NUMBER 97 August 2017

CODE OF PRACTICE REVIEW

PMCPA | Prescription Medicines Code of Practice Authority

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

PUBLIC REPRIMANDS AND EXTENSION OF ASTELLAS' SUSPENSION

Astellas UK and Astellas Europe have each been publicly reprimanded by the Code of Practice Appeal Board for a lamentable lack of concern for patient safety and wholly inadequate oversight and control of prescribing information.

In Cases AUTH/2939/2/17 and AUTH/2940/2/17 Astellas UK and Astellas Europe had each voluntarily admitted multiple failings in relation to prescribing information: Astellas UK voluntarily admitted that there were issues with the prescribing information for seven medicines (Flomaxtra, Vesomni, Vesicare, Advagraf, Prograf, Modigraf and Mycamine); Astellas Europe voluntarily admitted that there were issues with the prescribing information for four medicines (Vesomni, Vesicare, Mycamine and Qutenza). In both cases the prescribing information had been incomplete by the omission of some adverse events and the like, for several years. The Code of Practice Panel was extremely concerned and noted that it was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about their medicines. 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 and Astellas Europe to the Appeal Board.

The Appeal Board considered that these cases raised very serious matters due to the companies' total failure to control prescribing information, the potential consequences for patient safety and the continuing nature of the failure over many years. The Appeal Board publicly reprimanded each company and also decided to require an audit of both Astellas UK and Astellas Europe's procedures in relation to the Code to take place in October 2017. The Appeal Board reported both companies to the ABPI Board.

The ABPI Board noted and endorsed the Appeal Board's views. It was a woeful state of affairs.

The ABPI Board gave serious consideration to expelling Astellas UK from membership of the ABPI. However, it noted the commitments from Astellas Europe, the global company and of the new UK General Manager. The companies had made voluntary admissions and it was now imperative that the October re-audits showed significant progress.

The ABPI Board decided that it would extend the suspension of Astellas UK from membership of the ABPI for another 12 months. This further period would run uninterruptedly from the initial period of suspension (from June 2016) and would then amount to the maximum suspension (two years) allowed under the ABPI Articles of Association.

The ABPI Board also decided that it wanted sight of the report of the October 2017 re-audits of Astellas UK and Astellas Europe so that it could review the position before the end of 2017. If the report of the re-audits did not show significant improvement and progress at both companies, then the ABPI Board would consider expelling Astellas UK from membership of the ABPI.

The MHRA was advised of the ABPI Board's very serious concerns about the conduct of Astellas UK and Astellas Europe particularly in relation to the matters concerning patient safety. European Federation of Pharmaceutical Industries and Associations was also updated and asked to ensure the EFPIA Board was informed of the position.

The interim case reports for Cases AUTH/2939/2/17 and AUTH/2940/2/17 can be found on the PMCPA website.

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 are:

Friday 15 September, 2017 – Fully booked.
Friday 8 December, 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

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

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

Heather Simmonds:	020 7747 1438
Etta Logan:	020 7747 1405
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.

CASE AUTH/2884/10/16

CLINICAL COMMISSION GROUP MEMBER v INTRAPHARM

Letter to GP practices

A member of the medicines management team at a clinical commissioning group (CCG), complained to Intrapharm Laboratories about a letter it had sent to GP practices in the CCG. The complainant copied her complaint to the Authority.

The letter in question was headed 'New Carbocisteine in Sachets – supported by your CCG' and was accompanied by a double-sided A4 advertisement. The letter provided details about the new sachets and their advantages over the currently available capsules and liquid. Readers were informed that the sachets were '… the most cost effective option' and that 'your local CCG has endorsed the use of the Carbocisteine Sachets'.

The complainant stated that the statement that 'your local CCG has endorsed the use of the Carbocisteine Sachets' was not true as the CCG did not support or endorse Carbocisteine Sachets.

Intrapharm had written to the complainant to apologise for the error which it stated was due to a mix up with the postcodes because nearby CCGs, which also formed part of the same support unit had endorsed Carbocisteine Sachets. The company enclosed a copy of a letter, for the complainant's approval, to recall the original letter and apologise for the mistake made. Intrapharm stated that it planned to send the letter to the named CCG GPs immediately.

The detailed response from Intrapharm is given below.

The Panel noted that the letter in question had been sent to GPs in the named CCG. For those recipients the claim that 'your local CCG has endorsed the use of the Carbocisteine Sachets' was not true. The letter was misleading and the claim could not be substantiated. Breaches of the Code were ruled. The Panel noted Intrapharm's remedial action following notification of the error. However, the Panel ruled a breach as the company had failed to maintain high standards.

At the completion of the case Intrapharm refused to pay the full administrative charge and was reported to the Appeal Board in accordance with Paragraph 16.6 of the Constitution and Procedure (Paragraphs 5, 7.1 and 8.1 also referred).

The Appeal Board decided in accordance with Paragraph 11.4 that if full payment was not received within ten working days further action would be taken.

The administrative charge was received from Intrapharm on 5 May 2017. No further action was required

A member of the medicines management team at a clinical commissioning group (CCG), complained to Intrapharm Laboratories Limited about a letter (ref ccf-222-001) it had sent to GP practices in the named CCG. The complainant copied her complaint to the Authority.

The letter in question was headed 'New Carbocisteine in Sachets – supported by your CCG' and was accompanied by a double-sided A4 advertisement for Carbocisteine Sachets.

The letter provided details about the new sachets and their advantages over the currently available capsules and liquid. Readers were informed that the sachets were '… the most cost effective option' and that 'your local CCG has endorsed the use of the Carbocisteine Sachets'.

COMPLAINT

The complainant stated that for recipients in the CCG the statement that 'your local CCG has endorsed the use of the Carbocisteine Sachets' was not true as the CCG did not support or endorse Carbocisteine Sachets.

Intrapharm had written to the complainant to apologise for the error which it stated was due to a mix up with the postcodes because the surrounding CCGs, which formed part of the same support unit had endorsed Carbocisteine Sachets. The company enclosed a copy of a letter, for the complainant's approval, to recall the original letter and apologise for the mistake made. Intrapharm stated that it planned to send the letter to the named CCG GPs immediately.

When writing to Intrapharm, the Authority asked it to consider Clauses 7.2, 7.4 and 9.1 of the Code.

RESPONSE

Intrapharm stated that it had not intended to make false claims or mislead the GP practices in the CCG.

Carbocisteine Sachets were endorsed by the surrounding CCGs since they offered patient benefits and valuable savings to the NHS. Intrapharm submitted that, with agreement from the CCGs, it wanted to inform the local GPs through a mailing. During the mail merge process, the named CCG postcodes were accidently included and this was entirely down to human error.

Intrapharm submitted that it only knew of this error when it received the complainant's email on 19 October 2016 and it responded with an immediate apology and full explanation. In addition, the company offered immediate corrective remedy by

writing a formal recall and apology letter to all the GPs in the CCG, which was sent to the complainant for prior approval. The complainant approved this letter on 20 October 2016 and this was immediately sent out on 26 October 2016 to the GPs. The complainant had been informed of this action. Intrapharm sincerely hoped that its positive and speedy actions to rectify a genuine error showed its commitment to adhere to the highest standards of the Code.

The company stated that it had also reviewed its internal mail merge quality control process to ensure that such errors did not recur.

The letter stated that the company wished to recall the letter and apologise for the mistake and that 'Carbocisteine Sachets have not been endorsed by your CCG'.

PANEL RULING

The Panel noted that the letter in question had been sent to GPs in the named CCG. For those recipients the claim that 'your local CCG has endorsed the use of the Carbocisteine Sachets' was not true. The letter was thus misleading in that regard. A breach of Clause 7.2 was ruled. The claim could not be substantiated. A breach of Clause 7.4 was ruled. The Panel noted Intrapharm's remedial action following notification of the error. However, the Panel considered that in sending the letter in question to GP practices within the named CCG the company had failed to maintain high standards and a breach of Clause 9.1 was ruled.

At the completion of the case Intrapharm refused to pay the full administrative charge due. It offered to pay a lesser amount. Consequently Intrapharm was reported to the Appeal Board in accordance with Paragraph 16.6 of the Constitution and Procedure (Paragraphs 5, 7.1 and 8.1 also referred).

The Appeal Board decided in accordance with Paragraph 11.4 that if full payment was not received within ten working days further action would be taken.

The administrative charge was received from Intrapharm on 5 May 2017. No further action was required

Complaint received	**19 October 2016**
Undertaking received	**29 November 2016**
Appeal Board consideration of the report	**26 April 2017**
Proceedings completed	**5 May 2017**

CASE AUTH/2903/11/16 *NO BREACH OF THE CODE*

DIRECTOR v NOVO NORDISK

Clinical trial disclosure (Ryzodeg)

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 Ryzodeg (insulin degludec/insulin aspart).

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 nine evaluable trials (two Phase I and II and seven 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 61%. The disclosure percentage at 31 July 2015 was 70%.

Ryzodeg was first approved and commercially available in January 2013. The Second 2012 Code and thus the Joint Position 2009 were relevant.

The Panel noted Novo Nordisk's submission that the Phase I and II trials had no UK involvement including no UK patients, investigators or UK funding and neither of the studies were conducted on behalf of Novo Nordisk Ltd (the UK legal entity). The Panel considered that as there was no UK involvement in either of the 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 seven Phase III trials that had not been disclosed within the timeframe; six had still not been disclosed by 31 July 2015. The Panel noted Novo Nordisk's submission that only two Phase III trials had any UK involvement (UK sites and patients). Both studies completed on 2 December 2010 ie before Ryzodeg was launched 21 January 2013 and so results from these trials should have been published by 20 January 2014.

The Panel noted that although Novo Nordisk's submission and the table it provided differed slightly, the results for both trials with UK involvement had been disclosed by 20 January 2014. Thus the Panel ruled no breach of the Code including no breach of Clause 2.

The Panel noted that although, according to the CMRO publication, there were seven Phase III trials that had not been disclosed within the timeframe Novo Nordisk provided details of fifteen additional Phase III trials. Two of those are detailed above. The Panel noted Novo Nordisk's submission that the remaining thirteen trials had no UK involvement including no UK patients, investigators or UK funding and none of the studies 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 remaining thirteen 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.

Ryzodeg

The supplemental information gave details of disclosure of clinical trial results for each product irrespective of sponsor. The data for Ryzodeg (insulin degludec/insulin aspart) 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	9	0	9	7	78%	9	8	89%
Phase III	15	1	14	7	50%	14	8	57%
Phase IV	0	0	0	0		0	0	
Other	0	0	0	0		0	0	
Total	**24**	**1**	**23**	**14**	**61%**	**23**	**16**	**70%**

Footnote (company communication): Results of the seven remaining undisclosed trials (one phase I and six phase III) have since been posted on ClinicalTrials.gov and/or the company's own registry in October 2015, following the approval of the product in the US in September 2015, in compliance with the 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 stated that it was committed to transparency of its clinical trials and took this matter very seriously. It submitted that 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 Clinical Trials Register by EMA according to the EU Clinical Trials 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, Phases I-IV in adults, was provided to EU Clinical Trials Register at the date of last patient last visit plus 12 months. Only results for Phases II-IV trials would be disclosed. It provided a summary of results for paediatric clinical trials, Phase I-IV, to EU Clinical Trials 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 Ryzodeg was first licensed on 21 January 2013 in the EU. It was also commercially available from this date in Denmark. It was not commercially available in the UK. It was first licensed in the US 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 trials; 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 two Phase III studies with UK involvement (UK sites and patients). These were NN5401-3594 and extension study NN5401-3645. 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 during its audit. The EU Clinical Trials Register and the EudraCT results database was back in operation as of 13 Jan 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. The results would be made publicly available by the ClinicalTrials.gov staff once they had completed their review.

Novo Nordisk stated that the results for the two trials with UK involvement were made publicly available by August 2012 (NN5401-3594) and November 2013 (NN5401-3645), both within 12 months of the product being licensed in the EU. Therefore the company submitted that it had not breached Clauses 13.1, 9.1 or 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 studies, nor were any of the studies 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 13 of the 15 trials listed in the table provided titled 'Overview of trials with UK involvement (Ryzodeg)'. 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 two trials highlighted (NN5401-3594 and NN5401-3645) 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.

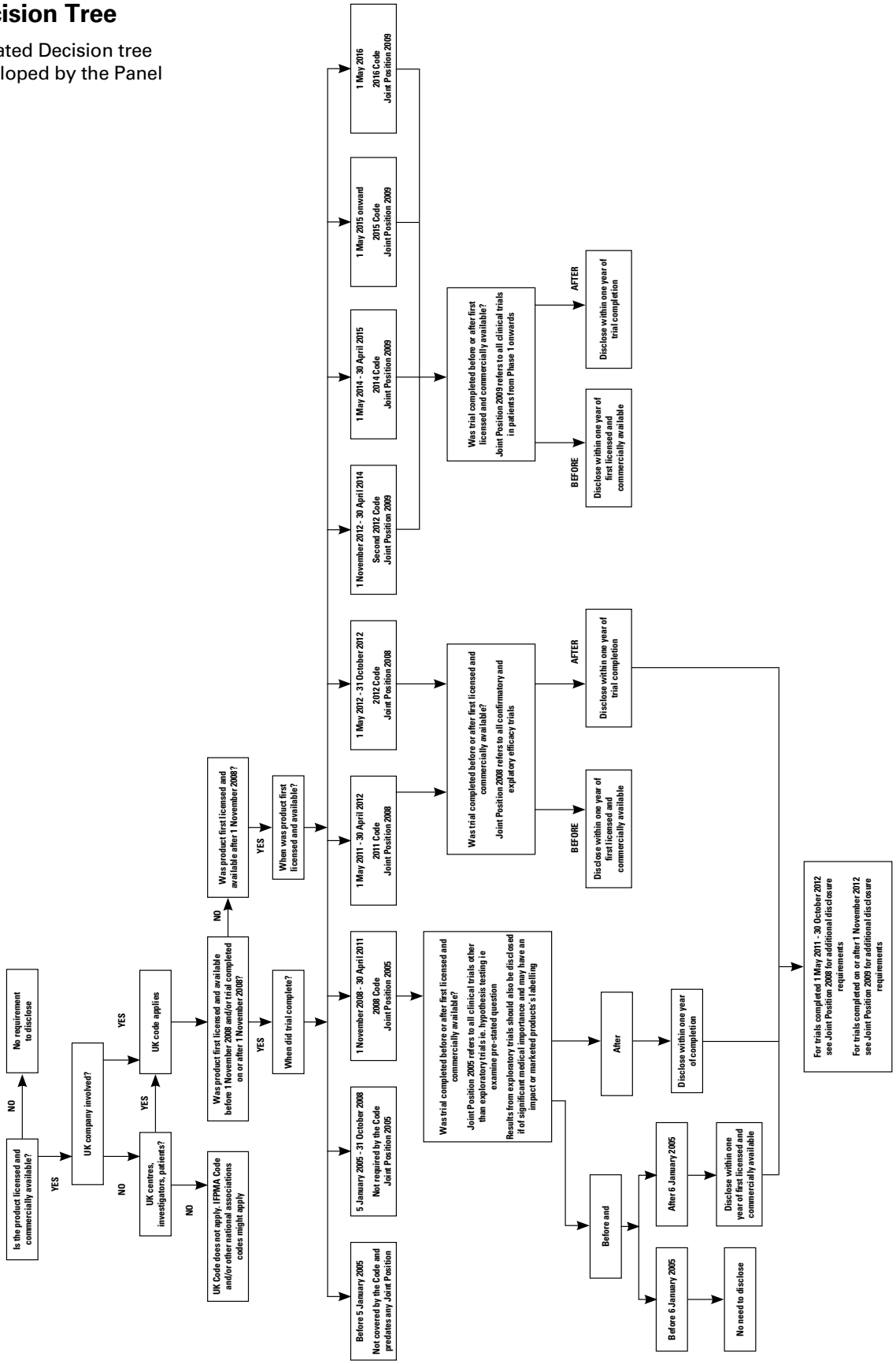
Noting that the CMRO study referred to licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed 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.

Decision Tree

Updated Decision tree developed by the Panel



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 nine evaluable trials (two Phase I and II and seven 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 61%. The disclosure percentage at 31 July 2015 was 70%.

The Panel noted Novo Nordisk's submission that Ryzodeg was first approved and commercially available in Denmark on 21 January 2013. The Second 2012 Code and thus the Joint Position 2009 were relevant.

The Panel noted Novo Nordisk's submission that the Phase I and II trials had no UK involvement including no UK patients, investigators or UK funding and neither of the studies were conducted on behalf of Novo Nordisk Ltd (the UK legal entity). The Panel considered that as there was no UK involvement in either of the 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 seven Phase III trials that had not been disclosed within the timeframe; six had still not been disclosed by 31 July 2015. The Panel noted Novo Nordisk's submission that 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.

