of date. The materials at issue were a Vfend (voriconazole) leavepiece (ref VFE1771), a Tygacil (tigecycline) leavepiece (ref TYG162), an Ecalta (anidulafungin IV) leavepiece (ref ECA359), and documents headed ‘Prescribing Information’ for Depo-Provera (medroxyprogesterone acetate) (ref DP 13_0) and Sayana Press (medroxyprogesterone acetate) (ref PP-SAY-GBR-0071).

In response to a request for more information from the case preparation manager, the complainant explained that the parts he/she considered were missing from the prescribing information for the various medicines was based on a review of the date of creation of the prescribing information on the items compared with the latest versions on the electronic medicines compendium (eMC) (emc.org.uk). The complainant stated that he/she focussed on when the information in Section 4.4 [Special warnings and precautions for use] had been updated, since it was highly likely to be of direct clinical impact.

The complainant referred to the prescribing information for Depo-Provera on the Pfizer website which was dated July 2015 whereas the eMC for Depo-Provera had been updated twice with the latest change stipulating an update to the adverse drug reaction (ADR) frequency.

The date of the prescribing information for Sayana Press on the Pfizer website was May 2015 whereas the eMC had been updated once or twice since then.

The complainant also referred to changes on the eMC for Ecalta and Tygacil.

In writing to Pfizer, attention was drawn to the requirements of Clauses 4.1, 4.2 and 9.1 of the Code.

a) Vfend

RESPONSE

Pfizer stated that the Vfend prophylaxis leavepiece (ref VFE 1771), was certified in September 2015.

In May 2015, Pfizer submitted a type II variation to update the Vfend summary of product characteristics (SPC) to reflect new safety and efficacy data. Regulatory authority approval of this labelling change was received on 17 December 2015. As a result, the SPC was updated to the current version with changes to Sections 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.1, Pharmacodynamic properties.

Consequently, the previous version of the prescribing information (ref VF 23_0; 06/2014) was thus updated to the current version (ref VF 24_0; 11/2015) by incorporating additional material under ‘Warnings and Precautions’ and ‘Side Effects’ to reflect the SPC changes. The new material under ‘Warnings and Precautions’ involved dermatological adverse reactions and reference to the higher frequency of liver enzyme elevations in the paediatric population. The ‘Side Effects’ section was updated to include new material under the ‘very common’ and ‘common’ sub-sections.

Pfizer submitted that all promotional materials were updated with the new prescribing information including the Vfend prophylaxis leavepiece which was updated and recertified in January (ref VFE 1803; January 2016). The Vfend section of the Pfizer website was certified in December 2016 (ref PP-VFE-GBR-0035). Pfizer submitted that whilst it had taken care to ensure that the website itself provided access to the current and up-to-date Vfend prescribing information (ref VF 24_0), the older version of the Vfend prophylaxis leavepiece (ref VFE1771) containing the out-of-date prescribing information was erroneously incorporated instead of the updated piece containing the updated prescribing information. This was an entirely unintended oversight due to human error and was an isolated incident. All other promotional materials, including the leavepiece not on the website, were updated correctly with the new prescribing information, and as stated above, the website itself was updated with the new prescribing information. Pfizer accepted

that there had been a breach of Clauses 4.1 and 4.2 in this isolated incident which it sincerely regretted. Pfizer submitted that the error had been corrected.

PANEL RULING

The Panel noted that Clause 4.1 of the Code required the prescribing information listed in Clause 4.2 to be provided in a clear and legible manner. Clause 4.2 stated that the prescribing information consisted of, *inter alia*, a succinct statement of common side-effects likely to be encountered in clinical practice, serious side-effects and precautions and contra-indications relevant to the indications in the advertisement. The Panel noted that despite the prescribing information being updated in November 2015 and a new version of the Vfend leavepiece with the updated prescribing information being certified in January 2016, the previous version of the leavepiece with out-of-date prescribing information remained on the website when viewed by the complainant in January 2017. The out-of-date prescribing information did not inform the reader that a higher frequency of liver enzyme elevations was observed in the paediatric population and also referred to rare reports of serious cutaneous reaction whereas the updated prescribing information did not use the word rare and gave more details of the serious cutaneous reactions that could occur. The out-of-date prescribing information did not list any common side-effects and did not include respiratory distress in the list of very common side effects. It also did not include new material under the 'very common' and 'common' side effects sections.

The Panel noted that a breach of Clause 4.2 had been alleged. Clause 4.2 listed the components of prescribing information and it was a requirement of Clause 4.1 that such be provided. The Panel considered that as the prescribing information in the Vfend leavepiece available on the pfizerpro.co.uk was not up-to-date with regard to precautions and side-effects it did not comply with the Code. A breach of Clause 4.1 was ruled.

b) Tygacil

RESPONSE

Pfizer submitted that the Tygacil leavepiece at issue was certified in September 2015. This piece included the current and up-to-date prescribing information (refTL 7_0) that had been effective since May 2015.

The complainant referred to revisions to the Tygacil SPC noted on the eMC. Pfizer stated that the SPC had been revised four times since the current prescribing information was approved in May 2015. However, none of those revisions had an impact on the prescribing information and as a result the prescribing information had remained unchanged.

With the first revision in June 2015, the changes were confined to Section 5.1 Pharmacodynamic properties, apart from minor administrative/formatting changes. The second revision in February 2016, impacted Sections 4.2 Posology and method of

administration, 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation and 4.8 undesirable effects. The changes to Sections 4.2 and 4.4 were non-content related reordering of text and additional headings. Changes to Section 4.6 did not include any additional warnings that impacted the prescribing information. The changes to Section 4.8 only involved reformatting undesirable effects into a table format.