The Panel noted Novo Nordisk's submission regarding EudraCT submission deadlines and IT issues but considered that the applicable joint position 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 only two Phase III trials (NN5401-3594 and extension study NN5401-3645) had any UK involvement (UK sites and patients).

Studies NN5401-3594 and NN5401-3645 both completed on 2 December 2010 ie before Ryzodeg was launched 21 January 2013 and so results from these trials should have been published by 20 January 2014.

The Panel noted Novo Nordisk's submission that according to the table which it provided, the results for the two trials with UK involvement were made publicly available by August 2012 (NN5401-3594) and November 2013 (NN5401-3645). The Panel noted that the table actually stated that first results for both studies were available on Novonordisk-trials.com on 28 November 2013 with first full publication on 28 August 2012 (NN5401-3594) and February 2016 (NN5401-3645) respectively. The Panel noted that although Novo Nordisk's submission and the table it provided differed slightly, in both cases the results for both trials had been disclosed by 20 January 2014. Thus the Panel ruled no breach of Clause 13.1 of the Code and consequently no breach of Clauses 9.1 and 2.

The Panel noted that although, according to the CMRO publication, there were seven Phase III trials that had not been disclosed within the timeframe Novo Nordisk provided details of fifteen additional Phase III trials. Two of those were referred to above. The Panel noted Novo Nordisk's submission that the remaining thirteen trials had no UK involvement including no UK patients, investigators or UK funding and none of the studies 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 remaining thirteen 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 **23 February 2017**

CASE AUTH/2928/1/17 and AUTH/2929/1/17

ANONYMOUS v PFIZER AND NOVARTIS

Pharmacovigilance compliance, promotion of an unlicensed indication and breach of undertaking

An anonymous, non-contactable complainant, who stated that he/she was a pharmacovigilance (PV) consultant referred to Case AUTH/2847/5/16. The complainant stated that this case contained important PV considerations not previously addressed.

Cases AUTH/2840/4/16 and AUTH/2847/5/16 concerned the promotion of Ultibro Breezhaler (indacaterol (long acting beta agonist (LABA))/ glycopyrronium (long acting muscarinic antagonist (LAMA)) and Seebri Breezhaler (glycopyrronium) by Novartis and Pfizer.

Ultibro Breezhaler and Seebri Breezhaler were both indicated as maintenance bronchodilator treatments to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD).

The complainant stated that in Case AUTH/2847/5/16 Pfizer (although not the marketing authorisation holder for Ultibro Breezhaler) was obliged to collect and record relevant information including off-label use to pass to the marketing authorisation holder, Novartis.

The complainant stated that the current Ultibro Breezhaler campaign was likely to encourage replacement of fixed dose combinations of inhaled corticosteroids (ICS)/LABAs with the aim of modifying or preventing clinically relevant exacerbations. In the event of increased safety reports of clinically relevant exacerbations associated with morbidly and mortality (however likely or unlikely) associated with Ultibro Breezhaler use, this theoretical PV safety signal resulting from a widespread change in prescribing habits/patterns might be missed in terms of being directly linked with Ultibro Breezhaler off-label use. Information on how the current promotional campaign for Ultibro Breezhaler might lead to a widespread change in prescribing habits/patterns was provided.

The complainant stated that Cases AUTH/2840/4/16 and AUTH/2847/5/16 confirmed that Pfizer knew about the alleged off-label nature of promotional activities in April 2016. In the four months that followed the organisation seemed not to have thoroughly considered the PV implications because by September 2016 the extent of off-label promotion was not curbed as expected but actually intensified as evidenced by the headline, 'Exacerbation risk reduction in your hands' used on an electronic advertisement shown on an exhibition stand at the European Respiratory Society (ERS) congress in London 3-7 September 2016. The copy of the advertisement provided by the complainant referred to both Novartis and Pfizer.

Both companies had failed to identify and clarify what constituted off-label use. It would seem that this failure might have existed for a considerable amount of time which was serious when considering PV obligations. It was likely that potentially thousands of interactions between Pfizer personnel (field or office based) and valid reporters regarding the use of Ultibro Breezhaler to reduce exacerbations in COPD patients had taken place.

The complainant alleged that Pfizer and Novartis had previously failed to adequately train personnel to recognise that the use of Ultibro Breezhaler to reduce exacerbations in COPD was off-label resulting in numerous off-label use case reports that had not been collated for PV maintenance obligations.

The complainant alleged that the PMCPA ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16 was likely to be applicable beyond UK borders such that the number of company interactions where relevant off-label information was not flagged across the whole of Europe would be unacceptably high.

The complainant stated that at the British Thoracic Society (BTS) conference, 7-9 December, Pfizer's campaign for Ultibro Breezhaler included the headline, 'Ultibro Breezhaler, an evidence based solution for patients with COPD with or without a history of exacerbations'.

The clinical development programme for Ultibro Breezhaler included studies where recruited patients had a history of exacerbations (Wedzicha *et al* 2016 and Zhong *et al* 2014) and also at least one study where recruited patients did not have a history of exacerbations (Wedzicha *et al* 2013). The first half of the headline referred to Ultibro Breezhaler being a 'solution' and projected the perception that it was a solution for patients with exacerbations. The complainant alleged that had Pfizer thoroughly considered the pharmacovigilance implications first and developed effective corrective and preventative actions (CAPAs) then continuation of off-label promotion was avoidable.

The complainant stated that in order to understand the legitimacy of the FDC-LABA/LAMA class being promoted for exacerbation risk reduction it was important to consult the relevant regulatory framework ie the guideline on clinical investigation of medicines in the treatment of COPD – EMA/ CHMP/700491/2012. The complainant provided detailed comments including that this document primarily covered the maintenance treatment of COPD and not the treatment and management of acute exacerbations and essentially outlined three possible aims of maintenance treatment.

1 Provide symptomatic relief through improvement of airway obstruction
2 Modify or prevent exacerbations
3 Modify the course of the disease or modify disease progression.

Also discussed was the importance of recognising the severity of exacerbations where the document stated that, '... the rate of moderate or severe exacerbations is a clinically relevant endpoint related to the associated morbidity and mortality, and the usually significantly increased health-care requirement costs'.

Assessment of risk in terms of the rate of moderate or severe exacerbations was the main requirement for a treatment licensed to be used to modify or prevent exacerbations and had distinctive study criteria to meet before a licence was granted for use in COPD patients.

Meeting two criteria enabled a treatment to be licensed specifically for use in symptomatic COPD patients despite bronchodilator therapy with a history of exacerbations. The two criteria highlighted were clearly challenging as demonstrated by Ultibro Breezhaler. In 2016 the manufacturer announced that a pivotal study (NCT01946620 – ClinicalTrials.Gov) did not meet the primary endpoint of demonstrating statistically significant superiority in the reduction of annualised rates of moderate or severe COPD exacerbations when compared to mono-component LABA treatment alone. The manufacturer indicated that the primary endpoint result would not allow it to make a regulatory filing for the COPD indication in Europe. Had this study (NCT01946620) been successful then specific wording of the licence indication for COPD would reflect the existence of respective, suitable, supporting data for clinically relevant exacerbations as was the case for other currently licensed FDC-ICS/LABA medicines in COPD.

An obvious dichotomy existed from a regulatory perspective in that Ultibro Breezhaler could not progress towards a licence in COPD after missing the primary endpoint for a study designed in accordance with the two criteria defined and subsequently the manufacturer simply did not promote Ultibro Breezhaler for use in COPD. Whereas, FDC-LABA/LAMAs were granted licences solely for maintenance treatment aimed at symptomatic relief through improvement of airway obstruction; yet without meeting the two defined study criteria, Ultibro Breezhaler was simultaneously being positioned and promoted as a suitable alternative to licensed FDC-ICS/LABAs for exacerbation risk reduction. In effect, regulatory requirements outlined in EMA/CHMP/700491/2012 related to exacerbation risk reduction were being circumvented by promoting Ultibro Breezhaler for exacerbation risk reduction without being granted a licence that reflected the existence of respective, suitable, supporting data for clinically relevant exacerbations.

The complainant alleged that exhibitor activities for Ultibro Breezhaler at the BTS were in breach of the undertaking for Case AUTH/2847/5/16.

The complainant provided an overview of published evidence for Ultibro Breezhaler in terms of alignment with key study criteria for exacerbation risk reduction stated in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012).

Despite the fact that the study (NCT01946620) involving FDC-fluticasone/formoterol ensured that the clinically relevant primary endpoint – moderate or severe exacerbations was measured and the treatment period was 12 months, progression towards attaining a COPD licence was not possible because the study criteria were challenging and the study eventually missed its primary endpoint. In the case of FDC-LABA/LAMA studies none of the eight Ultibro Breezhaler studies met all three criteria stated, these being clinically relevant primary endpoint for exacerbations, duration of study sufficient to assess exacerbations and above minimal clinically important difference >20% and just one of the eight publications related to Ultibro Breezhaler involved a study where the clinically relevant primary endpoint – moderate or severe exacerbations was measured over a 12 month treatment period (Wedzicha *et al* 2013) and only a 12% reduction in clinically relevant exacerbations vs the comparator was shown (ie below the threshold of 20%).

The lack of Ultibro Breezhaler studies meeting key study criteria for exacerbation risk reduction stated in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012), prompted a broader analysis of other FDC-LABA/LAMAs publications none of the 7 citations involving other FDC-LABA/LAMAs (Buhl *et al* 2015, Celli *et al* 2014, Decramer *et al* 2014, Donohue *et al* 2013, Donohue *et al* 2014, D'Urzo *et al* 2013 and Singh *et al* 2013) met all three criteria.

Out of nine FDC-LABA/LAMAs publications that had a secondary endpoint measure of exacerbations almost all publications did not define exacerbations such that it was not clear to the reader that clinically relevant exacerbations were not measured in these studies. Potentially, this might lead to a misunderstanding and exaggeration of clinical benefit.

The complainant stated that the literature review and assessment undertaken confirmed that there was insufficient evidence to support the use of Ultibro Breezhaler for exacerbation risk reduction. To date, Pfizer and Novartis had simply not undertaken clinical trials in accordance with recommendations in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012). This was concerning given the continuation of off-label promotion. Pfizer used the recent FLAME study (Wedzicha *et al* 2016) as the main reference to support the claims appearing in the promotional materials cited by the complainant. It was not entirely clear to the complainant why Novartis, chose not to undertake this study in accordance with recommendations in the guideline on clinical investigation of medicinal products in the treatment of COPD (EMA/CHMP/700491/2012). It made it problematic

to adequately assess the results alongside other supporting studies for other medicines that were actually licensed to be used in COPD patients with the aim of modifying or preventing clinically relevant exacerbations (EMA/CHMP/700491/2012).

The complainant stated that the totality of data suggested that the extent of protection from bronchodilation via dual bronchodilators, against the development of clinically relevant exacerbations was insufficient.

The complainant stated that exhibitor activities for Ultibro Breezhaler at the BTS conference 7/9 December suggested that those on the exhibition stand were specifically briefed to discuss the medicine in the context of newly issued recommendations within the GOLD 2017 Report.

The updated GOLD Report represented a positive step forward in simplifying the ABCD matrix which previously posed challenges in categorising COPD patients with three different sub-categories possible depending on the presence of either one or both risk factors, namely, FEV1, staging and exacerbations risk. The updated GOLD Report was however concerning from a patient safety perspective as it stated:

- **'Recommendations by the GOLD Committee for use of any medication are based on the best evidence available from published literature and not on labelling directives from government regulators'.**

    - **FDC-LABA/LAMAs were recommended first-line in category D COPD patients and as step up from a LAMA in category C COPD patients. Both of these two recommendations essentially involved use of FDC- LABA/LAMAs in an unlicensed indication or manner.**

- **'It should be noted that there is a lack of direct evidence supporting the therapeutic recommendations for patients in groups C and D'.**

    - **FDC-LABA/LAMAs were recommended first-line in category D COPD patients, but there was no evidence that FDC-LABA/LAMAs compared to LAMAs could significantly reduce the risk of clinically relevant exacerbations which were associated with morbidity and mortality ie moderate or severe exacerbations.**
    - **Furthermore, although the FLAME study reported that in a secondary endpoint, Ultibro Breezhaler was superior to FDC-fluticasone/ formoterol in terms of clinically relevant moderate or severe exacerbations, this effect was not demonstrated in patients with a history of more than one exacerbation, and category C COPD patients were not included in this study (Wedzicha *et al* 2016).**

The complainant noted that in the GOLD Report there was no ratified European Pharmacovigilance Risk Assessment Committee (PRAC) recommendation stating a positive risk-benefit balance for FDC-ICS/LABAs in COPD (eg the magnitude of benefit in terms of clinically relevant exacerbation reduction observed was as much as ten-fold greater compared to the slight increased risk in terms of pneumonia (Corradi *et al* 2016)). Yet a major factor cited within the updated GOLD Report for recommending usage of FDC-LABA/ LAMAs in an unlicensed indication or manner was the frequently repeated reference to the risk of pneumonia with use of FDC-ICS/LABAs. This seemed not to be balanced because the respective PRAC recommendations were excluded. Moreover, these risks of pneumonia were not qualified in the updated GOLD Report, in terms of not translating into a greater risk of mortality (Festic *et al* 2016).

The complainant alleged that when taking into consideration both Pfizer's continued off-label promotion with the revised GOLD Report recommendations that essentially involved recommending use of FDC-LABA/LAMAs in an unlicensed indication or manner, it was clear that there was a underlying move towards circumventing the regulatory requirements outlined in EMA/ CHMP/700491/2012 related to exacerbation risk reduction by promoting/recommending products for exacerbation risk reduction without these medicines being granted licences that reflected the existence of respective, suitable, support data for clinically relevant exacerbations.

The complainant alleged that the regulatory processes in place to protect public health were being marginalised. If the pharmaceutical industry embarked on charting a strategic direction that inadvertently (or otherwise) undermined the very regulatory foundations that were meant to keep patients safe then the industry was entering unwelcomed territory which inevitably would discredit it.

The obvious concern was whilst an unavoidable delay might actually benefit Pfizer commercially. A similar protracted period of time prior to completion of this PV related PMCPA case would not be in the best interest of patient safety. The complainant therefore urged the PMCPA to prioritise completion of this case if possible given the far reaching patient safety implications.

The detailed response from Pfizer and Novartis is given below.

The Panel was extremely concerned that a complaint had been received which included allegations about Novartis' and Pfizer's activities in relation to pharmacovigilance which was vital for patient safety. There were extensive requirements for pharmacovigilance which went beyond the Code. The Panel could only consider allegations in relation to the requirements in the Code.

The Panel noted the complainant's comments about the regulatory requirements outlined in EMA/CHMP/700491/2012 being circumvented by promoting FDC-indacaterol/glycopyrronium for exacerbation risk reduction without being granted a licence that reflected the existence of respective,

suitable, supporting data for clinically relevant exacerbations. The Panel was concerned about activities in relation to the Code. It was not for the Panel to determine whether Novartis' and Pfizer's activities including clinical trials were in line with the regulatory requirements *per se*.

The Code stated that companies must comply with all applicable codes, laws and regulations to which they are subject. The relevant clause had not been raised and the complainant had not provided evidence that the companies had been found in breach of other laws and regulations.

The Panel noted that the complainant had referred to implications across Europe. The Panel could only consider matters which were covered by the UK Code and/or occurred in the UK. The fact that pharmacovigilance reporting in other countries might be lacking was of concern but was not in itself a matter necessarily covered by the ABPI Code.

The Panel noted that both Ultibro Breezhaler and Seebri Breezhaler were indicated as maintenance bronchodilator treatments to relieve symptoms in adult patients with COPD. Section 5.1 of the respective SPCs referred to each medicine's positive impact on exacerbations of COPD compared to other medicines. The Ultibro SPC was last revised on 10 November 2016. The Panel noted the companies' comments in relation to changes to the SPC.

The Panel noted its rulings in the previous cases, Cases AUTH/2840/4/16 and AUTH/2847/5/16. In particular that in some of the materials at issue in those cases, for example the claim that 'Ultibro Breezhaler offers benefits beyond current standard COPD maintenance therapies' and 'vs salmeterol/ fluticasone Ultibro Breezhaler can significantly reduce your patients' rate of moderate or severe exacerbations' appeared to be a consequence of using Ultibro Breezhaler as a maintenance therapy and not the reason to prescribe *per se*, as alleged. In that regard, no breaches of the Code had been ruled.

Other material was ruled in breach as it did not clearly state that Ultibro Breezhaler was a maintenance therapy to relieve COPD symptoms. For example boxed text in a leavepiece 'Reduces exacerbation risk beyond tiotropium (open label) and [salmeterol/fluticasone]' would not be read within the context of the licensed indication. In the Panel's view the leavepiece implied that Ultibro Breezhaler could be prescribed to reduce exacerbations rather than the reduction in exacerbations being a benefit of using the medicine as maintenance therapy. The leavepiece was inconsistent with the particulars listed in the Ultibro Breezhaler SPC. The leavepiece implied that that exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler which was misleading. Breaches of the Code had been ruled including that high standards had not been maintained. Similarly a speaker slide deck (ref UK/ULT/16-0025) entitled 'Evolving science; Dual bronchodilation' examined the burden of COPD and the challenges of treatment and included an overview of clinical studies for, *inter alia*, Ultibro Breezhaler might give the impression that Ultibro Breezhaler could be prescribed for the reduction of exacerbations *per se* which was not consistent with the particulars listed in its SPC. That the presentation implied that Ultibro Breezhaler could be used to reduce COPD exacerbations and was a primary reason to prescribe the product was misleading. Breaches of the Code were ruled including that high standards had not been maintained.