The third revision in April 2016 involved the addition of 'hypofibrinogenaemia' as an undesirable effect (Section 4.8) under the 'frequency not known' category and thus did not warrant a prescribing information update. The fourth revision of the SPC undertaken in June 2016 only impacted Section 10 involving updates to dates of revision/approval. In summary, Pfizer submitted these SPC changes did not warrant any amendments to the prescribing information and hence there had not been any prescribing information updates. Since the prescribing information was current and up-to-date, Pfizer denied a breach of Clauses 4.1 or 4.2.

PANEL RULING

The Panel noted Pfizer's submission that although there had been four revisions of the SPC since the current prescribing information was approved in May 2015, none of those revisions had necessitated a change to the prescribing information. The May 2015 prescribing information thus remained up-to-date. The Tygacil leavepiece referred to by the complainant was certified in September 2015 and contained the current and up-to-date prescribing information that had been effective since May 2015. The Panel therefore ruled no breach of Clause 4.1.

c) Ecalta

RESPONSE

Pfizer submitted that the Ecalta leavepiece at issue was certified in January 2016 and had the current and up-to-date prescribing information that had been effective since July 2014.

Pfizer noted that although the complainant referred to revisions to the Ecalta SPC noted on the eMC, the only change had been a change to Section 6.5 Nature and contents of container, which had no impact on the prescribing information. Since the prescribing information was current and up-to-date, Pfizer denied any breach of Clauses 4.1 or 4.2.

PANEL RULING

The Panel noted Pfizer's submission that the Ecalta leavepiece at issue was certified in January 2016 and that it contained the current prescribing information that had been effective since July 2014. The only intervening change to the Ecalta SPC had been to Section 6.5 Nature and contents of container, which did not impact on the prescribing information. The Panel thus considered that the leavepiece contained the up-to-date prescribing information and so it ruled no breach of Clause 4.1.

d) Sayana-Press

RESPONSE

Pfizer submitted that the website had the current and up-to-date prescribing information which had been effective since May 2016. Pfizer noted that the date of the prescribing information as shown against 'Last Updated' was May 2016 and not 'May 2015' as the complainant had stated. Further, the complainant had stated that the eMC showed again that the prescribing information had been updated once or twice since the available prescribing information. Pfizer submitted, however, that the eMC only referred to changes to the SPC (and not the prescribing information) and only showed one revision to the SPC since the date of approval of the current prescribing information. This revision involved Section 5.1, Pharmacodynamic properties/mode of action and thus had no impact on the prescribing information. Therefore Pfizer did not accept there had been any breach of Clauses 4.1 or 4.2.

PANEL RULING

The Panel noted Pfizer's submission that the prescribing information on the Sayana-Press website which was last updated in May 2016, and not May 2015 as referred to by the complainant, was current and up-to-date. The only revision to the SPC since that date involved Section 5.1 which did not necessitate a change to the prescribing information. The Panel therefore ruled no breach of Clause 4.1.

e) Depo-Provera

RESPONSE

Pfizer submitted that the Depo-Provera prescribing information on the website had been effective since July 2015. Pfizer noted that the complainant referred to the eMC to support the claim that the prescribing information had been updated twice since then. Pfizer submitted, however, that the eMC only referred to SPC updates and the complainant had incorrectly concluded them to be prescribing information updates. Not all SPC updates required revisions to the prescribing information.

The first of the two SPC updates (February 2016) involved Section 5.1, Pharmacodynamic properties and thus had no impact on the prescribing information. The second resulted from a type II variation that was submitted to the regulatory authority to primarily update Section 4.8 of the SPC in line with the Company Core Data Sheet. The update involved relocation of three clinically non-serious side effects under the 'Very Common' category (they were moved from 'Common' and 'Other' categories) as well as clinically non-significant changes to other sections. The regulatory approval for this variation was received in December 2016 and as a result the SPC was updated. The prescribing information had also been updated to reflect these changes to a new version which was now effective on all materials but at the time of the complaint the previous prescribing information was effective. Therefore Pfizer did not accept there had been any breach of Clauses 4.1 or 4.2.

In response to a request for further information, Pfizer submitted that regulatory approval for the type II variation referred to above was received on the 8 December 2016 and accordingly the SPC was updated the same day. A copy of the updated Depo-Provera prescribing information (ref DP 14-0) was provided. Pfizer submitted that it was the master copy and therefore a certificate of approval did not form part of the document in accordance with Pfizer's global process for the management of all regulatory labelling documentation (including the prescribing information) which was created, maintained and stored in its regulatory document management system. The prescribing information was approved by medical affairs to ensure compliance with Clause 4 of the Code. The approved prescribing information itself was not certified until the document was attached to a promotional item. At this stage, the prescribing information would be certified as an integral part of the promotional item through Pfizer's approval and certification management system.

PANEL RULING

The Panel noted Pfizer's submission that the Depo-Provera SPC was updated in December 2016 such that three clinically non-serious side effects were moved to the 'Very Common' category from the 'Common' (nervousness) and 'Other' (weight increase, weight decrease) categories. The Panel noted Pfizer's submission that the prescribing information had since been updated to reflect these changes and that a new version was now effective on all materials but that at the time of the complaint (2 January) the previous prescribing information was effective. The Panel noted Pfizer's submission that regulatory approval for the type II variation was received on Thursday, 8 December 2016 and the SPC was updated the same day. The Panel further noted that according to the eMC, the updated SPC was displayed on Wednesday, 14 December 2016. The Panel noted that the general principle was that the prescribing information (defined in Clause 4.2) must be up-to-date, must comply with Clauses 4.1 and 4.2 of the Code and must not be inconsistent with the particulars given in the SPC. The Panel considered that the prescribing information seen by the complainant on 2 January when the complaint was received was not up-to-date. The website thus contained out-of-date prescribing information for Depo-Provera which was not in line with the SPC and the Panel ruled a breach of Clause 4.1.

f) Summary

COMPLAINT

The complainant stated that each instance might be technically following the requirements of the Code if the sections that had been updated had not altered the prescribing information but together pointed to a concerning picture when all four were out-of-date. The complainant queried whether the processes were rigorous enough to prevent this from happening.