The Panel noted that the complaint in Cases AUTH/2840/4/16 and AUTH/2847/5/16 was received in April 2016 and the requisite undertaking was received on 16 September. The ERS congress referred to by the complainant in Cases AUTH/2928/1/17 and AUTH/2929/1/17 took place from 3 – 7 September. This meant that the activities at that meeting were not covered by the requisite undertaking given in Cases AUTH/2840/4/16 and AUTH/2847/5/16. There could be no breach of that undertaking so the Panel ruled no breaches of the Code including Clause 2.

The Panel accepted the companies' submission that the material used at the ERS meeting reiterated topics that had already been considered by the PMCPA and ruled upon in Cases AUTH/2840/4/16 and AUTH/2847/5/16. The Panel decided that these materials were covered by that ruling and thus decided not to make a separate ruling of breaches of the Code in that regard.

The Panel was concerned that given its rulings in Cases AUTH/2840/4/16 and AUTH/2847/5/16 it appeared that the companies had failed in some representative briefing materials to make Ultibro Breezhaler's licensed indication clear. It did not consider that this necessarily meant that the companies had failed to make it clear to staff what constituted off label use of the product as alleged in Cases AUTH/2928/1/17 and AUTH/2929/1/17. Although it was likely that staff might not be clear, the Panel did not consider that the complainant had shown on the balance of probabilities that the companies had failed to adequately train personnel to recognise that the use of FDC-indacaterol/ glycopyrronium to reduce exacerbations in COPD was off label. Further there was no evidence that there would be numerous off label use case reports and if so that these had not been collated for pharmacovigilance maintenance obligations. The Panel therefore ruled no breaches of the Code including Clause 2.

The Panel noted the companies' submission that they were fully committed to protecting and enhancing patient safety and operated extensive, robust scientific services and pharmacovigilance systems. The Panel did not consider that the companies' failures in Cases AUTH/2840/4/16 and AUTH/2847/5/16 necessarily meant that the relevant staff were not fully conversant with pharmacovigilance requirements relevant to their work nor had the complainant provided evidence in that regard. The Panel therefore ruled no breach of the Code.

With regard to the materials used at the BTS Winter meeting in December 2016, the Panel noted the companies' submission that the material provided by

the complainant had not been used at that meeting, it was likely to be a journal advertisement from early 2016 and it preceded the date the undertakings were provided in Cases AUTH/2840/4/16 and AUTH/2847/5/16. The Panel noted, however, that the title of the piece 'Ultibro Breezhaler. An evidence-based solution for patients with or without a history of exacerbations' was the same as the current material provided by Pfizer and Novartis.

The Panel considered that the complainant had not shown, on the balance of probabilities, that the companies had used the Ultibro advertisement he/she provided at the British Thoracic Society (BTS) meeting in December 2016 and had therefore promoted Ultibro Breezhaler for an unlicensed indication at that meeting as alleged. The Panel therefore ruled no breaches of the Code. The Panel also considered that in these circumstances there could be no breach of the undertaking given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 and thus ruled no breaches in that regard including Clause 2.

With regard to the allegation that there was a suggestion that staff on the stand were specifically briefed to discuss Ultibro in the context of the GOLD 2017 Report, the Panel examined the materials available on the stand. These included Wedzicha *et al* 2016 (FLAME) and various promotional material some of which referred to the GOLD Guidelines including that 'the goal of treatment was to manage symptoms and reduce the risk of exacerbations'.

The Panel noted that Pfizer and Novartis had briefed staff on 18 November 2016 regarding the GOLD 2017 Report. The Panel noted that the companies briefed its staff regarding an important update on materials following the PMCPA ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16 on 16 September 2016. The briefing stated 'You must ensure that when you are talking about exacerbation data for, *inter alia*, Ultibro Breezhaler your customers are clear that the reason to prescribe Ultibro Breezhaler is as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. It is acceptable to present data about exacerbations as long as the customer is not left with the impression that Ultibro is for treating exacerbations or that the primary reason to prescribe is to reduce exacerbations.

The Panel queried why this had not been re-iterated to staff at BTS considering Ultibro was to be promoted and the briefing regarding the GOLD 2017 Report which had been issued recently. The briefing summarised key points and listed the main considerations with regard to Ultibro Breezhaler. This included that key definitions for patient classifications would be based only on symptoms and exacerbations and that dual bronchodilators such as Ultibro Breezhaler were recommended as first line treatment regardless of their exacerbation risk and prior to the use of ICS marking a significant shift away from ICS containing combination therapies. The instructions also stated that the FLAME study was included as providing evidence for the use of dual bronchodilation; stating that a LAMA/LABA combination was superior to a LABA/ICS combination in preventing exacerbations and other patient reported outcomes in Group D patients. It was important that Pfizer confidently communicated to clinicians the reference behind this statement in order to position Ultibro Breezhaler as the new standard of care for patients with COPD with or without a history of exacerbations.

The briefing material concluded by stating that as could be seen from the significant changes to the GOLD Guidelines which directly impacted Ultibro, treatment decisions were now much more focused on the symptom burden for the patient and LAMA/LABAs had been given a far more prominent role in the management of COPD. This represented a valuable opportunity for the company to provide prescribers with a simple algorithm to follow which would ensure that patients received the right therapy to manage their COPD and increase their chances of living a healthy, active life.

The briefing material referred to Ultibro as 'the evidence based choice of LAMA/LABA for breathless patients regardless of their exacerbation history' and as 'the new standard of care'. In addition, the Panel queried whether the briefing material was sufficiently clear about the need to ensure that any discussion about the reduction in exacerbations should be a benefit of maintenance therapy and not a reason to prescribe *per se*. The Panel considered, on balance, that the briefing material was not sufficiently clear in this regard and thus ruled a breach of the Code.

The Panel did not consider, however, that the complainant had proved, on the balance of probabilities, that based on the exhibitor activities for Ultibro Breezhaler at BTS in December that those on the exhibition stand were specifically briefed to discuss the medicine within the context of the newly issued recommendations within the revised GOLD Report as alleged. The Panel ruled no breach in that regard.

A slide deck for payors (ref UK/ULTSBR/16-0068(1) 'Supporting the management of COPD' consisted of 68 slides including the burden of COPD on the health system, disease management, the benefits of Ultibro Breezhaler and the future of COPD care. The deck referred to the GOLD guidelines that ICS + LABA was recommended for use only in patients in groups C and D (slide 25). This document included claims that Ultibro Breezhaler was an appropriate steroid free option for the patient for whom LABA/ICS was considered (eg slide 31) which also included the Ultibro indication making it clear the primary reason for prescribing Ultibro and therefore no breach was ruled. The FLAME study (Wedzicha *et al* 2016) results were given on slide 32 including a comparison of exacerbation rates of Ultibro and Seretide as well as FEV1 and rescue medication use. The Panel considered the FLAME study results were set within the context of the licensed indication and thus it ruled no breach of the Code.

Material (ref UK/ULTSBR/16-0286) described as 'FLAME Business Card – eprint URL link' promoting

the results of FLAME (Wedzicha *et al* 2016) referred to the exacerbation outcomes and their impact on patients at risk of future exacerbations without setting these in the context of the Ultibro licensed indication. A breach was ruled. In addition, this material implied that the exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler which was misleading. Breaches of the Code were ruled including that high standards had not been maintained. Pfizer and Novartis had failed to comply with their undertakings given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 and a breach of the Code was ruled. The Panel noted the importance of undertakings and considered that failure to comply with the undertakings and assurance previously given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 had brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel thus ruled a breach of Clause 2 of the Code.

The Panel noted that four webinars were conducted in which health professionals were invited to attend a global broadcast about the updated GOLD Report. Representatives were required to show an introductory slide with all obligatory information including Ultibro's licensed indication for an audience of UK health professionals. The Panel noted its comments above regarding the GOLD briefing and the webinars and considered that whilst the GOLD briefing was not sufficiently clear, the 'upfront' slide required to be shown to UK health professionals set out the indication and therefore the webinars were clear about Ultibro Breezhaler's licensed indication and in that regard were not in breach of the Code.

An anonymous, non-contactable complainant, who stated that he/she was a pharmacovigilance (PV) consultant who regularly looked at published cases to identify PV related cases, referred to Case AUTH/2847/5/16. The complainant stated that this case contained important PV considerations not previously identified and addressed. The complainant referred to Good Pharmacovigilance Practices (GVP) which led to a genuine collaborative and cross-functional approach to product promotion and the importance of a strong culture of PV compliance across an organisation.

Cases AUTH/2840/4/16 and AUTH/2847/5/16 concerned the promotion of Ultibro Breezhaler (indacaterol (long acting beta agonist (LABA))/ glycopyrronium (long acting muscarinic antagonist (LAMA)) and Seebri Breezhaler (glycopyrronium) by Novartis Pharmaceuticals UK Ltd and Pfizer Limited. Ultibro Breezhaler and Seebri Breezhaler were both indicated as maintenance bronchodilator treatments to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD). Both products were required to show an inverted black triangle to denote that additional monitoring was required in relation to adverse reactions.

COMPLAINT

The complainant stated that the marketing authorisation holder (MAH) was responsible for continuously monitoring the safety of its medicines, for informing the authorities of any changes that might have an impact on the marketing authorisation, and for ensuring that the product information was kept up-to-date.

Beyond collation of spontaneous safety reports involving adverse events, Article 23 of Directive 2001/83/EC required the MAH to report to the competent authorities any other new information which might influence the evaluation of the benefit-risk balance of the medicine concerned, including data on the use of a medicine outside the terms of its marketing authorisation. Furthermore, chapter V.B.8.5.4 of GVP Module V outlined the specification of post-marketing safety updates and stated that it should include off-label use information sourced within the European Union (EU). Off-label use was use in an unlicensed indication or manner.

There was a legal requirement to include information regarding off-label use in Periodic Safety Update Reports (PSURs) and Risk Management Plans (RMPs) (regardless of whether there was an associated adverse reaction or not). The MAH should have a procedure in place to collect and record relevant information including off-label use in order to competently:

- Identify patterns of use and new safety signals
- Continuously monitor the benefit-risk balance of medicines
- Produce PSURs/Periodic Benefit-Risk Evaluation Report (PBRER)
- Inform regulators of any changes to the benefit-risk balance.

In Case AUTH/2847/5/16 Pfizer (although not the MAH for Ultibro Breezhaler) was obliged, as the distributor/co-promoter, to ensure that a suitable process was in place to collect and record relevant information including off-label use in order to pass on all relevant information to the MAH, Novartis, within timeframes outlined in the Safety Data Exchange Agreement (SDEA) between Pfizer and Novartis.

Patterns of use important to safety signals

The complainant referred to the 2012 benfluorex scandal in France as a reminder of the potential risks of not effectively collating information on off-label use of any medicine especially where it involved exposure to broad patient populations. Benfluorex was routinely used off-label. Eventually it was found to cause fatal valvular heart disease and resulted in major changes to the French regulatory system. A robust system for collating information on off-label use was therefore an important aspect of safeguarding public health.

In the complainants view lessons from the benfluorex incident were applicable to Ultibro Breezhaler because it was not specifically recommended or licensed for use in symptomatic COPD patients despite bronchodilator therapy with a history of exacerbations;

> (in order to modify or prevent exacerbations – clinically relevant exacerbations which are associated with morbidity and mortality i.e.

moderate or severe exacerbations – EMA/CHMP/700491/2012. The complainant's view was that the totality of data suggested that the extent of protection from bronchodilation via dual bronchodilators, against the development of clinically relevant exacerbations was insufficient. Nor was such use within the terms of the Marketing Authorisation. The complainant stated the relevance of this was discussed below.)

The complainant stated that the current promotional campaign for Ultibro Breezhaler was likely to encourage replacement of fixed dose combinations of inhaled corticosteroids (ICS)/LABAs with the aim of modifying or preventing clinically relevant exacerbations (relevance of specifying exacerbation severity was discussed below). In the event of increased safety reports of clinically relevant exacerbations associated with morbidly and mortality (however likely or unlikely) associated with Ultibro Breezhaler use, this theoretical PV safety signal resulting from a widespread change in prescribing habits/patterns might be missed in terms of being directly linked with Ultibro Breezhaler off-label use. Information on how the current promotional campaign for Ultibro Breezhaler might lead to a widespread change in prescribing habits/patterns was discussed below.

Failure to clarify what constituted off-label use

The complainant stated that Clause 25.1 outlined the requirement to collate information through a scientific service and Clause 15.6 also referred to this obligation from a representative's perspective. Guidance on company procedures relating to the Code section 18 Training; stated that 'all personnel (and other retained by way of contract) must be fully conversant with pharmacovigilance requirements relevant to their work and this must be documented'.

Cases AUTH/2840/4/16 and AUTH/2847/5/16 confirmed that Pfizer knew about the alleged off-label nature of promotional activities in April 2016. In the four months that followed the organisation seemed not to have thoroughly considered the PV implications because by September 2016 the extent of off-label promotion was not curbed as expected but actually intensified as evidenced by the headline, 'Exacerbation risk reduction in your hands' used on an electronic advertisement shown on an exhibition stand at the European Respiratory Society (ERS) congress in London 3-7 September 2016. The copy of the advertisement provided by the complainant referred to both Novartis and Pfizer.

The complainant alleged that neither Pfizer nor Novartis had recognised the off-label use of Ultibro Breezhaler for exacerbation risk reduction given the intensification in the tone of off-label promotion at the ERS congress 2016. Both companies had failed to identify and clarify what constituted off-label use. It would seem that this failure might have existed for a considerable amount of time which was serious when considering ongoing PV maintenance obligations. It was likely that potentially thousands of interactions between Pfizer personnel (field or office based) and valid reporters regarding the use of Ultibro Breezhaler to reduce exacerbations in COPD patients had taken place.

The complainant alleged that Pfizer and Novartis had previously failed to adequately train personnel to recognise that the use of Ultibro Breezhaler to reduce exacerbations in COPD was off-label resulting in numerous off-label use case reports that had not been collated for PV maintenance obligations. This training was an essential part of the process that ensured reports of off-label use of medicines associated with an adverse reaction were flagged. In the absence of such specific training the process to flag reports of off-label use was inadequate due to the failure of both Pfizer and Novartis to identify and clarify what constituted off-label use. Failure to clarify what constituted off-label use had been cited as a finding in previous pharmacovigilance inspections by the Medicines and Healthcare products Regulatory Agency (MHRA).

The complainant alleged that the PMCPA ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16 was likely to be applicable beyond UK borders such that the number of company interactions where relevant off-label information was not flagged across the whole of Europe would be unacceptably high.

Alleged Pharmacovigilance system deficiencies and corrective actions

The complainant stated that these alleged PV system deficiencies would ordinarily expect robust and swift MAH action internally, deriving Corrective And Preventative Actions (CAPAs) including:

1 Referral of findings to the organisation's highest internal safety committee
2 Updating the RMP for the product to capture findings
3 Implementation of corrective and preventative actions related to each finding ie:

   a) Issuing a 'Dear Dr Letter' to rectify the confusion and misunderstanding resulting from prolonged promotional activities that were prohibited
   b) Updating the safety data exchange agreement (SDEA) between Novartis and Pfizer to reflect CAPAs and also to tighten up on off-label reporting processes in general
   c) Re-training all personnel with the aim of identifying and clarifying what constituted off-label use
   d) Amendment of promotional materials and associated briefing documents to comply with signed PMCPA undertakings.

These measures were fundamental to GVP and in the interest of patient safety. It was not possible to assess whether measures 1, 2, 3, 3a, 3b and 3c above had been followed through. Point 3d could be assessed in part through recent scientific journal advertisements and exhibitor activities.

The complainant stated that at a national scientific respiratory conference, 7-9 December, Pfizer's campaign for Ultibro Breezhaler included the

headline, 'Ultibro Breezhaler, an evidence based solution for patients with COPD with or without a history of exacerbations'. A picture of the material was provided.

The clinical development programme for Ultibro Breezhaler included studies where recruited patients had a history of exacerbations (Wedzicha *et al* 2016 and Zhong *et al* 2014) and also at least one study where recruited patients did not have a history of exacerbations (Wedzicha *et al* 2013). The first half of the headline referred to Ultibro Breezhaler being a 'solution' and projected the perception that it was a solution for patients with exacerbations. The complainant alleged that had Pfizer thoroughly considered the pharmacovigilance implications first and developed effective CAPAs then continuation of off-label promotion was avoidable.