RESPONSE

Pfizer regretted that there had been a breach of Clauses 4.1 and 4.2 due to an isolated incident as

a result of human error on the Vfend leavepiece (ref VFE1771). However, all other materials for all products referred to by the complainant had the correct and up-to-date prescribing information and there were no breaches of Clauses 4.1 or 4.2 in these examples. Thus Pfizer strongly believed that high standards had been maintained in compliance with Clause 9.1.

PANEL RULING

The Panel noted its rulings above and considered that high standards had not been maintained. Up-to-date prescribing information had not been provided in the case of the Vfend leavepiece available on the Pfizer website. The out-of-date prescribing information did not refer to dermatological adverse events and higher frequency of liver enzyme elevations in the paediatric population in the Warnings and Precautions Section. It also did not include the addition of new very common and common side effects. Further, out-of-date Depo-Provera prescribing information was provided at the time of the complaint such that three clinically non-serious side effects were not listed as 'Very Common'.

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

2 Champix reprint

COMPLAINT

The complainant referred to a page on Pfizer's Champix (varenicline) website from which a copy of a new landmark study, EAGLES, the largest comparative randomised controlled trial of approved smoking cessation medicines could be downloaded. The complainant stated that although it was clear that the document was held on a different site, as health professionals were proactively encouraged to

use the link, the complainant queried whether it was an independent item or whether it was promotional in nature.

RESPONSE

Pfizer submitted that with regard to the complainant's query about the link to an e-reprint hosted on the Elsevier website about Champix, the hyperlinked publication was part of the same material that was referenced by the complainant as health professionals had, in effect, been invited to access the publication. All requirements of the Code had been met with regard to the page and the associated e-reprint. The requirements of Clauses 4.1 and 4.2 were met through the provision of prescribing information on the website as a clickable link in close proximity to the link to the e-reprint.

As the Elsevier website that hosted the e-reprint was not itself owned by Pfizer, a clear statement to that effect was provided to comply with data privacy requirements.

PANEL RULING

The Panel noted Pfizer's submission that health professionals had, in effect, been invited to access the publication and that Pfizer had certified the e-print for promotional use. The Panel considered that upon visiting the website and possibly downloading the publication, relevant prescribing information should, at the same time, be available to the health professional and in that regard it noted that prescribing information could be accessed via a separate but prominent link in the same screenshot as the link to the publication. No breach of Clause 4.1 was ruled.

Complaint received **3 January 2017**

Case completed **3 April 2017**

PHARMACEUTICAL PHYSICIAN v STIRLING ANGLIAN

Use of the word 'new'

A pharmaceutical physician, who until recently worked in the industry but now provided oncology consultancy services, complained that on its website for health professionals, Stirling Anglian Pharmaceuticals described Stirlescent (naproxen effervescent tablets) and theiCal-D3 (1000mg/880IU chewable tablet) as 'new' despite both having been on the market for over 12 months. The complainant could see no evidence that any part of the website had been certified.

The detailed response from Stirling Anglian is given below.

The Panel noted that, as acknowledged by Stirling Anglian, theiCal-D3 was still described as 'new' on its health professional website on 2 January 2017, despite the product having been available for more than 12 months. A breach of the Code was ruled.

With regard to Stirlescence, although, as stated on the website, it was licensed in the UK on 3 December 2015, it was not generally available until 25 May 2016. The medicine, however, had been promoted to health professionals from 10 March 2016 and so in that regard it could continue to be described as 'new' until 9 March 2017. The Panel noted that this complaint was received in January 2017 and thus it ruled no breach of the Code.

The Panel noted that the Constitution and Procedure was such that complainants had the burden of proving their complaint on the balance of probabilities. The complainant had alleged that he/she could see no evidence that any part of the Stirling Anglian website had been certified for promotional use. Stirling Anglian stated that although the website had been certified, no certificate could be found. This was highly unsatisfactory. Noting the company's account and that the complainant bore the burden of proof, and given the lack of evidence that the website had not been certified, the Panel ruled no breach of the Code.

A pharmaceutical physician, who until recently worked in the industry but now provided oncology consultancy services, complained about Stirling Anglian Pharmaceuticals Limited's use of the word 'new' on its website for health professionals to describe Stirlescent (naproxen effervescent tablets) and theiCal-D3 (1000mg/880IU chewable tablet).

COMPLAINT

The complainant stated that both Stirlescent and theiCal-D3 were described as new but both had been on the market for over 12 months. The complainant could not see evidence that any part of the website had been certified for promotional use which probably explained why in both instances it had not been updated in a timely manner.

When writing to Stirling Anglian, attention was drawn to the requirements of Clauses 7.11 and 14.1 of the Code.

RESPONSE

Stirling Anglian stated that an internal review recognised that the website certification process should be improved. An external agency was undertaking a review of the content and resetting the process and procedures to ensure that the company complied with the Code in future.

Stirling Anglian accepted that in the health professional area of its website the word 'new' was inappropriately used to describe theiCal-D3 when viewed by the complainant on 2 January 2017. This area of the website was intended for health professional use only and not members of the public. Stirling Anglian apologised unreservedly. This area of the website was checked before the end of November 2016 and regretfully this instance was missed.

On receipt of the complaint Stirling Anglian immediately removed the instances of the use of the word and had contracted an external company to undertake a compliance review of the website.

Stirling Anglian submitted that Stirlescent was first made generally available on 25 May 2016 with stock following a notification on 5 January 2016 that it was listed in the Electronic Medicines Compendium (eMC). The company did not accept that the use of 'new' was inappropriate when the complainant viewed the website (2 January 2017). It had however removed the word 'new' from the Stirlescent health professional only area. The company submitted that 'generally available' would start from the moment that the medicine was promoted and available with stock in the market which in this instance was 25 May 2016 but in case the date of the eMC listing was taken as the start of the 12 months it had taken this action.