Lack of consistency with regulatory framework

The complainant stated that as a PV consultant he/she routinely cross referenced with the latest PV guidance/legislation. Taking a similar approach in order to understand the legitimacy of the FDC-LABA/LAMA class being promoted for exacerbation risk reduction it was important to consult the relevant regulatory framework ie the guideline on clinical investigation of medicines in the treatment of COPD – EMA/CHMP/700491/2012 which replaced the previous guideline Points to Consider CPMP/EWP/562/98, 19 May 1999.

This document primarily covered the maintenance treatment of COPD and not the treatment and management of acute exacerbations and essentially outlined three possible aims of maintenance treatment.

1 Provide symptomatic relief through improvement of airway obstruction
2 Modify or prevent exacerbations
3 Modify the course of the disease or modify disease progression.

Also discussed was the importance of recognising the severity of exacerbations where the document stated that, '... the rate of moderate or severe exacerbations is a clinically relevant endpoint related to the associated morbidity and mortality, and the usually significantly increased health-care requirement costs'.

Assessment of risk in terms of the rate of moderate or severe exacerbations was the main requirement for a treatment licensed to be used to modify or prevent exacerbations and had distinctive study criteria to meet before a licence was granted for use in COPD patients as outlined in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012). These being:

1 A requirement to undertake one or more comparative studies over 12 months or more that measured the reduction in moderate (clinical interventions with oral steroids +/- antibiotics) or severe (hospitalisation) exacerbations, as a primary-endpoint.
2 Reduction in frequency of 20% (minimally important clinical difference) had been suggested as being clinically relevant vs the comparator in the reduction of moderate or severe exacerbations. This was also acknowledged by the National Institute for Health and Care Excellence (NICE) in its evidence summary review of Ultibro Breezhaler.

Meeting these two criteria enabled a treatment to be licensed specifically for use in symptomatic COPD patients despite bronchodilator therapy with a history of exacerbations (in order to modify or prevent exacerbations – clinically relevant exacerbations which were associated with morbidity and mortality ie moderate or severe exacerbations - EMA/CHMP/700491/2012). The two criteria highlighted above, were clearly challenging as demonstrated by Ultibro Breezhaler. In the summer of 2016 the manufacturer announced that a pivotal study (NCT01946620 – ClinicalTrials.Gov) undertaken in accordance with the criteria mentioned did not meet the primary endpoint of demonstrating statistically significant superiority in the reduction of annualised rates of moderate or severe COPD exacerbations when compared to mono-component LABA treatment alone. The manufacturer indicated that the primary endpoint result would not allow it to make a regulatory filing for the COPD indication in Europe. The chief executive officer stated that, '... COPD is a complex and highly variable disease and these trial results highlight the challenge in demonstrating reductions of exacerbations ...'. Had this study (NCT01946620) been successful then specific wording of the licence indication subsequently granted for COPD would reflect the existence of respective, suitable, supporting data for clinically relevant exacerbations as was the case for other currently licensed FDC-ICS/LABA medicines in COPD.

An obvious dichotomy existed from a regulatory perspective in that Ultibro Breezhaler could not progress towards a licence in COPD after missing the primary endpoint for a study designed in accordance with the two criteria defined above and subsequently the manufacturer simply did not promote Ultibro Breezhaler for use in COPD. Whereas, FDC-LABA/LAMAs were granted licences solely for maintenance treatment aimed at symptomatic relief through improvement of airway obstruction; yet without meeting the two defined study criteria, Ultibro Breezhaler was simultaneously being positioned and promoted as a suitable alternative to licensed FDC-ICS/LABAs for exacerbation risk reduction. In effect, regulatory requirements outlined in EMA/CHMP/700491/2012 related to exacerbation risk reduction were being circumvented by promoting Ultibro Breezhaler for exacerbation risk reduction without being granted a licence that reflected the existence of respective, suitable, supporting data for clinically relevant exacerbations.

The complainant alleged that exhibitor activities for Ultibro Breezhaler at the national scientific respiratory conference, 7-9 December, were in breach of the undertaking associated with Case AUTH/2847/5/16 when taking into consideration the regulatory framework described above.

Insufficient evidence for exacerbation risk reduction with Ultibro Breezhaler based on criteria defined in EMA/CHMP/700491/2012

The complainant provided a table which was an overview of published evidence for Ultibro Breezhaler in terms of alignment with key study criteria for exacerbation risk reduction stated in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012):

- Clinically relevant primary endpoint – Moderate (clinician intervention with oral steroids +/- antibiotics) or severe (hospitalisation) exacerbations
- Treatment period of 12 months or more
- Reduction of frequency of 20% in the rate of moderate or severe exacerbations versus comparator.

Eight publications for Ultibro Breezhaler were identified and evaluated (Bateman *et al* 2013, Dahl *et al* 2013, Gebner *et al* 2014, Mahler *et al* 2014, Vogelmeier *et al* 2013, Wedzicha *et al* 2013, Wedzicha *et al* 2016 and Zhong *et al*).

Despite the fact that the study (NCT01946620) involving FDC-fluticasone/formoterol ensured that the clinically relevant primary endpoint – moderate or severe exacerbations was measured and the treatment period was 12 months, progression towards attaining a COPD licence was not possible because the study criteria were challenging and the study eventually missed its primary endpoint. In the case of FDC-LABA/LAMA studies:

- None of the eight Ultibro Breezhaler studies met all three criteria stated above
- Just one of the eight publications related to Ultibro Breezhaler involved a study where the clinically relevant primary endpoint – moderate or severe exacerbations was measured over a 12 month treatment period (Wedzicha *et al* 2013) and only a 12% reduction in clinically relevant exacerbations vs the comparator was shown (ie below the threshold of 20%).

The lack of Ultibro Breezhaler studies meeting key study criteria for exacerbation risk reduction stated in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012), prompted a broader analysis of other FDC-LABA/LAMAs publications:

- None of the 7 citations involving other FDC-LABA/LAMAs (Buhl *et al* 2015, Celli *et al* 2014, Decramer *et al* 2014, Donohue *et al* 2013, Donohue *et al* 2014, D'Urzo *et al* 2013 and Singh *et al* 2013) met all three criteria.

Out of nine FDC-LABA/LAMAs publications that had a secondary endpoint measure of exacerbations almost all publications did not define exacerbations such that it was not clear to the reader that clinically relevant exacerbations were not measured in these studies. Potentially, this might lead to a misunderstanding and exaggeration of clinical benefit.

The complainant stated that the literature review and assessment undertaken confirmed that there was insufficient evidence to support the use of Ultibro Breezhaler for exacerbation risk reduction. To date, Pfizer and Novartis had simply not undertaken clinical trials in accordance with recommendations in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012). This was concerning given the continuation of off-label promotion.

Pfizer used the recent FLAME study (Wedzicha *et al* 2016) as the main reference to support the claims appearing in the promotional materials cited by the complainant. It was not entirely clear to the complainant why the sponsor of the study, Novartis, chose not to undertake this study in accordance with recommendations in the guideline on clinical investigation of medicinal products in the treatment of COPD (EMA/CHMP/700491/2012). It made it problematic to adequately assess the results alongside other supporting studies for other classes of medicines that were actually licensed to be used in COPD patients with the aim of modifying or preventing clinically relevant exacerbations (EMA/CHMP/700491/2012). Therefore regulators would need reassurance via further data and studies which might also clarify understanding in specific areas such as:

- The primary outcome was 'all exacerbations' where 40% were essentially a brief worsening of breathlessness (ie mild exacerbations). Ultimately these were not clinically relevant exacerbations which were associated with morbidity and mortality and thus unlikely to impact healthcare and disease progression to the same extent as clinically relevant exacerbations. A further study was required with the primary endpoint moderate to severe exacerbations.
- Data on previous treatment history of the study population seemed to suggest that a significant proportion of patients were already on dual LABA/LAMA therapy albeit via separate inhalers. It was important to understand if this could impact the two study treatment arms disproportionally as all patients were stepped-down to tiotropium (LAMA) during the run-in phase and then subsequently stepped-up during the treatment phase to an Ultibro Breezhaler or FDC-fluticasone/salmeterol.
- The study population categorised in terms of airflow limitation mainly included Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 (33.3%) and GOLD stage 3 (58%) patients. It was important to understand if this could impact results. Also, only approximately half had inhaled corticosteroids prior to study entry which supported the deduction that a significant proportion of patients were likely to be already on dual LABA/LAMA therapy prior to study entry.
- Recent studies involving COPD drug classes had observed a background rate of clinically relevant exacerbations of less than 1 event/patient/year rate (Dransfield *et al* 2013, Wedzicha *et al* 2014, Albert *et al* 2011 and Martinez *et al* 2015). So the actual clinically relevant exacerbation rate of around 1 vs.0.9 predicted leading to a surprisingly

greater magnitude in risk reduction compared to 'all exacerbations' contrasted with study protocol assumptions. In comparison to other recent studies, those four studies above and Wedzicha *et al* 2016, this anomaly also needed to be better understood in relation to geographic location of study centres.
- Almost 10% were excluded in the per protocol analysis for the primary end-point only and per protocol analysis was not available in the publication for secondary endpoint results making their evaluation challenging.

The complainant stated that the totality of data suggested that the extent of protection from bronchodilation via dual bronchodilators, against the development of clinically relevant exacerbations was insufficient.

Marginalising the regulatory framework

The complainant stated that exhibitor activities for Ultibro Breezhaler at the national scientific respiratory conference 7/9 December suggested that those on the exhibition stand were specifically briefed to discuss the medicine in the context of newly issued recommendations within the GOLD 2017 Report.

The recently revised GOLD Report was an important reference and was compiled by international experts. The update represented a positive step forward in simplifying the ABCD matrix which previously posed challenges in categorising COPD patients with three different sub-categories possible depending on the presence of either one or both risk factors, namely, FEV1, staging and exacerbations risk. The recent update of the GOLD Report was however concerning from a patient safety perspective as it stated:

- 'Recommendations by the GOLD Committee for use of any medication are based on the best evidence available from published literature and not on labelling directives from government regulators'.
    - FDC-LABA/LAMAs were recommended first-line in category D COPD patients and as step up from a LAMA in category C COPD patients. Both of these two recommendations essentially involved use of FDC-LABA/LAMAs in an unlicensed indication or manner.
- 'It should be noted that there is a lack of direct evidence supporting the therapeutic recommendations for patients in groups C and D'.
    - FDC-LABA/LAMAs were recommended first-line in category D COPD patients, but there was no evidence that FDC-LABA/LAMAs compared to LAMAs could significantly reduce the risk of clinically relevant exacerbations which were associated with morbidity and mortality ie moderate or severe exacerbations.
    - Furthermore, although the FLAME study reported that in a secondary endpoint, Ultibro Breezhaler was superior to FDC-fluticasone/formoterol in terms of clinically relevant moderate or severe exacerbations, this effect was not demonstrated in patients with a history of more than one exacerbation, and category C COPD patients were not included in this study (Wedzicha *et al* 2016).

The complainant noted that in the GOLD Report there was no ratified European Pharmacovigilance Risk Assessment Committee (PRAC) recommendation stating a positive risk-benefit balance for FDC-ICS/LABAs in COPD (eg the magnitude of benefit in terms of clinically relevant exacerbation reduction observed was as much as ten-fold greater compared to the slight increased risk in terms of pneumonia (Corradi *et al* 2016)). Yet a major factor cited within the updated GOLD Report for recommending usage of FDC-LABA/LAMAs in an unlicensed indication or manner was the frequently repeated reference to the risk of pneumonia with use of FDC-ICS/LABAs. This seemed not to be balanced because the respective PRAC recommendations were excluded. Moreover, these risks of pneumonia were not qualified in the updated GOLD Report, in terms of not translating into a greater risk of mortality (Festic *et al* 2016).

The complainant alleged that when taking into consideration both Pfizer's continued off-label promotion with the revised GOLD Report recommendations that essentially involved recommending use of FDC-LABA/LAMAs in an unlicensed indication or manner, it was clear that there was a underlying move towards circumventing the regulatory requirements outlined in EMA/CHMP/700491/2012 related to exacerbation risk reduction by promoting/recommending products for exacerbation risk reduction without these medicines being granted licences that reflected the existence of respective, suitable, support data for clinically relevant exacerbations.

Prescribing boundaries for the use of medicines defined by their marketing authorisation granted by regulatory agencies were also important in ensuring clarity for related PV obligations.

The complainant alleged that the regulatory processes in place to protect public health were being marginalised through the actions described above. If the pharmaceutical industry embarked on charting a strategic direction that inadvertently (or otherwise) undermined the very regulatory foundations that were meant to keep patients safe then the industry was entering unwelcomed territory which inevitably would discredit it.

Vilhelmsson et al 2016 'Pharmaceutical Industry Off-label Promotion and Self-regulation. A Document Analysis of Off-label Promotion Rulings by the UK PMCPA 2003-2012'.

The complainant stated that the evaluation undertaken by Vilhelmsson *et al* 2016 was an area of research that was of significant relevance to much of what had already been discussed and a major factor in taking the step to submit the complaint.

Within the authors' conclusion was a recommendation to UK authorities to:

'... consider introducing increased incentives and protection for whistleblowers combined with US-style government investigations and meaningful sanctions.'

The complainant stated this was the main reason for remaining anonymous as the complainant.

Pfizer knew about the alleged off-label nature of promotional activities in April 2016. During a prolonged period of over eight months whilst the case remained ongoing, Pfizer continued to press ahead with off-label promotion and actually intensified the tone of off-label promotion during this period. Pfizer never seemed to have taken a step back to reflect and consider the PV implications of its actions. Vilhelmsson *et al*'s suggestion that current sanctions might not go far enough seemed to reflect the case of Pfizer with its continuation of off-label activities and probably anticipated that the eventual sanctions would be 'palatable'. This situation might also reflect weakness in the SDEA between Novartis and Pfizer. If Pfizer was the MAH perhaps it would have taken appropriate action much earlier.

The obvious concern was whilst an unavoidable delay might actually benefit Pfizer commercially in seeing a similar protracted period of time prior to completion of this PV related PMCPA case, it certainly would not be in the best interest of patient safety. If a prolonged period of time were to elapse whereby scores of company interactions where relevant off-label information was not flagged across the whole of Europe continued, this would be unacceptable. The complainant therefore urged the PMCPA to prioritise completion of this case if possible given the far reaching patient safety implications.

When writing to Pfizer and Novartis the Authority asked the companies to respond in relation to Clauses 2, 3.2, 7.2, 9.1, 15.9, 16.2 and 29 in addition to Clauses 25.1 and 15.6 cited by the complainant.

RESPONSE

The response was provided on behalf of both Pfizer Limited and its alliance partner Novartis Pharmaceuticals UK Limited.

Pfizer and Novartis submitted that the topics covered in the complaint were wide-ranging and many fell outside the scope of the Code for example, comments regarding pharmacovigilance systems, the CHMP guideline for clinical investigation of medicines in the treatment of COPD and the recently revised GOLD Global Strategy for the Diagnosis, Management and Prevention of COPD. The companies focused their response on the topics that they considered fell within the scope of the Code. The companies highlighted the following general points which they submitted were important to provide context to the response:

1 Ultibro Breezhaler, a fixed dose combination of two bronchodilators, was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD.

2 Much of the complaint was based on the assertion that Ultibro Breezhaler was being promoted and used off-label. The complainant stated that it was not specifically recommended or licensed for use in symptomatic COPD patients despite bronchodilator therapy with a history of exacerbations. The companies absolutely disagreed with this assertion. The licensed indication for Ultibro Breezhaler, as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD, did not stipulate or preclude its use in any subgroup of symptomatic COPD patients including presence or absence of a history of exacerbations, previous therapy, or success of previous therapy. Therefore, as established in Cases AUTH/2840/4/16 and AUTH/2847/5/16, use of Ultibro Breezhaler in adults with COPD who required maintenance bronchodilator therapy to relieve symptoms, irrespective of a history of exacerbations, was entirely within the licensed indication.

3 Following the rulings in Cases AUTH/2840/4/16 and AUTH/2847/5/16, Novartis and Pfizer each gave undertakings that in the promotion of Ultibro Breezhaler, reference to reduced exacerbation would be set within the context of the primary reason to prescribe, ie maintenance therapy to relieve symptoms of COPD. However, it should also be noted that claims for a benefit for Ultibro Breezhaler in reducing exacerbations were deemed acceptable within the context of the primary reason to prescribe ie as a maintenance therapy to relieve symptoms. Subsequently, marketing and promotion remained focused on this primary reason to prescribe Ultibro Breezhaler.

4 Elements of the complaint reflect topics considered in Cases AUTH/2840/4/16 and AUTH/2847/5/16 and referred to events which predated the rulings in these cases.