In response to a request for further information, Stirling Anglian submitted that Stirlescent was first promoted to health professionals on 10 March 2016 and this promotional material was reviewed and certified by its now departed medical department on 29 February 2016. The company was notified by the NHS Business Services Authority (NHSBSA) via eMC In-Demand that Stirlescent was approved as a 'new' product and listed on eMC. 'New' was removed from the relevant page on the company website on 6 January 2017.

All content for the website was discussed and updated on a beta site before signatories verbally agreed to add this to the live website. Although the certification of the website content was made by the two members of staff, due to staff changes unfortunately this could not now be found.

Stirling Anglian stated that as a result of the importance of the key functions in compliance it had reviewed its company structure and performance. Within this, it had replaced its medical department and was introducing new systems and processes with two very experienced pharmaceutical signatories. Although the company considered that its website contained appropriate material, the situation had highlighted shortcomings. Stirling Anglian submitted that it would take its product and clinical website areas down and review every piece of information, update and recertify, using its new process, as a matter of urgency.

PANEL RULING

The Panel noted that Clause 7.11 stated that the word 'new' must not be used to describe any product or presentation which had been generally available, or any therapeutic indication which had been promoted, for more than 12 months in the UK.

The Panel noted that, as acknowledged by Stirling Anglian, theiCal-D3 was described on its health professional website as 'new' on 2 January 2017, despite the product having been available for more than 12 months (the product was launched on 2 October 2014). A breach of Clause 7.11 was ruled.

With regard to Stirlescence, although, as stated on the website, the product was licensed in the UK on 3 December 2015, it was not generally available until 25 May 2016. The medicine, however, had been promoted to health professionals from 10 March

2016 and so in that regard it could continue to be described as 'new' until 9 March 2017. The Panel noted that this complaint was received in January 2017 when Stirling Anglian could still describe Stirlescence as 'new' and thus it ruled no breach of Clause 7.11. The Panel noted Stirling Anglian's submission that 'new' was removed from the relevant page on the company website on 6 January 2017, three days after the receipt of this complaint.

The Panel noted that the Constitution and Procedure was such that complainants had the burden of proving their complaint on the balance of probabilities. The complainant had alleged that he/she could see no evidence that any part of the Stirling Anglian website had been certified for promotional use. Stirling Anglian stated that the website had been certified but that the signatories had now left the company and no certificate could be found. This was highly unsatisfactory. Clause 14.6 of the Code required companies to keep certificates and the relevant accompanying information for not less than three years after final use of the material. Noting the company's account and that the complainant bore the burden of proof, and given the lack of evidence that the website had not been certified, the Panel ruled no breach of Clause 14.1.

The Panel noted Stirling Anglian's submission that this case had highlighted deficiencies and that it was introducing new systems and processes.

Complaint received **2 January 2017**

Case completed **23 February 2017**

ANONYMOUS, NON-CONTACTABLE v ROCHE

Article on the BBC website

An anonymous, non-contactable complainant, who stated that he/she was a co-owner of a healthcare public relations company, submitted a complaint about an article which was posted on the BBC website on 22 December 2016 and extensively covered in broadcast media by the BBC.

The BBC article was entitled 'Multiple sclerosis drug "a landmark"'. The article outlined two trials of Roche's unlicensed medicine, ocrelizumab. One trial was in primary progressive multiple sclerosis (MS) and the other in relapsing remitting MS. The BBC website referred to trials published in the New England Journal of Medicine (NEJM) and included quotations from Professor Gavin Giovannoni from Barts and The London School of Medicine and Dentistry, Dr Aisling McMahon, from the MS Society and Dr Peter Calabresi, Johns Hopkins University, Baltimore.

The article stated that '... the percentage of patients that had deteriorated fell from 39% without treatment to 33% with ocrelizumab'. The complainant stated that this did not sound 'landmark'. The complainant referred to another statement 'the relapse rate with ocrelizumab was half that of those using another drug'. The complainant understood that some other MS medicines might have a greater effect on relapse rate so was not sure if this was 'landmark' either.

The complainant was confused as to how this promotion of a medicine to the public was permitted particularly before a licence was issued.

The detailed response from Roche is given below.

The Panel noted that when complaints were received about what an independent journalist had published in the press, its rulings were made upon the material released by the company that might have prompted the article and not the article itself.

The Panel noted that the article on the BBC website was headed 'Multiple sclerosis drug "a landmark"' and began by stating that ocrelizumab had been described as 'big news' and a 'landmark' in treating MS by doctors and charities. The 'big news' quotation had come independently from the MS Society and the NEJM editorial by Dr Calabresi had described the studies as 'landmark' studies. The article referred to the positive results for ocrelizumab in primary progressive MS and in relapsing remitting MS. It quoted Professor Giovannoni who co-operated with Roche to state that 'The results shown by these studies have the potential to change how we approach treating both relapsing and primary progressive MS' and 'It's very significant because this is the first time a phase three trial has been positive in primary progressive MS'. The BBC article also referred

to Dr Calabresi warning doctors to stay vigilant because of the risk of side-effects. Weakening the immune system increased the risk of infection and of cancer emerging.

The Panel noted that the press release issued by Roche UK did not describe either ocrelizumab or the trial as 'landmark' nor did it contain reference to or quotations from Dr McMahon or Dr Calabresi. The Panel had no evidence about how ocrelizumab had been described verbally by Roche's spokespersons. The press release was headed 'Phase III results for Roche's investigational medicine ocrelizumab published in New England Journal of Medicine'. The press release referred to the role of B-cells in both early and more advanced MS. It included a quotation from Professor Giovannoni, a member of the scientific steering committee for the studies who stated that a significant reduction in disease activity and disability progression as a result of ocrelizumab treatment, compared with standard-of-care high-dose interferon was seen and that 'The consistency and robustness of the outcomes seen in these clinical studies, and the favourable safety profile and high-efficacy of ocrelizumab supports a growing consensus on the importance of early effective treatment in MS'. The press release referred to the consistent and clinically meaningful reductions in major markers of disease activity and progression compared with Rebif (interferon beta-1a) in relapsing remitting MS and with placebo in primary progressive MS.

The Panel noted that the editorial in the NEJM referred to the significance of the results and that ocrelizumab was the first medicine to show a significant effect in slowing disability progression in a phase three trial in primary progressive MS and therefore the trial represented a landmark study in the field. The editorial referred to the need to consider side-effects including the higher than normal risk of herpes reactivation and of neoplasms, especially breast cancer. The editorial concluded with the need to study these side-effects in future trials and the need for phase four monitoring in the community to understand the extent of the risk. Clinicians were urged to stay vigilant with regard to monitoring for side-effects that could be managed effectively if detected early.

The Panel noted that ocrelizumab was not licensed. It considered that there would understandably be much interest in this product and particularly in the results in treating primary progressive MS given Roche's submission that no other medicine had demonstrated a statistically significant treatment effect in primary progressive MS. The Panel considered that the BBC website went beyond the press release issued by Roche. It reflected some of the language used in the NEJM editorial.

The Panel noted the complainant's concerns about the use of the word 'landmark' in the BBC article with regard to two quotations in particular. 'Landmark', however, was not used in the Roche press release. It was clear from the press release that the product was investigational and that the marketing applications were under review. The Panel considered that the tone of the Roche press release was different to that of the article and the positive language used in the NEJM and did not appear to have led to the 'landmark' claim in the BBC article. Although the use of 'landmark' might encourage members of the public to ask their health professionals to prescribe a specific prescription only medicine, the Panel did not consider this would be a consequence of the Roche press release at issue. The Panel ruled no breaches of the Code including Clause 2 on the narrow ground alleged.

An anonymous, non-contactable complainant, who stated that he/she was a co-owner of a healthcare public relations company with nearly 30 years' experience, submitted a complaint about an article which was posted on the BBC website on 22 December 2016 and extensively covered in broadcast media by the BBC.

The BBC article was entitled 'Multiple sclerosis drug "a landmark"'. The article outlined two trials of Roche Products Limited's unlicensed medicine, ocrelizumab. One trial was in primary progressive multiple sclerosis (MS) and the other in relapsing remitting MS. The BBC website referred to trials published in the New England Journal of Medicine (NEJM) and included quotations from Professor Gavin Giovannoni, Chair of Neurology, Barts and The London School of Medicine and Dentistry, Dr Aisling McMahon, Head of Clinical Trials at the MS Society and Dr Peter Calabresi, Johns Hopkins University, Baltimore.

COMPLAINT

The complainant referred to a statement in the BBC article '... the percentage of patients that had deteriorated fell from 39% without treatment to 33% with ocrelizumab'. The complainant stated that whilst his/her and his/her colleagues' knowledge of MS was not extensive, this did not sound 'landmark' to them. The complainant referred to another statement 'the relapse rate with ocrelizumab was half that of using another drug'. The complainant understood that some other MS medicines might have an even greater effect on relapse rate so was not sure if this was 'landmark' either.

The complainant and his/her colleagues had been trained by clients on the Code and had also attended seminars run by the PMCPA and were confused as to how this promotion of a medicine to the public was permitted particularly before a licence was issued. In the complainant's experience, where company sponsored trials of a medicine were being communicated via broadcast media, the company's UK affiliate or parent company was always extensively involved in the content, language and tone. The agencies, as directed by the manufacturer, then tended to brief the media, charities and physicians. It might be that the parent company was

responsible for this article placement but it would be good to know if this therefore made it acceptable.

The complainant stated that the reason that he/she had brought this to the PMCPA's attention was to request an assessment of the article and associated media of this story in the UK and for some clarity of whether or not a breach of the Code had occurred. In addition, the healthcare communications field would welcome some guidance – issued by the PMCPA – on the dos and don'ts of communicating medicines to the public within the UK. Companies often called this a grey area; some took a conservative line and others had very few limitations.

When writing to Roche the Authority asked it to bear in mind the requirements of Clauses 26.2, 9.1 and 2 of the Code.

RESPONSE

Roche submitted that all activities had been in accordance with the letter and spirit of the Code and in particular, Clauses 26.2, 9.1 and 2.

Roche submitted that on 21 December 2016, phase three clinical trial results from the ocrelizumab clinical trial programme in primary progressive MS and relapsing remitting MS were published in the prestigious NEJM (Hauser *et al* 2016 and Montalban *et al* 2016 and an associated editorial by Calabresi).

No other medicine had demonstrated a statistically significant treatment effect in primary progressive MS, a disease area with a high unmet medical need. In relapsing remitting MS, ocrelizumab was shown to be a high efficacy medicine with a favourable safety profile. Safety concerns plagued most high efficacy options and typically led to complex and burdensome patient monitoring algorithms as a result. Ocrelizumab appeared to be positively different in that respect.

Given that ocrelizumab was the first and only medicine to have compelling clinical data in both primary progressive MS and relapsing remitting MS, Roche considered publication of these clinical trial results was newsworthy.

Being aware of the anticipated publication of these important and newsworthy results in the NEJM, Roche Products Ltd (the UK trading company for Roche's pharmaceutical operations) drafted and approved a press release to coincide with the publication. Whilst the Code required examination of press releases, Roche certified the final version which was completed in a timely manner by one medical final signatory and one senior employee (non-medical). Particular care and attention was given to ensure adherence to all previously published PMCPA guidance in relation to press releases and guidance contained in Clause 26 and its supplementary information.

Roche submitted that the press release was factual and accurate; it commented on the results of the study within the context of the regulatory process in a balanced manner. There were no superlative statements or claims of any description with a

brief passing commentary on the key primary and secondary endpoints that were met in the studies. There was no use of the word 'landmark' which appeared in the BBC article in question and which the anonymous complainant had particularly commented upon. Importantly, the press release was not intended to raise unfounded hopes or to encourage members of the public to ask their health professionals for the medicine.