Licensed indication

The companies disagreed with the complainant's assertion that Ultibro Breezhaler was not licensed for use in COPD patients with a history of exacerbations; it might be used as a maintenance bronchodilator in COPD patients with or without exacerbations. Furthermore, Section 5.1 of the Ultibro Breezhaler SPC included data on the various cohorts of patient types and outcomes studied in the clinical development programme (this included patients with a history of exacerbations and the effect of Ultibro Breezhaler on COPD exacerbations). Results from the FLAME study (Wedzicha *et al* 2016), demonstrating the non-inferiority (and superiority) of Ultibro Breezhaler vs fluticasone/salmeterol in rate of all COPD exacerbations, had recently been added to this section of the SPC. The Ultibro Breezhaler SPC did not include any restrictions, contraindications or special warnings or precautions for the use of Ultibro Breezhaler in COPD patients with a history of exacerbations. Consequently, data relating to exacerbation risk reduction, or other clinically relevant endpoints described in Section 5.1, might

be used in promotional materials as long as these were set within the context of the primary reason to prescribe Ultibro Breezhaler (ie as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD), consistent with Clause 3.2 and the rulings in Cases AUTH/2840/4/16 and AUTH/2847/5/16.

Additionally, the complainant's reference to benfluorex was irrelevant as this medicine was initially approved for use as a hypolipidemic and hypoglycemic agent in patients with diabetes and was subsequently used off-label in the general population as an anorexic, ie the off-label use was in a different population and with a different clinical objective compared with on-label use. Furthermore, this off-label use continued despite the fact that similar medicines (fenfluramine and dexfenfluramine) had been withdrawn from many markets because they were known to be associated with pulmonary hypertension and valvular insufficiency. In contrast, Ultibro Breezhaler had been extensively studied within the COPD population, including in patients with a history of exacerbations and who had been on previous bronchodilator therapy, and was found to have a favourable benefit:risk profile. The companies were concerned that, if published in the Case report, this inaccurate comparison between benfluorex and Ultibro Breezhaler had the potential to cause unwarranted alarm amongst health professionals and COPD patients which could lead to patients inappropriately stopping treatment and their condition deteriorating.

Collation of information through a scientific service

With regard to the complainant's reference to the obligations of pharmaceutical companies to have a scientific service to compile and collate information relating to the use of their products, including safety information, Novartis and Pfizer pointed out that the complainant did not make any specific complaint or provide any evidence of alleged non-compliance in this respect.

Novartis and Pfizer submitted that they were fully committed to protecting and enhancing patient safety and operated extensive and robust scientific services and pharmacovigilance systems which complied with the relevant regulatory and legal frameworks and with Clause 25.1. All personnel in both companies were trained on requirements to transmit information received relating to use of medicines, including reports of adverse reactions, to the respective scientific service as required by Clause 15.6.

Novartis and Pfizer stated that they collected, processed and reported all safety data according to worldwide regulatory requirements, and provided integrated medical safety evaluations and risk-benefit assessments for all marketed or investigational products. Single and aggregate safety reports were submitted to the worldwide regulatory authorities as required. Dedicated safety teams performed continuous monitoring of the product-risk-benefit profile and supported the pharmacovigilance activities from a medical perspective including medical assessment of Individual Case Safety Reports (ICSRs), preparation of aggregated safety reviews including Development Safety Update Reports (DSURs) and Periodic Safety Update Reports (PSURs), evaluation of the product safety profiles with appropriate reflection in Company Core Data Sheets (CDS), identification of new or changing safety signals including impact and their medical management and identification of risks, preparation of Risk Management Plans (RMPs) and relevant global risk management systems including risk minimization activities.

All Novartis and Pfizer employees completed adverse event (AE) training on an annual basis and were fully aware of their obligations for safety reporting. Where a third party managed activities on behalf of Novartis or Pfizer, it would ensure that the AE training was completed. Novartis and Pfizer each maintained a standard operating procedure (SOP) addressing requirements for AE training (Novartis SOP-7018026 and Pfizer Corporate Policy CP903, respectively).

Exhibition stand at European Respiratory Society (ERS) meeting

The complainant's comments regarding an exhibition stand at the ERS meeting appeared to reiterate topics which had already been ruled upon in Cases AUTH/2840/4/16 and AUTH/2847/5/16. Consequently the companies had not provided any materials relating to this meeting but would be happy to do so if requested.

Novartis and Pfizer gave undertakings to ensure that, in the promotion of Ultibro Breezhaler, reference to reduced risk of exacerbations would be set within the context of the primary reason to prescribe, ie maintenance therapy to relieve symptoms of COPD. The ERS meeting was held 3-7 September 2016. Novartis and Pfizer received the PMCPA's ruling after the ERS meeting had closed and the undertakings were provided to the PMCPA on 16 September 2016. Since the undertakings had not been given at the time of the ERS meeting, they could not have been breached then and therefore the companies denied a breach of Clause 29.

In accordance with the undertakings, promotional and training materials were revised or withdrawn and sales personnel were briefed regarding the requirements of the PMCPA ruling. As evidence of adherence to its undertakings, the companies provided a list of the materials that were withdrawn following the ruling and the briefing delivered to representatives on the withdrawals (which was shared by email and WebEx meeting). In total, 115 items were withdrawn of which 28 were revised and recertified. Four revised items were provided as examples, these being the most comprehensive and therefore representative of the revisions made. Five of the revised items were sales materials. The revised sales aid, a FLAME clinical summary and a FLAME leavepiece were provided. A further five items were payor materials and the payor slide deck was provided. Fifteen of the revised items were on demand webinars; these were edited to add the licensed indication for Ultibro Breezhaler

at the beginning of each webinar and at relevant sections throughout. Additionally, all speaker slide decks were reviewed and certified to ensure that the licensed indication was clearly presented as the primary reason to prescribe Ultibro Breezhaler.

Training of personnel on pharmacovigilance requirements

The complainant alleged that Novartis and Pfizer had previously failed to adequately train personnel to recognise that the use of Ultibro Breezhaler to reduce exacerbations in COPD was off-label. The ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16 addressed this point and concluded that information relating to Ultibro Breezhaler and exacerbation risk reduction, consistent with the particulars listed in the SPC, might be used in promotion provided that exacerbation risk reduction was not promoted as the primary reason to prescribe. Novartis and Pfizer provided undertakings in this respect on 16 September 2016, as described above.

There did not appear to be an allegation of non-compliance in this respect subsequent to the companies' undertakings and no evidence to this effect had been provided. The companies submitted that the briefing provided to representatives following the ruling complied with the Code and the companies' undertakings. Therefore there was no breach of Clause 15.9.

Furthermore, as described above, all personnel in both companies were trained on pharmacovigilance requirements relevant to their work as detailed in Novartis SOP-7018026 and Pfizer Corporate Policy CP903, respectively. Therefore there was no breach of Clause 16.2.

British Thoracic Society (BTS) Winter Meeting

The BTS Winter Meeting was held 7-9 December 2016 and the companies assumed this was the 'national scientific respiratory conference' referred to by the complainant. Materials on display at the Pfizer exhibition stand had been newly created and had been reviewed and certified as reflecting the ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16.

The item referred to by the complaint, with the headline 'Ultibro Breezhaler. An evidence-based solution for patients with COPD with or without a history of exacerbations' was not an item used at the BTS; due to the poor quality of the image and the fact that the job bag number was not shown in the image the companies were not able to accurately determine the instance of use the cited material had been extracted from, but it was likely to be a journal advertisement from early 2016 (and certainly preceded the undertakings given by Novartis and Pfizer of 16 September 2016). If deemed necessary, if a clearer image of the item or its job bag number was provided the companies could then source the item and provide a copy.

Novartis and Pfizer submitted that they always aimed to fully comply with the Code and were confident that all activities and materials which supported Ultibro Breezhaler were firstly in accordance with its marketing authorisation and secondly not inconsistent with the particulars listed in the SPC. Furthermore, the undertakings had been complied with. Therefore the companies concluded that there had been no breach of Clauses 3.2 or 29 of the Code. Information, claims and comparisons made in these materials and activities were accurate, balanced, fair, objective and unambiguous and were not misleading. The companies therefore concluded that there had been no breach of Clause 7.2.

The companies provided copies of all materials displayed or available at the BTS stand and briefings for staff manning the stand; these included a general 'stand crew' briefing and a briefing on the results of the CRYSTAL study which were being presented at the BTS meeting.

Out of scope topics

The companies submitted that the complainant's comments on EU directives and guidelines, including those referring to PSURs, RMPs, and clinical investigation of medicines were outside the scope of the Code and consequently not addressed. The companies noted that there were a number of factual inaccuracies contained in the complainant's comments on these topics, in particular the remarks about the clinical investigation of medicines. The companies requested the opportunity to address these inaccuracies in further detail should these areas form part of the PMCPA's substantive review.

The companies stated that the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was an independent body of clinical experts which developed evidence-based strategy documents for COPD management and worked with health professionals and public health officials to raise awareness of COPD and to improve prevention and treatment of this lung disease for patients around the world. The complainant's comments on GOLD's recently revised guidelines on the management of COPD fell outside the scope of the Code and consequently the companies did not address these.

Summary

The companies submitted that high standards had been maintained and there had been no instances of bringing discredit upon the pharmaceutical industry and there had therefore no breach of Clauses 9.1 or 2.

Further Information

Following a request for further information, Pfizer and Novartis submitted a joint response and clarified their comment about the revised GOLD 2017 Report. The companies noted that the complainant was critical of the GOLD 2017 Report; in their view the derivation of the GOLD recommendations and what the GOLD panel of experts deemed appropriate management strategies for COPD patients, including the evidence it chose to review or not, fell out of scope of the Code. The GOLD committee was an independent body of clinical experts which developed evidence-based strategy documents for COPD management. The manner in which it operated was not governed by the Code.

The companies agreed, however, that any of their materials that related to the GOLD 2017 Guidelines might fall under the remit of the Code.

Pfizer and Novartis answered the questions raised by the Panel.

Representatives briefing about the GOLD 2017 Guidelines:

The companies stated that all representatives, including those on the exhibition stand at the BTS meeting, received instruction about the updated GOLD 2017 Guidelines. A copy of the representative briefing issued on 18 November 2016 was provided.

Pfizer and Novartis explained that four spotlight webinars were conducted in which health professionals were invited to attend a global broadcast about the new GOLD 2017 Guidelines. These webinars were organised by Novartis Pharma AG, based in Switzerland, for a global audience and were certified in accordance with the Code through the Novartis-Pfizer Alliance Zinc platform. The webinars ran on 30 November 2016 (twice) and 1 December 2016 (twice) and featured live talks from two international key opinion leaders, both of whom were authors of the GOLD 2017 Guidelines, after an introduction from a Novartis global medical director. All representatives were briefed to organise webinar meetings and they were given a flyer to invite health professionals to the webinars. Representatives were sent a second briefing before the webinars instructing them to show an introductory slide with all the obligatory information for an audience of UK health professionals, including the licensed indication for Ultibro. The introductory slide was needed as the slide decks shown at the webinar were produced for a global audience. These were certified before the meeting (copies of the briefings, the flyer and of the slides were provided).

At the time of the BTS Congress (7-9 December 2016) there were no Novartis-Pfizer Alliance materials in circulation that referred to the updated GOLD 2017 Guidelines.

The companies noted that whilst the representative briefing material issued in November 2016 referred to 'next steps' including incorporation of the GOLD 2017 Guidelines into materials (representative triggered email, sales aid etc) over the coming months and generation of a simple leavepiece, none of these had yet been finalised.

Representatives Activity at the BTS Congress 7-9 December 2016:

The companies explained that eight representatives worked on the promotional stand at the BTS meeting. They had been briefed about the new GOLD 2017 Guidelines as described above which was provided before the BTS meeting and was not connected with it. This was in addition to the BTS 'stand crew' briefing and a briefing on the results of the CRYSTAL study, which were to be presented at the BTS Congress and referred to previously. Representatives had also been briefed about the undertaking to the PMCPA, also referred to previously. No specific briefing on the GOLD 2017 Guidelines was issued to the representatives attending the BTS Congress.

The GOLD 2017 Guidelines went live on the GOLD website in November 2016 to coincide with World COPD Day.

Pfizer and Novartis explained that there were significant changes to the GOLD 2017 Guidelines compared with the previous edition; treatment decisions became much more focused on the symptom burden for the patient. This emphasis was on symptomatic treatment and a recognition of the clinical evidence of bronchodilation in all patients regardless of exacerbation history. In this regard, the GOLD 2017 Guidelines were in line with the Ultibro licensed indication as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD.

The companies stated that they had used the GOLD Guidelines as follows:

1 Since the publication of the 2017 GOLD Guidelines, all Ultibro materials had been reviewed and reference checked. Where previous GOLD Guidelines were referenced, information provided about the GOLD Guidelines had been reviewed and, where necessary, revised to be consistent with the GOLD 2017 Guidelines. References had been updated accordingly.

2 Four Spotlight Webinars had been conducted in which health professionals were invited to attend a broadcast about the new guidelines. These were described above as activities prior to the BTS meeting.

3 A local account manager sales aid referred to as the Value Slide Deck had been updated and re-issued (replacing UK/ULTSBR/16-0068). The revised material included information about the GOLD 2017 Guidelines.

4 A health professional master speaker deck had been updated which included information about the GOLD 2017 Guidelines.

PANEL RULING

The Panel noted that the complainant was anonymous and although a mailing address had been provided there was no response to a letter sent to that address. Anonymous complaints were accepted and like all complaints judged on the evidence provided by the parties. The complainant had the burden of proving his/her complaint on the balance of probabilities.

The Panel was extremely concerned that a complaint had been received which included allegations about Novartis' and Pfizer's activities in relation to pharmacovigilance which was vital for patient safety. There were extensive requirements for pharmacovigilance which went beyond the Code. The Panel could only consider allegations in relation to the requirements in the Code.

The Panel noted the complainant's allegations about the regulatory requirements outlined in EMA/CHMP/700491/2012 being circumvented by promoting FDC-indacaterol/glycopyrronium for exacerbation risk reduction without being granted a licence that reflected the existence of respective, suitable, supporting data for clinically relevant exacerbations. The Panel was concerned about activities in relation to the Code. It was not for the Panel to determine whether Novartis' and Pfizer's activities including clinical trials were in line with the regulatory requirements *per se*.

Clause 1.11, however, stated that companies must comply with all applicable codes, laws and regulations to which they are subject. This clause had not been raised and the complainant had not provided evidence that the companies had been found in breach of other laws and regulations.

The Panel noted that the complainant had referred to implications across Europe. The Panel could only consider matters which were covered by the UK Code and/or occurred in the UK. The fact that pharmacovigilance reporting in other countries might be lacking was of concern but was not in itself a matter necessarily covered by the ABPI Code.

The Panel noted that both Ultibro Breezhaler and Seebri Breezhaler were indicated as maintenance bronchodilator treatments to relieve symptoms in adult patients with COPD. Section 5.1 of the respective SPCs referred to each medicine's positive impact on exacerbations of COPD compared to other medicines. The Ultibro SPC was last revised on 10 November 2016. The Panel noted the companies' comments in relation to changes to the SPC.

Rulings in Case AUTH/2840/4/16 and AUTH/2847/5/16

The Panel noted its rulings in the previous cases, Cases AUTH/2840/4/16 and AUTH/2847/5/16. In particular that in some of the materials at issue in those cases, for example the claim that 'Ultibro Breezhaler offers benefits beyond current standard COPD maintenance therapies' and 'vs salmeterol/fluticasone Ultibro Breezhaler can significantly reduce your patients' rate of moderate or severe exacerbations' appeared to be a consequence of using Ultibro Breezhaler as a maintenance therapy and not the reason to prescribe *per se*, as alleged. In that regard, no breach of Clause 3.2 was ruled. Given the context in which it appeared, the claim was not misleading with regard to the licensed indication for Ultibro Breezhaler. No breach of Clause 7.2 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

An Ultibro Breezhaler training course presentation (ref UK/ULT/15-0474) referred to COPD maintenance and that health professionals effectively control COPD symptoms through optimal bronchodilation as a cornerstone of COPD management. In a section entitled 'Ultibro Campaign Material "Benefits Beyond"', the structure of the sales aid was discussed and a flow diagram included a box labelled 'Ultibro promise exacerbations'. Three subsequent slides discussed exacerbation data using the same slides as used in the sales aid. The Panel considered that the training presentation could have benefitted from a more explicit statement as to the licensed indication for Ultibro Breezhaler and that any reduction in exacerbations was to be discussed as a benefit of maintenance therapy and not as a reason to prescribe *per se*. Nonetheless, on balance, the Panel did not consider that the material encouraged representatives to promote Ultibro Breezhaler for exacerbation reduction. No breach of Clause 15.9 was ruled. The Panel considered that high standards had been maintained. No breach of Clause 9.1 was ruled.