The Roche press release included a quotation from Professor Giovannoni which Roche had proactively sought. The email exchange with Professor Giovannoni and approval of the quotation on this topic was provided. Roche recognised that it was responsible for all aspects of the press release including any quotations within. Professor Giovannoni's quotation was fair, balanced and appropriate within the context of the press release.

For additional background information, in November 2016, Roche was asked by the MS Society for the anticipated publication of this data in the NEJM. Accordingly, the MS Society was informed of the NEJM publications reactively.

Roche stated that before it proactively distributed the press release to appropriate health journalists, it was approached by a BBC health journalist, James Gallagher, for more information about the NEJM publication. Having previously submitted his name to the NEJM database and mailing list, he was independently notified of the impending publication of the ocrelizumab clinical trial programme by the NEJM a week before publication. Upon this notification, Mr Gallagher contacted the MS Society, which then referred him to Roche as documented in the email exchange. This email exchange was initiated by the MS Society to Mr Gallagher and included a quotation from Dr Aisling McMahon, at the society. Roche had no input into this quotation, nor awareness of it until a member of its public relations team was copied into the email. The quotation was not used in Roche's press release.

Upon his request, Roche provided James Gallagher with the embargoed Roche press release and facilitated access to Professor Giovannoni.

Roche did not approach Dr Calabresi for either a quotation or to facilitate an interview at any time. Roche noted that the NEJM editorial, written by Dr Calabresi, stated that the data was 'landmark'. Given James Gallagher's awareness of the NEJM editorial therefore, Roche submitted that he might have used this language as a result of reading this editorial.

In summary, Roche submitted that the press release was factual, accurate and presented in a balanced manner with no potential to either raise unfounded hopes or to encourage members of the public to ask their health professionals to prescribe a specific prescription only medicine. It therefore submitted that the press release was in accordance with the requirements of Clause 26.2.

Roche submitted that high standards were maintained throughout the creation, review, approval

and dissemination of the press release in accordance with the requirements of the Code. Roche thus did not believe the activities were in breach of Clause 9.1.

Finally, given its position with regard to Clauses 26.2 and 9.1, Roche did not believe any of these activities had brought discredit upon or reduced confidence within the pharmaceutical industry and therefore it denied a breach of Clause 2.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. Like all complaints, anonymous complaints were judged on the evidence provided. The complainant bore the burden of proving his/her complaint on the balance of probabilities.

The Panel noted that Clause 26.1 prohibited the advertising 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 had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific prescription only medicine.

The supplementary information to Clause 26.2 made it clear that companies could provide non-promotional information about prescription only medicines to the press and others. The Panel noted that the material at issue had appeared on the BBC website.

The press release was issued by Roche UK but in response to the point raised by the complainant about the possible involvement of the parent company, it was a well-established principle that the UK company was responsible under the Code for the activities of overseas companies in the UK. The Panel noted that when complaints were received about what an independent journalist had published in the press, its rulings were made upon the material released by the company that might have prompted the article and not the article itself.

The Panel noted that the article on the BBC website was headed 'Multiple sclerosis drug "a landmark"' and began by stating that the medicine had been described as 'big news' and a 'landmark' in treating MS by doctors and charities. The 'big news' quotation had come independently from the MS Society and the NEJM editorial had described the studies as 'landmark' studies. The article referred to the positive results for ocrelizumab in primary progressive MS and in relapsing remitting MS. It quoted Professor Giovannoni who co-operated with Roche to state that 'The results shown by these studies have the potential to change how we approach treating both relapsing and primary progressive MS' and 'It's very significant because this is the first time a phase three trial has been positive in primary progressive MS'. The article quoted Dr McMahon from the MS Society who stated that 'This is really big news for

people with the primary progressive form of [MS]' and Dr Calabresi was quoted as stating that 'This is the first drug to show a significant effect in slowing disability progression in a phase three trial in primary progressive [MS] and therefore represents a landmark study in the field'. This statement was also in the editorial in the NEJM which he had written. The BBC article also referred to Dr Calabresi warning doctors to stay vigilant because of the risk of side-effects. Weakening the immune system increased the risk of infection and of cancer emerging.

It appeared from email correspondence provided that it was the MS Society that referred the journalist to Roche; Roche in turn provided the journalist with an embargoed copy of the press release in response to his request for more information on the NEJM papers and facilitated contact with Professor Giovannoni. In the Panel's view the emails provided did not contain any inappropriate claims for ocrelizumab.

The Panel noted that the press release issued by Roche UK did not describe either ocrelizumab or the trial as 'landmark' nor did it contain reference to or quotations from Dr McMahon or Dr Calabresi. The Panel had no evidence about how ocrelizumab had been described verbally by Roche's spokespersons. The press release was headed 'Phase III results for Roche's investigational medicine ocrelizumab published in New England Journal of Medicine'. The press release referred to the role of B-cells in both early and more advanced MS. It included a quotation from Professor Giovannoni, a member of the scientific steering committee for the studies who stated that a significant reduction in disease activity and disability progression as a result of ocrelizumab treatment, compared with standard-of-care high-dose interferon was seen and that 'The consistency and robustness of the outcomes seen in these clinical studies, and the favourable safety profile and high-efficacy of ocrelizumab supports a growing consensus on the importance of early effective treatment in MS'. The press release referred to the consistent and clinically meaningful reductions in major markers of disease activity and progression compared with Rebif (interferon beta-1a) in relapsing remitting MS and with placebo in primary progressive MS. Emails showed that Roche had provided Professor Giovannoni with a suggested quotation which he had then amended slightly.

The press release also included a quotation from Roche UK referring to the potential impact ocrelizumab might have on improving patient outcomes, especially in primary progressive MS where there were no treatments currently available. Roche also referred to the work to address the unmet needs of and provide high-efficacy treatment options for the 100,000 people in the UK who had these forms of MS.