Other material was ruled in breach of Clauses 3.2 and 7.2 as it did not clearly state that Ultibro Breezhaler was a maintenance therapy to relieve COPD symptoms. For example boxed text in a leavepiece 'Reduces exacerbation risk beyond tiotropium (open label) and [salmeterol/fluticasone]' would not be read within the context of the licensed indication. In the Panel's view the leavepiece implied that Ultibro Breezhaler could be prescribed to reduce exacerbations rather than the reduction in exacerbations being a benefit of using the medicine as maintenance therapy. The leavepiece was inconsistent with the particulars listed in the Ultibro Breezhaler SPC and a breach of Clause 3.2 was ruled. The leavepiece implied that that exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler which was misleading. A breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

A speaker slide deck (ref UK/ULT/16-0025) entitled 'Evolving science; Dual bronchodilation' examined the burden of COPD and the challenges of treatment and included an overview of clinical studies for, *inter alia*, Ultibro Breezhaler. In the Panel's view, given the length of the slide deck and the number of topics discussed, it was possible that, after 101 slides, some viewers would have forgotten exactly what Ultibro Breezhaler was indicated for; some viewers might be left with the impression that Ultibro Breezhaler could be prescribed for the reduction of exacerbations *per se* which was not consistent with the particulars listed in its SPC. A breach of Clause 3.2 was ruled. That the presentation implied that Ultibro Breezhaler could be used to reduce COPD exacerbations and was a primary reason to prescribe the product was misleading and a breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel noted its rulings and comments in relation to Ultibro and Seebri (not referred to here) but considered that the matters were not such as to bring discredit upon, or reduce confidence in, the industry. No breach of Clause 2 was ruled.

Cases AUTH/2928/1/17 and AUTH/2929/1/17

The Panel noted that the complaint in Cases AUTH/2840/4/16 and AUTH/2847/5/16 was received on 25 April 2016. The companies were notified of the Panel's rulings on 8 September and the requisite undertaking was received on 16 September. The ERS

congress referred to by the complainant in Cases AUTH/2928/1/17 and AUTH/2929/1/17 took place from 3 – 7 September. This meant that the activities at that meeting were not covered by the requisite undertaking given in Cases AUTH/2840/4/16 and AUTH/2847/5/16. There could be no breach of that undertaking so the Panel ruled no breach of Clause 29 and consequently no breach of Clauses 9.1 and 2.

The Panel accepted the companies' submission that the material used at the ERS meeting reiterated topics that had already been considered by the PMCPA and ruled upon in Cases AUTH/2840/4/16 and AUTH/2847/5/16. The Panel decided that these materials were covered by that ruling and thus decided not to make a separate ruling of breaches of Clauses 3.2 and 7.2 in that regard.

The Panel was concerned that given its rulings in Cases AUTH/2840/4/16 and AUTH/2847/5/16 it appeared that the companies had failed in some representative briefing materials to make Ultibro Breezhaler's licensed indication clear. It did not consider that this necessarily meant that the companies had failed to make it clear to staff what constituted off label use of the product as alleged in Cases AUTH/2928/1/17 and AUTH/2929/1/17. Although it was likely that staff might not be clear, the Panel did not consider that the complainant had shown on the balance of probabilities that the companies had failed to adequately train personnel to recognise that the use of FDC-indacaterol/glycopyrronium to reduce exacerbations in COPD was off label. Further there was no evidence that there would be numerous off label use case reports and if so that these had not been collated for pharmacovigilance maintenance obligations. The Panel therefore ruled no breach of Clause 16.2 and consequently no breach of Clauses 9.1 and 2.

With regard to the scientific service, the Panel noted the companies' submission that they were fully committed to protecting and enhancing patient safety and operated extensive, robust scientific services and pharmacovigilance systems. The Panel did not consider that the companies' failures in Cases AUTH/2840/4/16 and AUTH/2847/5/16 necessarily meant that the relevant staff were not fully conversant with pharmacovigilance requirements relevant to their work nor had the complainant provided evidence in that regard. The Panel therefore ruled no breach of Clauses 25.1 and 15.6 of the Code. The Panel consequently ruled no breach of Clause 9.1 in that regard.

With regard to the materials used at the British Thoracic Society Winter meeting in December 2016, the Panel noted that the companies had not been able to identify the material from the complaint. The companies submitted that the material provided by the complainant had not been used at that meeting and it was likely to be a journal advertisement from early 2016. The companies submitted that the material certainly preceded the date the undertakings were provided in Cases AUTH/2840/4/16 and AUTH/2847/5/16. The Panel noted, however, that the title of the piece 'Ultibro Breezhaler. An evidence-based solution for patients with or without a history of exacerbations' was the same as the current material provided by Pfizer and Novartis (updated sales aid ref UK/ULT/16-0543). The Panel noted Pfizer and Novartis' submission that the licensed indication for Ultibro Breezhaler, as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD, did not stipulate or preclude its use in any subgroup of symptomatic COPD patients including the presence or absence of a history of exacerbations, previous therapy, or success of previous therapy and that it was established in Case AUTH/2840/5/16 and AUTH/2847/5/16, use of Ultibro Breezhaler in adults with COPD who required maintenance bronchodilator therapy to relieve symptoms, irrespective of a history of exacerbations, was entirely within the licensed indication.

The Panel noted that what was actually stated in the Panel ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16 was that Section 5.1 of the SPC referred to Ultibro's positive impact on exacerbations and the Panel accepted that patients whose symptoms were well controlled might be less likely to experience an exacerbation of their condition than patients with poorly controlled symptoms and in that regard the Panel considered that reference to exacerbation might be included in the promotion of COPD maintenance therapy but there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition.

The Panel noted the difference of opinion between the complainant and the companies and considered that the complainant had not shown, on the balance of probabilities, that the companies had used the Ultibro advertisement he/she provided at the British Thoracic Society (BTS) meeting in December 2016 and had therefore promoted Ultibro Breezhaler for an unlicensed indication at that meeting as alleged. The Panel therefore ruled no breach of Clauses 3.2 and 7.2 of the Code. The Panel also considered that in these circumstances there could be no breach of the undertaking given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 and thus ruled no breach of Clause 29. Consequently there was no breach of Clauses 9.1 and 2.

With regard to the allegation that there was a suggestion that staff on the stand were specifically briefed to discuss Ultibro in the context of the GOLD 2017 Report, the Panel noted the companies' submission that the comments on the derivation of GOLD's recently revised recommendations and what the GOLD committee deemed appropriate management strategies for COPD patients, including the evidence they chose to review or not fell outside the scope of the Code. The companies did, however, agree with the Panel's view that any Novartis – Pfizer materials that related to the GOLD 2017 Report might well fall under the remit of the Code. The Panel examined the materials available on the stand. These included Wedzicha *et al* 2016 (FLAME) and various promotional material some of which referred to the GOLD Guidelines including that 'the goal of treatment was to manage symptoms and reduce the risk of exacerbations'.

The Panel noted that Pfizer and Novartis had briefed staff on 18 November 2016 regarding the GOLD 2017 Report. The Panel noted that the companies briefed its staff regarding an important update on materials following the PMCPA ruling on 16 September 2016. The briefing stated 'You must ensure that when you are talking about exacerbation data for, *inter alia*, Ultibro Breezhaler your customers are clear that the reason to prescribe Ultibro Breezhaler is as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. It is acceptable to present data about exacerbations as long as the customer is not left with the impression that Ultibro is treating exacerbations or that the primary reason to prescribe is to reduce exacerbations.

The Panel queried why this had not been re-iterated to staff at BTS considering Ultibro was to be promoted and the briefing regarding the GOLD 2017 Report which had been issued recently (18 November 2016). The briefing document (ref UK/ULT/160673) was headed 'To be used only by authorised Pfizer representatives to respond to external inquiries'. It was dated 18 November 2016 and was sent to the Pfizer Respiratory field team, ADs, RCDs, CECs, LAMs. The briefing summarised key points and listed the main considerations with regard to Ultibro Breezhaler. This included that key definitions for patient classifications would be based only on symptoms and exacerbations and that dual bronchodilators such as Ultibro Breezhaler were recommended as first line treatment regardless of their exacerbation risk and prior to the use of ICS marking a significant shift away from ICS containing combination therapies. The instructions also stated that the FLAME study was included as providing evidence for the use of dual bronchodilation; stating that a LAMA/LABA combination was superior to a LABA/ICS combination in preventing exacerbations and other patient reported outcomes in Group D patients. It was important that Pfizer confidently communicated to clinicians the reference behind this statement in order to position Ultibro Breezhaler as the new standard of care for patients with COPD with or without a history of exacerbations.

The briefing material concluded by stating that as could be seen from the significant changes to the GOLD Guidelines which directly impacted Ultibro, treatment decisions were now much more focused on the symptom burden for the patient and LAMA/LABAs had been given a far more prominent role in the management of COPD. This represented a valuable opportunity for the company to provide prescribers with a simple algorithm to follow which would ensure that patients received the right therapy to manage their COPD and increase their chances of living a healthy, active life.

The briefing material referred to Ultibro as 'the evidence based choice of LAMA/LABA for breathless patients regardless of their exacerbation history' and as 'the new standard of care'. In addition, the Panel queried whether the briefing material was sufficiently clear about the need to ensure that any discussion about the reduction in exacerbations should be a benefit of maintenance therapy and not a reason to prescribe *per se*. The Panel considered, on balance, that the briefing material was not sufficiently clear in this regard and thus ruled a breach of Clause 15.9.

The Panel did not consider, however, that the complainant had proved, on the balance of probabilities, that based on the exhibitor activities for Ultibro Breezhaler at the national scientific concerence in December that those on the exhibition stand were specifically briefed to discuss the medicine within the context of the newly issued recommendations within the revised GOLD Report as alleged. The Panel ruled no breach of Clause 15.9 in that regard.

A slide deck for payors (ref UK/ULTSBR/16-0068(1) 'Supporting the management of COPD' consisted of 68 slides including the burden of COPD on the health system, disease management, the benefits of Ultibro Breezhaler and the future of COPD care. The deck referred to the GOLD guidelines that ICS + LABA was recommended for use only in patients in groups C and D (slide 25). This document included claims that Ultibro Breezhaler was an appropriate steroid free option for the patient for whom LABA/ICS was considered (eg slide 31) which also included the Ultibro indication making it clear the primary reason for prescribing Ultibro and therefore no breach of Clauses 3.2 and 7.2 was ruled. The FLAME study (Wedzicha *et al* 2016) results were given on slide 32 including a comparison of exacerbation rates of Ultibro and Seretide as well as FEV1 and rescue medication use. The Panel considered the FLAME study results were set within the context of the licensed indication and thus it ruled no breach of Clauses 3.2 and 7.2 of the Code.

Material (ref UK/ULTSBR/16-0286) described as 'FLAME Business Card – eprint URL link' promoting the results of FLAME (Wedzicha *et al* 2016) referred to the exacerbation outcomes and their impact on patients at risk of future exacerbations without setting these in the context of the Ultibro licensed indication. A breach of Clause 3.2 was ruled. In addition, this material implied that the exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler which was misleading. A breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. Pfizer and Novartis had failed to comply with their undertakings given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 and a breach of Clause 29 was ruled. The Panel noted the importance of undertakings and considered that failure to comply with the undertakings and assurance previously given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 had brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel thus ruled a breach of Clause 2.

The Panel did not accept that there was necessarily an issue if the recommendations in the GOLD 2017 Report were based on best evidence in published literature rather than labelling directives from government regulators. Companies had to ensure that they did not promote a product in a way that was inconsistent with the particulars listed in the SPC. Ultibro was indicated as maintenance therapy to relieve symptoms in COPD.

The Panel noted that the GOLD Report recommended starting therapy with a LABA/LAMA combination because: 'In studies with patient reported outcomes as the primary endpoint LABA/LAMA combination showed superior results compared to the single substances. If a single bronchodilator is chosen as initial treatment, a LAMA is preferred for exacerbation prevention based on comparison to LABAs'. 'A LABA/LAMA combination was superior to a LABA/ICS combination in preventing exacerbations and other patient reported outcomes in Group D patients' and 'Group D patients were at higher risk of developing pneumonia when receiving treatment with ICS'. The Panel noted the complainant's concerns that the GOLD Report did not refer to the PRAC recommendation stating a positive risk – benefit balance for FDC-ICS/LABAs in COPD (that the magnitude of benefit in terms of clinically relevant exacerbation reduction observed was as much as ten-fold greater compared to the slightly increased risk in terms of pneumonia).

In the Panel's view, the GOLD Report implied that Ultibro Breezhaler could be prescribed to reduce exacerbations rather than the reduction of exacerbations being a benefit of using the medicine as maintenance therapy.

The Panel noted that four spotlight webinars were conducted in which health professionals were invited to attend a global broadcast about the updated GOLD Report. Representatives were required to show an introductory slide with all obligatory information including Ultibro's licensed indication for an audience of UK health professionals. The Panel noted its comments above regarding the GOLD briefing and the webinars and considered that whilst the GOLD briefing was not sufficiently clear, the 'upfront' slide required to be shown to UK health professionals set out the indication and therefore the webinars were clear about Ultibro Breezhaler's licensed indication and in that regard were not in breach of Clause 3.2.

Complaint received **4 January 2017**

Case completed **6 July 2017**

CASE AUTH/2930/1/17

HEALTH PROFESSIONAL CONSULTANT TO A PHARMACEUTICAL COMPANY v JOHNSON & JOHNSON

Nicorette advertisement

A complaint was received in a private capacity from a health professional who stated that he/she worked as a consultant to a pharmaceutical company.

The complaint concerned an online advertisement for Nicorette (nicotine) issued by Johnson & Johnson published in Pulse.

The complainant provided a screenshot of a banner advertisement. It included 'Nicorette. Do something incredible'. The complainant did not believe that the word 'incredible' was suitable. This information did not appear to be balanced and was exaggerated. The claim was taken directly from material aimed at the general public and it appeared that Johnson & Johnson had not undertaken a sufficiently robust review when translating to promotion aimed at health professionals.

The detailed response from Johnson & Johnson is given below.

The Panel noted that the banner advertisement continuously revolved through four banners, one after the other, over 10 seconds. The statement at issue 'Do something incredible' appeared immediately adjacent to the Nicorette product logo on the first, second and fourth banner and in the Panel's view would be read as describing a quality of the product. The statement was unqualified on banners 1 and 4, but appeared adjacent to the product logo and question 'HOW DO YOU EMPOWER THEM TO QUIT FOR GOOD?' on the second banner. The third banner read 'Combination NRT is 43% more effective than patch alone' which Johnson & Johnson stated referred to combination NRT in general, all brands and formulations; the Panel considered that some readers might nonetheless not unreasonably associate that claim with Nicorette given the adjacent prominent picture of Nicorette product packs and the claim 'Nothing beats Nicorette dual support' on that banner.

The Panel did not agree with Johnson & Johnson's submission that the statement in question 'Do something incredible' related to the focus of the banners ie how do you empower patients to quit for good and that the health professional could make an informed opinion of the therapeutic value of Nicorette in the context of a quit attempt. Johnson & Johnson also submitted that a patient's achievement in quitting smoking was incredible and not the Nicorette brand. The Panel considered that the difficulty smokers had in quitting would be well understood by the audience and that success would not unreasonably be considered to be an incredible feat. However, whether one considered the first, second and fourth banners individually or the cumulative effect of all four the Panel considered that the implication was that the statement in question related to a feature of Nicorette, that the product itself had incredible features and/or that health professionals would be doing something incredible by prescribing it. The implication was misleading and exaggerated and breaches of the Code ruled.

The complainant stated at the time of submitting the complaint that he/she was a health professional who worked as a consultant to Novartis. It had previously been decided, following consideration by the then Code of Practice Committee and the ABPI Board of Management, that private complaints from pharmaceutical company employees had to be accepted. To avoid this becoming a means of circumventing the normal procedures for intercompany complaints, the employing company would be named in the report. The complainant would be advised that this would happen and be given an opportunity to withdraw the complaint.

This issue came to the fore many years ago when an employee of a pharmaceutical research company complained in a private capacity about a journal advertisement issued by GlaxoSmithKline UK Ltd (Case AUTH/1498/7/03). In Case AUTH/1498/7/03 it was decided that the pharmaceutical research company would be named in the case report whilst making it clear that the complaint was made in a private capacity.

The case preparation manager decided that the principles set out above would apply to consultants. Consultancy status should not be used to circumvent the normal rules for inter-company complaints.

The complainant was advised that if he/she wished to proceed with the complaint in a private capacity Novartis would be named in the case report; and the respondent company would be informed of his/her professional status and the connection with pharmaceutical companies. The complainant so agreed.

Novartis stated that it had no knowledge of, or involvement in, the complaint and did not know the complainant's identity.

The complaint concerned an online advertisement for Nicorette (nicotine) issued by Johnson & Johnson Limited and was published in Pulse (ref UK/NI/16-7663).

COMPLAINT

The complainant provided a screenshot of a banner advertisement. It included 'Nicorette. Do something incredible'. The complainant alleged that whilst he was sure that Nicorette was a useful treatment in

smoking cessation, he/she did not believe that the word 'incredible' was suitable. The complainant referred to the definitions 'impossible to believe' or 'difficult to believe/extraordinary'.

This information did not appear to be balanced and was exaggerated. The claim was taken directly from material aimed at the general public (https://www.nicorette.co.uk/get-motivated-stop-smoking/do-something-incredible) and it appeared that Johnson & Johnson had not undertaken a sufficiently robust review when translating to promotion aimed at health professionals.

When writing to Johnson & Johnson attention was drawn to the requirements of Clauses 7.2 and 7.10 of the Code.

RESPONSE

Johnson & Johnson stated that the advertisement in question was a 'rolling banner' whereby the reader of the website would see each of four rolling banners which flicked through automatically, one after the other (copy provided). The advertisement should be considered as one piece rather than four individual banners.

The tagline 'Do something incredible' had been used globally by Johnson & Johnson for several years. The tagline was a 'call to action' to encourage smokers to make a quit attempt and highlighted the incredible journey that quitters go on to overcome their addiction to tobacco products and ultimately stop smoking. Previous 'Do something incredible' campaigns and advertising had focused on patient stories as a means to motivate smokers to consider quitting tobacco smoking. The tagline was associated with making an attempt to quit smoking rather than using a product to help the patient do so.

Johnson & Johnson stated that according to the World Health Organisation smoking was still one of the most preventable causes of death worldwide; one out of every 2 smokers would die from their habit. Quitting smoking was extremely hard, and research showed that it could take a smoker several attempts to break free from their addiction. Yet quitting smoking remained one of the most important things a smoker could do for their health; and by extension, helping a patient quit could be one of the most effective and cost-effective health interventions a health professional could make.

Johnson & Johnson submitted that the most effective way to quit smoking was with the use of health professional support and pharmacological support. However, quit rates for patients attempting to stop smoking with NHS support had been declining for several years, as documented by the health and social care information centre. Therefore, in recent times the tagline had been used to not only encourage and support smokers to quit smoking, but also to encourage health professionals to support their patients to quit smoking; to help them 'Do something incredible' by breaking free from tobacco and increase their chances of living a long and healthy life.

The dictionary defined 'incredible' as meaning not just 'impossible to believe', but also 'difficult to believe; extraordinary' and synonyms includes 'remarkable', 'marvellous' and 'wonderful'. The term was used therefore in advertising to highlight that quitting smoking, or facilitating someone to quit smoking, was actually quite extraordinary and wonderful. Johnson & Johnson disagreed that the 'Nicorette. Do something incredible' tagline was unbalanced or exaggerated.

The advertisement should be considered in the context of the rolling banners. On the second banner was the question, 'How do you empower them to quit for good?'. Given the great difficulties health professionals faced in helping their patients to quit and the large numbers of failed quit attempts, in this context the health professional could 'do something incredible' by encouraging and helping patients to quit smoking. Equally, those patients who managed to quit for good had achieved something incredible regardless of how this was achieved; behavioural support, pharmacological products or willpower alone.

Furthermore, on banner 3, Johnson & Johnson stated that 'combination NRT is 43% more effective than patch alone'. This claim referred to combination nicotine replacement therapy (NRT) in general, all brands and formulations, and this highlighted that it was the act of quitting smoking that was incredible and not Nicorette brand.

It was unfortunate that the complainant did not approach the company directly to discuss the advertising, particularly because, as someone who had been working as a consultant to the industry, they were probably well aware of the self-regulation process. The company was sure that if it had had the opportunity it could have reassured the complainant and reached a mutually satisfactory conclusion to this complaint.

The complainant also included pages from the Nicorette website aimed at consumers. Nicorette was a general sales list (GSL) product therefore the information from the consumer website was subject to the Proprietary Association of Great Britain (PAGB) Code and had been fully reviewed and approved by both Johnson & Johnson and the PAGB.

Regarding Clause 7.2 Johnson & Johnson submitted that the tagline 'Do something incredible', in context, was balanced, fair and unambiguous. The focus of the rolling banners advertisement was the message within the banners ie, 'How do you empower them to quit for good?'. Encouraging the healthcare professional to support a patient through a quit attempt was not unbalanced and did not mislead either directly or by implication. The healthcare professional could generate an informed opinion of the therapeutic value of the Nicorette NRT medicine in the context of helping a patient through a quit attempt. Stopping smoking was indeed an incredible achievement that many patients could realise, with such support.

PANEL RULING

The Panel noted that the banner advertisement, published in Pulse today online, continuously revolved through four banners, one after the other, over 10 seconds. The Panel noted that the supplementary information to Clause 4.1 which covered prescribing information and other obligatory information stated in relation to electronic journals, *inter alia*, that the first part of an advertisement in an electronic journal, such as the banner, was often the only part of the advertisement that is seen by readers. The first part was often linked to other parts and in such circumstances the linked parts would be considered as one advertisement. The Panel considered that the purpose of the relevant supplementary information was, *inter alia*, to ensure that the prescribing information and other obligatory information were an integral part of the advertisement thus satisfying the requirements of Clause 4.1. The Panel noted that the link to the prescribing information was not the subject of the present complaint.

The Panel considered that there were differences between a static banner on which one proactively clicked to link to other material including the prescribing information, and a series of continuously revolving banners. The length of time that each banner was displayed within a revolving series would vary, could not be influenced by the reader and might be longer or shorter than those in the material in question which were displayed for 2.5 seconds each. The Panel considered that such cases should be considered individually in relation to the requirements of the Code. The Panel did not consider Johnson & Johnson's submission that the material should be viewed as one advertisement rather than four individual banners: this was not a point raised by the complainant.

The Panel noted that the statement at issue 'Do something incredible' appeared immediately adjacent to the Nicorette product logo on the first, second and fourth banner and in the Panel's view would be read as describing a quality of the product. The statement was unqualified on banners 1 and 4, but appeared adjacent to the product logo and question 'HOW DO YOU EMPOWER THEM TO QUIT FOR GOOD?' on the second banner. The third banner read 'Combination NRT is 43% more effective than patch alone' which Johnson & Johnson stated referred to combination NRT in general, all brands and formulations; the Panel considered that some readers might nonetheless not unreasonably associate that claim with Nicorette given the adjacent prominent picture of Nicorette product packs and the claim 'Nothing beats Nicorette dual support' on that banner.

The Panel did not agree with Johnson & Johnson's submission that the statement in question 'Do something incredible' related to the focus of the banners ie how do you empower patients to quit for good and that the health professional could make an informed opinion of the therapeutic value of Nicorette in the context of a quit attempt. Johnson & Johnson also submitted that a patient's achievement in quitting smoking was incredible and not the Nicorette brand. The Panel considered that the difficulty smokers had in quitting would be well understood by the audience and that success would not unreasonably be considered to be an incredible feat. However, whether one considered the first, second and fourth banners individually or the cumulative effect of all four the Panel considered that the implication was that the statement in question related to a feature of Nicorette, that the product itself had incredible features and/or that health professionals would be doing something incredible by prescribing it. The implication was misleading and exaggerated and a breach of Clauses 7.2 and 7.10 was ruled.

Complaint received **16 January 2017**

Case completed **18 May 2017**

CASE AUTH/2931/1/17

HEALTH PROFESSIONAL CONSULTANT TO A PHARMACEUTICAL COMPANY/DIRECTOR v PFIZER

Online advertisement for a meeting

A complaint was received in a private capacity from a health professional who stated that he/she worked as a consultant to a pharmaceutical company. It had previously been decided, following consideration by the then Code of Practice Committee and the ABPI Board of Management, that private complaints from pharmaceutical company employees had to be accepted. To avoid this becoming a means of circumventing the normal procedures for intercompany complaints, the employing company would be named in the report. The complainant would be advised that this would happen and be given an opportunity to withdraw the complaint.

The principles set out above were applied to this complaint. Consultancy status should not be used to circumvent the normal rules for inter-company complaints.

The complainant was advised that if he/she wished to proceed with the complaint in a private capacity Novartis would be named in the case report; and the respondent company would be informed of his/her professional status and the connection with pharmaceutical companies. The complainant so agreed.

As part of the complaint concerned an alleged breach of undertaking, that part of the complaint was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings.

The complaint concerned an advertisement published in Pulse today.co.uk inviting readers to a Pfizer meeting to be held in January 2017. The invitation was headed 'The ultimate stop smoking roadshow 2017 3 Events Across the UK' and details of a relevant website were given. The complaint also concerned two invitations sent by email in December 2016 and January 2017 to attend road show events.

The complainant stated that although there was a statement that Pfizer had funded the programme (displayed on the website and the emails but too blurry to read on the advertisement), it was not clear where editorial control resided. The emails and the advertisement all stated that Pfizer products might be mentioned, but the complainant could find no link to the relevant prescribing information. There was no clear prominent statement as to where it could be found. As a consequence, there was no adverse event statement. The description of 'ultimate stop smoking roadshow' was inappropriate language and, given it was taking place in January, might not be the case by the end of the year – if any event could be described as 'ultimate' – it was not the most appropriate taste and failed to recognise the professional standing of the audience.

Given the lack of clarity on the emails, the advertisement and the website, the complainant was concerned regarding materials that were used on the day. Had these too failed to have prescribing information where appropriate? The complainant had no knowledge of these, but was concerned that the same issues might be present.

In a subsequent email, the complainant stated that he/she noted that Case AUTH/2818/1/16 mentioned disguised promotion and lack of clarity of declarations of sponsorship. The complainant requested that this matter also be reviewed to determine whether Pfizer had complied with its undertaking given in that case.

The detailed response from Pfizer is given below.

The Panel examined the invitations at issue. The advertisement published online in Pulse was headed 'THE ULTIMATE STOP SMOKING ROADSHOW 2017' followed by '3 EVENTS ACROSS THE UK'. The date of the meeting was given followed by 3 bullet points: Meeting the challenges; Clinical study news; and KOL-led presentations. The Panel was unsure why the declaration statement in the advertisement provided by the complainant was blurry but noted Pfizer's submission that the online advertisement was clear and legible. The statement read 'This program is initiated and funded by Pfizer and may include reference to Pfizer medicines relevant to the agenda topics' followed by the Pfizer logo. The Panel also noted the references to Pfizer in the emails.

The Panel considered that Pfizer's role in the initiation and funding of the program had been made clear. No breach was ruled in relation to each email and the online invitation published in Pulse.

The Panel noted that there was no direct or implied mention of any medicine in the invitation and emails. Recipients would be clear that Pfizer's meeting would include treatment strategies and 'may include reference to Pfizer's medicines relevant to the agenda topics'. The Panel considered that whilst it might be prudent to provide prescribing information with the invitations as the invitation did not promote any specific Pfizer medicines, it was not a breach of the Code not to do so. The adverse event reporting requirements were thus not triggered. The Panel ruled no breach.

The Panel noted that 'ultimate', as used in the material in question, was used to describe the event

rather than a medicine. The Panel did not consider that the term 'ultimate' was a direct or indirect claim for a medicine on the materials at issue. The Panel thus ruled no breaches of the Code.

The Panel considered that, on balance, describing the series of meetings on the three items at issue as 'the ultimate stop smoking roadshow' did not recognise the special nature of medicines and the professional standing of the audience and a breach was ruled.

The Panel noted the complainant's concern that materials used on the day failed to have prescribing information where appropriate. The Panel noted that the complainant had not seen the materials but posed a series of questions about them and a hypothetical scenario. The Panel noted Pfizer's submission that the audience was made aware of the availability of prescribing information as necessary from the outset of the presentation and, in addition, material with prescribing information was available to attendees at the meeting. The Panel reviewed the slides and noted that although Pfizer medicines were included, no prescribing information was given nor did the slides state where such could be found.

[Post meeting note. On completion of this case Pfizer advised that of the presentations, all of which stated 'This program is initiated and funded by Pfizer and may include reference to Pfizer medicines relevant to the agenda topics', those presentations that referred to Champix (varenicline tartrate) included reference to the availability of its prescribing information at the meeting].

The Panel noted that it was an established principle that prescribing information for a presentation should either be part of it or be otherwise available to each delegate, a leavepiece provided to each delegate would suffice in this regard. If prescribing information formed part of the presentation in the absence of alternative formats, it should be displayed such that the audience had sufficient time to consider it. The Panel considered it prudent and good practice to include prescribing information on presentations at meetings even if the prescribing information was also made available on a leavepiece or similar. The Panel noted the nature of the allegation and Pfizer's explanation above about the availability of prescribing information at the meeting and therefore ruled no breach of the Code.

The Panel noted its rulings above and overall did not consider that high standards had not been maintained and therefore ruled no breach in that regard.

The Panel noted the complainant's further allegation that Pfizer might not have complied with its undertaking in Case AUTH/2818/1/16. In that case, the Panel considered that it was not sufficiently obvious at the outset that an email invitation to a Sayana Press webinar, sent by a third party event organiser on Pfizer's behalf, was promotional and from a pharmaceutical company. The Panel considered the promotional nature of that email was disguised and a breach was ruled. Turning to this case, Case AUTH/2931/1/17, the Panel noted its rulings above that the declaration of Pfizer's role in the initiation and funding of the programme was clear. The Panel did thus not consider that Pfizer had failed to comply with its undertaking given in Case AUTH/2818/1/16. The Panel ruled no breach of the Code including Clause 2.

The complainant stated at the time of submitting the complaint that he/she was a health professional who worked as a consultant to Novartis. It had previously been decided, following consideration by the then Code of Practice Committee and the ABPI Board of Management, that private complaints from pharmaceutical company employees had to be accepted. To avoid this becoming a means of circumventing the normal procedures for inter-company complaints, the employing company would be named in the report. The complainant would be advised that this would happen and be given an opportunity to withdraw the complaint.

This issue came to the fore many years ago when an employee of a pharmaceutical research company complained in a private capacity about a journal advertisement issued by GlaxoSmithKline UK Ltd (Case AUTH/1498/7/03). In Case AUTH/1498/7/03 it was decided that the pharmaceutical research company would be named in the case report whilst making it clear that the complaint was made in a private capacity.

The case preparation manager decided that principles set out above would apply to consultants. Consultancy status should not be used to circumvent the normal rules for inter-company complaints.

The complainant was advised that if he/she wished to proceed with the complaint in a private capacity Novartis would be named in the case report; and the respondent company would be informed of his/her professional status and the connection with pharmaceutical companies. The complainant so agreed.

Novartis stated that it had no knowledge of or involvement in, the complaint and did not know the complainant's identity.

As part of the complaint concerned an alleged breach of undertaking, that part of the complaint was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings.

The complaint concerned an advertisement published in Pulse today.co.uk inviting readers to a Pfizer meeting to be held in January 2017. The invitation was headed 'The ultimate stop smoking roadshow 2017 3 Events Across the UK' and details of a relevant website were given. The complaint also concerned two invitations sent by email in December 2016 and January 2017 to attend road show events.

COMPLAINT

The complainant stated that although there was a statement that Pfizer had funded the programme

(displayed on the website and the emails but too blurry to read on the advertisement), it was not clear where editorial control resided. The emails and the advertisement all mentioned that Pfizer products might be mentioned, but the complainant could find no link to the prescribing information for any products that might be mentioned. There was no clear prominent statement as to where it could be found. As a consequence, there was no adverse event statement. The description of 'ultimate stop smoking roadshow' was inappropriate language for an event aimed at health professionals and, given it was taking place in January, might not be the case by the end of the year – if any event could be described as 'ultimate' – it was not the most appropriate taste and failed to recognise the professional standing of the target audience.

Given the lack of clarity on the emails, the advertisement and the website, the complainant was concerned regarding materials that were used on the day. Had these too failed to have prescribing information where appropriate? Did the fact that the slides might have product information indicate that the speakers had provided their own slides and Pfizer was not aware of what the content was to be? The emails indicated that there had been meetings previously organised. The complainant had no knowledge of these, but was concerned that the same issues might be present.

In a subsequent email, the complainant stated that he/she noted that Case AUTH/2818/1/16 mentioned disguised promotion and lack of clarity of declarations of sponsorship. The complainant requested that this matter also be reviewed to determine whether Pfizer had complied with its undertaking given in that case.

Pfizer was asked to respond to the requirements of Clauses 4.1, 4.9, 7.10, 9.1, 9.2 and 9.10 of the Code in relation to the smoking cessation materials and Clauses 2, 9.1 and 29 in relation to the alleged breach of undertaking.

RESPONSE

Pfizer stated that it had spoken with the medical director at Novartis. Novartis had no knowledge of the complaint and did not support it.

Pfizer strongly refuted all the allegations.

Pfizer's submitted that its involvement in the meeting was prominently declared on all the materials. The wording 'this program was initiated and funded by Pfizer and may include reference to Pfizer medicines relevant to the agenda topics' was prominently shown alongside the Pfizer logo on the website, the invitation published in Pulse and email invitations to ensure that the promotional nature of the meeting was clear. As such, responsibility for the meeting and related materials, including meeting content, was with Pfizer. The meeting content had been appropriately certified; there was no ambiguity regarding editorial control as Pfizer was responsible for the materials and content of the meeting.

In reference to the comment that the advertisement was too blurry to read, this was not the case with the actual online advertisement which was clear and legible.