The press release concluded with information on the marketing applications submitted for relapsing remitting MS and primary progressive MS which had been validated and were currently under review by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). The notes to editors section of the press release gave details about the studies and their outcomes including data for adverse events.

The Panel noted that the editorial in the NEJM referred to the significance of the results and that ocrelizumab was the first medicine to show a significant effect in slowing disability progression in a phase three trial in primary progressive MS and therefore the trial represented a landmark study in the field. The editorial referred to the need to consider side-effects including the higher than normal risk of herpes reactivation and of neoplasms, especially breast cancer. The editorial concluded with the need to study these side-effects in future trials and the need for phase four monitoring in the community to understand the extent of the risk. Clinicians were urged to stay vigilant with regard to monitoring for side-effects that could be managed effectively if detected early.

The Panel noted that ocrelizumab was not licensed. It considered that there would understandably be much interest in this product and particularly in the results in treating primary progressive MS given Roche's submission that no other medicine had demonstrated a statistically significant treatment effect in primary progressive MS. The Panel considered that the BBC website went beyond the press release issued by Roche. It reflected some of the language used in the NEJM editorial.

The Panel noted the complainant's concerns about the use of the word 'landmark' in the BBC article with regard to two quotations in particular. 'Landmark', however, was not used in the Roche press release. It was clear from the press release that the product was investigational and that the marketing applications were under review. The Panel considered that the tone of the Roche press release was different to that of the article and the positive language used in the NEJM and did not appear to have led to the 'landmark' claim in the article. Although the use of 'landmark' might encourage members of the public to ask their health professionals to prescribe specific prescription only medicine, the Panel did not consider this would be a consequence of the Roche press release at issue. The Panel therefore ruled no breach of Clause 26.2 on the narrow ground alleged.

The Panel noted that the complainant referred to the BBC article as promoting an unlicensed medicine. The case preparation manager had not asked the company to respond in relation to the requirements of Clause 26.1 or Clause 3.1 of the Code so the Panel was unable to consider those requirements.

The Panel noted its ruling above and considered that Roche had not failed to maintain high standards and therefore ruled no breach of Clause 9.1.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure, and was reserved for such circumstances. The Panel noted its rulings above and did not consider that the press release brought discredit upon or reduced confidence in the industry, and ruled no breach of Clause 2.

Complaint received	4 January 2017
Case completed	7 February 2017

ANONYMOUS NON CONTACTABLE v MERCK SERONO

Conduct of a representative

An anonymous, non-contactable complainant, who described him/herself as an oncology nurse specialist in a large regional oncology centre, complained about the conduct of a representative from Merck Serono in the course of promoting Erbitux (cetuximab). Erbitux was for the treatment of metastatic colorectal cancer and squamous cell cancer of the head and neck.

The complainant stated that over the last six months or so the representative had focussed on trying to sign him/her up to the company's electronic communication system. This involved the complainant giving his/her consent to be contacted by email and text messages. The complainant repeatedly told the representative that he/she did not want to be contacted in that way. This had not stopped the representative from asking every time he/she was in the unit and being quite forceful about it. The complainant felt under a lot of pressure to agree and was not the only member of staff who had experienced this problem and felt the same way.

The complainant queried whether pharmaceutical companies were allowed to do this, as he/she considered that contacting people by their email and text messages was very invasive and unwelcome. Also, if someone said 'No' to this type of electronic communication once, then they should not be asked again and again.

The detailed response from Merck is given below.

The Panel noted that the complainant was anonymous and non-contactable and had not provided sufficient information so that the particular circumstances could be identified.

The Panel noted that Merck Serono had a process in place regarding how its representatives could approach health professionals to gain their consent to receive items by email and/or text. Representatives were trained on the process in 2016 and the company had several briefing documents regarding the collection of consent. The Panel noted that whilst representatives were not specifically briefed about what to do if a customer refused to be contacted by email or text, instructions had been issued by the company following notification of this complaint. The Panel further noted that Merck Serono representatives were not incentivised for collecting consents from health professionals. There was no evidence that any of its representatives had repeatedly asked for consent as alleged.

The Panel did not consider that the complainant had provided evidence to demonstrate on the balance of probabilities that a Merck Serono representative had acted as alleged. No breaches of the Code were ruled.

An anonymous, non-contactable complainant, who described him/herself as an oncology nurse specialist, complained about the conduct of a representative from Merck Serono Limited in the course of promoting Erbitux (cetuximab). Erbitux was for the treatment of metastatic colorectal cancer and squamous cell cancer of the head and neck.

COMPLAINT

The complainant stated that he/she worked as a specialist in a large regional oncology centre and for several years the Merck representative had visited his/her unit to promote Erbitux to the medical and nursing teams. In general, the complainant found these sales calls to be quite useful and the representative very pleasant.

The complainant stated, however, that over the last six months or so things had changed and the representative had focussed on trying to sign him/her up to the company's electronic communication system. This involved the complainant giving his/her consent to be contacted by email and text messages. The complainant repeatedly told the representative that he/she did not want to be contacted in that way and that he/she only had a personal mobile. This had not stopped the representative from asking every time he/she was in the unit and being quite forceful about it. The complainant felt under a lot of pressure to agree and was not the only member of staff who had experienced this problem and felt the same way.

The complainant queried whether pharmaceutical companies were allowed to do this, as he/she considered that contacting people by their email and text messages was very invasive and unwelcome. Also, if someone said 'No' to this type of electronic communication once, then they should not be asked again and again.

In writing to Merck Serono the Authority asked the company to respond in relation to Clauses 15.2 and 15.9 of the Code.

RESPONSE

Merck stated that it took any allegation of inappropriate conduct of its staff very seriously. On receipt of the complaint, it immediately launched an internal investigation and on 1 March the compliance manager sent a communication to all field staff to reinforce principles that had been previously communicated as detailed below.

Merck stated that it had a clearly defined and approved process describing how its representatives could approach health professionals to gain their consent to receive both promotional and non-promotional items by email and/or text. Representatives were trained twice in 2016 on the correct collection of emails and text consent.

Merck stated that its representatives were well-trained and all understood their obligations under the Code and that they must always maintain a high standard when dealing with health professionals and other decision makers. The job description for a representative clearly outlined obligations about integrity and compliance with company and industry guidelines. Merck submitted that it had found no evidence that any of its sales representatives had not acted in line with their job description nor had been in breach of Clause 15.2.

Merck had several clear and specific briefing documents regarding the collection of consent. The collection of written (hard copy) and electronic consent was dealt with and explained for representatives in these documents. Representatives were specifically trained on these briefing documents and the process for obtaining written consent on 20 April 2016. An agenda of the training session was provided. A follow up training session was conducted on 21 September 2016 with the oncology sales team where the company introduced the collection of electronic consent. A copy of the training record was provided. Merck denied a breach of Clause 15.9.

Merck stated that whilst its briefing documents did not specifically detail what a representative should do if a customer refused to be contacted by email or text, it would expect a professional sales representative to know not to repeatedly ask a health professional for consent when that individual had made it clear that they did not want to receive electronic communications. Although, Merck had no evidence that any of its representatives had repeatedly asked for consent in the alleged way, it had taken this on board and included further guidance in its communication to field staff on 1 March 2017.

Merck noted that representatives were not rewarded nor did they receive bonuses for collecting any form of written or electronic consent. In addition, representatives were not set any key performance indicators/targets regarding the collection of consent.

Merck hoped that its explanation and supporting documentation provided clear reasons as to why the Code had not been breached with regards to the allegations relating to Clauses 15.2 and 15.9.

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 complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. The complainant had not provided sufficient information so that the particular circumstances could be identified. The complainant could not be contacted for further information.

The Panel noted that Merck Serono had a process in place regarding how its representatives could approach health professionals to gain their consent to receive items by email and/or text. Representatives were trained on the process in 2016 and the company had several briefing documents regarding the collection of consent. The Panel noted that whilst representatives were not specifically briefed about what to do if a customer refused to be contacted by email or text, instructions had been issued by the company following notification of this complaint. The Panel further noted that Merck Serono representatives were not incentivised for collecting consents from health professionals. There was no evidence that any of its representatives had repeatedly asked for consent as alleged.

The Panel did not consider that the complainant had provided evidence to demonstrate on the balance of probabilities that a Merck Serono representative had acted as alleged. No breach of Clauses 15.2 and 15.9 were ruled.

Complaint received	16 February 2017
Case completed	17 March 2017

CODE OF PRACTICE REVIEW – May 2017

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

AUTH/2885/11/16	Anonymous, non contactable v Gedeon Richter	Promotion of Esmya	Breaches Clauses 2, 7.2 and 9.1 Required to issue a corrective statement by the Appeal Board	No appeal	Page 3
AUTH/2886/11/16	Pharmacosmos v Vifor	Promotion of Ferinject	No breach	No appeal	Page 8
AUTH/2887/11/16	Anonymous Health Professional v AstraZeneca	Meeting attendees and speaker reference to Saxagliptin	Breach Clause 9.1	No appeal	Page 14
AUTH/2888/11/16	Nurse v Napp	Promoting a switch to Remsima	Breaches Clauses 7.2, 7.4, 9.1 and 9.2	No appeal	Page 18
AUTH/2889/11/16	Ex-employee v AstraZeneca	Websites	Three breaches Clause 4.1 Breach Clause 4.6 Two breaches Clauses 7.2 and 7.3 Breach Clause 9.1	No appeal	Page 23
AUTH/2890/11/16	Health professional v Novo Nordisk	Company website	Breaches Clauses 9.10, 14.5 and 26.2	No appeal	Page 32
AUTH/2893/11/16	Anonymous, non contactable v GE Healthcare	Promotion of Vizamyl	Breaches Clauses 3.1, 7.2 and 9.1	No appeal	Page 36
AUTH/2898/11/16 and AUTH/2901/11/16	Director v Roche	Clinical trial disclosure (Kadcyla and Perjeta)	Breaches Clauses 9.1 and 13.1	No appeal	Page 42
AUTH/2906/11/16	Director v Novo Nordisk	Clinical trial disclosure (Tresiba)	Breaches Clauses 9.1 and 13.1	No appeal	Page 51
AUTH/2908/11/16	Director v Bayer	Clinical trial disclosure (Xofigo)	Breaches Clauses 9.1 and 13.1	No appeal	Page 60
AUTH/2912/12/16	Voluntary admission by Astellas Europe	Promotion of Betmiga to the public via social media and the Internet	Breaches Clauses 26.1, 26.2 and 9.1	No appeal	Page 69
AUTH/2918/12/16	Ex-employee v GlaxoSmithKline	Material on internal hosting server	No breach	No appeal	Page 74
AUTH/2920/12/16	Anonymous, non contactable ex representative v UCB	Promotion of Naxolone Minijet	Breaches Clauses 9.1 and 15.9	No appeal	Page 78

AUTH/2922/12/16	Assistant director medicines management v Meda	Conduct of representative	Breaches Clauses 7.2, 7.4 and 15.2	No appeal	Page 83
AUTH/2925/11/17	Health professional v Pfizer	Websites	Two breaches Clause 4.1 Breach Clause 9.1	No appeal	Page 88
AUTH/2926/1/17	Pharmaceutical Physician v Stirling Anglian	Use of word 'New'	Breach Clause 7.11	No appeal	Page 93
AUTH/2927/1/17	Anonymous, non contactable v Roche	Article on the BBC website	No breach	No appeal	Page 95
AUTH/2937/2/17	Anonymous, non contactable v Merck Serono	Conduct of representative	No breach	No appeal	Page 99

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 transfers 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.