Pfizer submitted that as the emails, the invitation published in Pulse and registration website did not contain any mention of specific product or promotional content, there was no requirement for prescribing information or adverse event reporting information to be provided.

The slides for the meeting had been certified as required under the Code and where Pfizer medicines were mentioned, the audience was made aware of the availability of prescribing information as necessary from the outset of the presentation. In addition, material with prescribing information was available to attendees at the meeting.

Pfizer submitted that the use of the word 'ultimate' was not a breach of the Code, as this was not used in relation to a product and was not making any claim about a product but rather aimed to convey to the reader the breadth of coverage and high quality of the faculty and meeting content. However, given the concern raised by the complainant, Pfizer intended to use alternative wording in future if similar meetings took place.

Pfizer submitted that previous meetings and associated materials in the same series of events were developed and conducted to the same high standards with full compliance with the Code.

Pfizer denied a breach of Clauses 4.1, 4.9, 7.10, 9.1, 9.2 and 9.10.

As mentioned above, Pfizer's involvement in the meeting was prominently declared on all the materials. The wording 'This program is initiated and funded by Pfizer and may include reference to Pfizer medicines relevant to the agenda topics' was prominently shown alongside the Pfizer logo on the website, advertisement and email invitations to ensure that the promotional nature of the meeting was clear. The opening slides shown at the meeting had the same wording and logo to ensure delegates were in no doubt of Pfizer's involvement in the meeting. Pfizer submitted that it had fully complied with the above mentioned undertaking and had not breached Clauses 2, 9.1 and 29.

In summary, Pfizer disagreed with all of the complainant's allegations and was of the opinion that it had fully complied with the Code and maintained high standards throughout.

PANEL RULING

The Panel examined the invitations at issue. The advertisement published online in Pulse was headed 'THE ULTIMATE STOP SMOKING ROADSHOW 2017' followed by '3 EVENTS ACROSS THE UK'. The date of the Leeds meeting was given followed by 3 bullet points: Meeting the challenges; Clinical study news; and KOL-led presentations. The Panel was unsure why the declaration statement in the advertisement

provided by the complainant was blurry but noted Pfizer's submission that this was not the case with the actual online advertisement which was clear and legible. The statement read 'This program is initiated and funded by Pfizer and may include reference to Pfizer medicines relevant to the agenda topics' followed by the Pfizer logo.

The December 2016 email stated the complainant's name followed by 'your invitation to: The Ultimate Stop Smoking Roadshow 2017'. The January 2017 email also stated the complainant's name followed by 'only a few places left for the Ultimate Stop Smoking Roadshow'. The subject heading of both was 'The Ultimate Stop Smoking Roadshow 2017' and the body of each was headed 'This program is initiated and funded by Pfizer and may include reference to Pfizer medicines relevant to the agenda topics' adjacent to the Pfizer logo. This was followed on both emails by a highlighted box which included the statement 'THE ULTIMATE STOP SMOKING ROADSHOW 2017' above registration details. The December 2016 email stated that presentations led by UK smoking cessation KOLs would include: The nature of nicotine addiction; How can we reduce smoking prevalence?; and smoking cessation options – including latest developments. Details of the three half-day events being held across the country were also provided. The January 2017 email did not provide details of the presentations but stated 'Remember … Each Roadshow event will reveal stimulating, up-to-date facts and expert opinions, plus the latest clinical study news and a comprehensive examination of the challenges faced by HCPs'. The website address for the roadshow was given and each email was signed by an events agency. At the bottom of each it was stated that the event was in association with Pulse, Nursing in Practice and the Pharmacist. It was endorsed by the Advisor. A statement towards the bottom of each read 'All meeting costs, including speaker honoraria, have been covered by Pfizer'.

The supplementary information to Clause 9.10, Declaration and Sponsorship, stated, *inter alia*, that the wording of the declaration must be unambiguous so that readers will immediately understand the extent of the company's involvement and influence over the material. The Panel noted Pfizer's submission that its involvement in the meeting was prominently declared on all the materials including the website, the invitation published in Pulse and email invitations to ensure that the promotional nature of the meeting was clear. The Panel further noted Pfizer's submission that it was responsible for the meeting and related materials. The Panel noted that Pfizer's role was clearly stated on the invitation published in Pulse. In relation to the emails, the company logo and declaration of its involvement appeared prominently in the body of the email as the heading to each. The Panel considered that Pfizer's role in the initiation and funding of the program had been made clear. No breach of Clause 9.10 was ruled in relation to each email and the online invitation published in Pulse.

The Panel noted that there was no direct or implied mention of any medicine in the invitation and emails. Recipients would be clear that Pfizer's meeting would include treatment strategies and 'may include reference to Pfizer's medicines relevant to the agenda topics'. The Panel considered that whilst it might be prudent to provide prescribing information with the invitations as the invitation did not promote any specific Pfizer medicines, it was not a breach of the Code not to do so. The adverse event reporting requirements were thus not triggered. The Panel ruled no breach of Clauses 4.1 and 4.9 in relation to each email and the online invitation published in Pulse.

The Panel noted the complainant's allegation that 'ultimate stop smoking roadshow' was inappropriate language for an event aimed at health professionals and failed to recognise the professional standing of the target audience. The Panel noted that, *inter alia*, exaggerated or all-embracing claims must not be made and superlatives must not be used except for those limited circumstances where they related to a clear fact about a medicine. Claims should not imply that a medicine or an active ingredient has some special merit, quality or property unless this could be substantiated. The Panel noted that 'ultimate', as used in the online advertisement and two emails in question, was used to describe the event rather than a medicine. The Panel did not consider that the term 'ultimate' was a direct or indirect claim for a medicine on the materials at issue. The Panel noted that there was no allegation about any subsequent use of the term at the events at issue. The Panel thus ruled no breach of Clause 7.10.

The Panel noted the requirement of Clause 9.2 that materials and activities must recognise the special nature of medicines and the professional standing of the audience and must not be likely to cause offence. The Panel noted Pfizer's submission that 'ultimate' aimed to convey to the reader the breadth of coverage and high quality of the faculty and meeting content but that it intended to use alternative wording in future if similar meetings took place. The Panel considered that the breadth of coverage etc could have been conveyed in other ways. The Panel considered that, on balance, describing the series of meetings on the three items at issue as 'the ultimate stop smoking roadshow' did not recognise the special nature of medicines and the professional standing of the audience and a breach of Clause 9.2 was ruled.

The Panel noted the complainant's concern that materials used on the day failed to have prescribing information where appropriate. The Panel noted that the complainant had not seen the materials but posed a series of questions about them and a hypothetical scenario. The Panel noted Pfizer's submission that the audience was made aware of the availability of prescribing information as necessary from the outset of the presentation and, in addition, material with prescribing information was available to attendees at the meeting. The Panel reviewed the slides provided by Pfizer and noted that although Pfizer medicines were included, no prescribing information was given nor did the slides state where such could be found.

[Post meeting note. On completion of this case Pfizer advised that of the presentations, all of which stated 'This program is initiated and funded by Pfizer and may include reference to Pfizer medicines relevant to the agenda topics', those presentations that mentioned Champix (varenicline tartrate) did include reference to the availability of its prescribing information at the meeting].

The Panel noted that in relation to presentations delivered at a meeting, it was an established principle that prescribing information for a presentation should either be part of it or be otherwise available to each delegate, a leavepiece provided to each delegate would suffice in this regard. If prescribing information formed part of the presentation in the absence of alternative formats, it should be displayed such that the audience had sufficient time to consider it. The Panel considered it prudent and good practice to include prescribing information on presentations at meetings even if the prescribing information also was made available on a leavepiece or similar. The Panel noted the nature of the allegation and Pfizer's explanation above about the availability of prescribing information at the meeting and therefore ruled no breach of Clause 4.1.

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 made a general statement regarding similar issues with previously organised meetings but had not identified the meetings or submitted any detailed reasons or allegations. Due to the lack of any specific *bona fide* allegations, the Panel did not consider this matter.

The Panel noted its rulings above and overall did not consider that high standards had not been maintained and therefore ruled no breach of Clause 9.1.

The Panel noted the complainant's further allegation that Pfizer might not have complied with its undertaking in Case AUTH/2818/1/16. In that case, the Panel considered that it was not sufficiently obvious at the outset that an email invitation to a Sayana Press webinar, sent by a third party event organiser on Pfizer's behalf, was promotional and from a pharmaceutical company. The Panel considered the promotional nature of that email was disguised and a breach of Clause 12.1 was ruled. Turning to this case, Case AUTH/2931/1/17, the Panel noted its rulings above that the declaration of Pfizer's role in the initiation and funding of the program was clear. The Panel did thus not consider that Pfizer had failed to comply with its undertaking given in Case AUTH/2818/1/16. The Panel ruled no breach of Clause 29 and subsequently no breach of Clauses 9.1 and 2.

Complaint received **16 January 2017**

Case completed **27 June 2017**

CASE AUTH/2933/2/17

HEALTH PROFESSIONAL CONSULTANT TO A PHARMACEUTICAL COMPANY v CHIESI

Promotion of Fostair

A complaint was received in a private capacity from a health professional who stated that he/she worked as a consultant to a pharmaceutical company. It had previously been decided, following consideration by the then Code of Practice Committee and the ABPI Board of Management, that private complaints from pharmaceutical company employees had to be accepted. To avoid this becoming a means of circumventing the normal procedures for intercompany complaints, the employing company would be named in the report. The complainant would be advised that this would happen and be given an opportunity to withdraw the complaint.

The principles set out above were applied to this complaint. Consultancy status should not be used to circumvent the normal rules for inter-company complaints.

The complainant was advised that if he/she wished to proceed with the complaint in a private capacity Novartis would be named in the case report; and the respondent company would be informed of his/her professional status and the connection with pharmaceutical companies. The complainant so agreed.

The complaint concerned an online advertisement for Fostair (beclomethasone and formoterol) issued by Chiesi. The advertisement included the claim 'Efficacy with only 3 steps per inhalation' and 'See the features of the Fostair NEXThaler device'. The advertisement also claimed 'Efficacy with only 3 steps per inhalation, 'open – inhale – close'. The claim was referenced to the Fostair NEXThaler 100/6 summary of product characteristics (SPC) and Kanniess *et al* 2015.

Fostair was indicated for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

The complainant compared the claim that there were three steps per inhalation – open, inhale, close to the five steps listed in the patient information leaflet (PIL). Those five steps had additional points beneath each including crucially the requirement to hold one's breath for 5-10 seconds to receive a therapeutic dose. The complainant alleged that the prescribing information was also out-of-date and omitted the special warning regarding pneumonia.

The complainant stated that the prescribing information on the website was similarly out-of-date.

The detailed response from Chiesi is given below.

The Panel noted Chiesi's submission about the timing of the update to the prescribing information. The update to the prescribing information had been prepared in July 2016 ahead of the formal approval of the summary of product characteristics (SPC) variation on 5 September 2016. The Panel considered that the prescribing information for the online advertisement and on the website was up-to-date and therefore ruled no breach of the Code.

The Panel noted that the Fostair NEXThaler 100/6 SPC dated 7 September 2016 stated that correct use was essential in order for the treatment to be successful. The PIL stated that optimal lung delivery was obtained if the patient inhaled by breathing in quickly and deeply through the inhaler. A breath holding period of 5-10 seconds, or as long as comfortable for the patient was suggested before breathing out. The PIL instructions which were also in the SPC referred to four steps, visual check, open, inhale, close. Each of these steps had a number of instructions. The 'open' section included an instruction 'before inhaling breathe out as far as is comfortable'.

The advertisement in question referred to 'Efficacy with only 3 steps per inhalation. See the features of the Fostair NEXThaler device. The Panel accepted that as far as the device was concerned it had to be opened by the patient, used for an inhalation and closed by the patient. However to take the medicine correctly in order for the dose to be efficacious there were more than three steps. These were set out in full in the PIL. In addition as far as the device was concerned the PIL referred to four steps. The Panel decided that the advertisement was misleading as it was inconsistent with the SPC and the PIL. A breach the Code was ruled.

The Panel did not consider that the advertisement failed to meet high standards and nor did the circumstances warrant a ruling of a breach of Clause 2 and ruled accordingly.

The complainant stated at the time of submitting the complaint that he/she was a health professional who worked as a consultant to Novartis. It had previously been decided, following consideration by the then Code of Practice Committee and the ABPI Board of Management, that private complaints from pharmaceutical company employees had to be accepted. To avoid this becoming a means of circumventing the normal procedures for intercompany complaints, the employing company would be named in the report. The complainant would be advised that this would happen and be given an opportunity to withdraw the complaint.

This issue came to the fore many years ago when an employee of a pharmaceutical research company complained in a private capacity about a journal advertisement issued by GlaxoSmithKline UK Ltd

(Case AUTH/1498/7/03). In Case AUTH/1498/7/03 it was decided that the pharmaceutical research company would be named in the case report whilst making it clear that the complaint was made in a private capacity.

The case preparation manager decided that the principles set out above would apply to consultants. Consultancy status should not be used to circumvent the normal rules for inter-company complaints.

The complainant was advised that if he/she wished to proceed with the complaint in a private capacity Novartis would be named in the case report; and the respondent company would be informed of his/her professional status and the connection with pharmaceutical companies. The complainant so agreed.

Novartis stated that it had no knowledge of, or involvement in, the complaint and did not know the complainant's identity.

The complaint concerned an online advertisement for Fostair (beclomethasone and formoterol) issued by Chiesi Limited (ref CHNEX20161340 Dec 16). The advertisement included the claim 'Efficacy with only 3 steps per inhalation' and 'See the features of the Fostair NEXThaler device'. The advertisement also claimed 'Efficacy with only 3 steps per inhalation, 'open – inhale – close'. The claim was referenced to the Fostair NEXThaler 100/6 summary of product characteristics (SPC) and Kanniess *et al* 2015.

Fostair was indicated for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

COMPLAINT

The complainant compared the claim that there were three steps per inhalation – open, inhale, close to the five steps listed in the patient information leaflet (PIL). Those five steps had additional points beneath each. Crucially one step was the requirement to hold one's breath for 5-10 seconds. If patients did not do this, they would not receive a therapeutic dose. The complainant alleged that the prescribing information was also out-of-date and omitted the special warning regarding pneumonia.

The complainant stated that the prescribing information on the website was similarly out-of-date.

In writing to Chiesi attention was drawn to the requirements of Clauses 2, 4.1, 7.2 and 9.1.

RESPONSE

Chiesi stated it was committed to maintaining high standards and strengthening the image of the pharmaceutical industry by operating in a responsible, ethical and professional manner, especially in relation to materials and activities.

1 Prescribing Information

Chiesi stated that the complainant was incorrect.

The hyperlink to the electronic medicines compendium (eMC) showing the history log of updates to the Fostair NEXThaler 100/6 summary of product characteristics (SPC) was provided by the complainant. The current SPC history log displayed five updates with the latest implemented on 7 September 2016. This history log confirmed that this SPC update included, *inter alia*, 4.4 Special warnings and precautions for use – pneumonia in patients with COPD.

The prescribing information for the digital banner advert for Fostair NEXThaler 100/6 (ref CHNEX20161340) was not provided by the complainant. Instead, a hyperlink was provided linking to the Chiesi website, subsequently alleging that the prescribing information for Fostair NEXThaler 100/6 (ref CHWEB20160717) was similarly out of date on the respiratory products section of the Chiesi website.

Chiesi confirmed that the prescribing information contained within the certified, digital banner advertisement for Fostair was the same version (date of preparation July 2016) as that which appeared on the respiratory products section of Chiesi's website.

Although not explicitly stated by the complainant, the clear implication was that prescribing information used in the digital banner advertisement and on the respiratory products section of Chiesi's website could not reflect the updated Fostair NEXThaler 100/6 SPC dated 7 September 2016, because the prescribing information was prepared in July 2016.

Chiesi stated that it took the matter of using up-to-date prescribing information very seriously and at the time of preparation, Chiesi was acutely aware of PMCPA guidance issued on 20 April 2016, that referred to, *inter alia*, some companies incorrectly assuming that there was a period of grace in which up-to-date prescribing information to reflect changes to the SPC was implemented. In response to the release of this guidance Chiesi implemented a risk minimising measure of preparing updated prescribing information in advance of completion of a Type 1A variation to the Fostair NEXThaler SPCs. The intention at the time was to embargo the updated version of the prescribing information until approval of this variation.

In July 2016, Chiesi's corporate regulatory department based in Italy informed the UK affiliate about the requirement to submit a Type 1A variation to implement the outcome of the referral Article 31 including, *inter alia*, 4.4 Special warnings and precautions for use – Pneumonia in patients with COPD, for the marketing authorisations of inhaled corticosteroid containing medicinal products indicated in the treatment of COPD. The specific wording required to update SPCs was made available by the European Medicines Evaluation Agency (EMA) at the time. Internally, within the UK medical affairs department a timetable of actions and activities were initiated by Chiesi:

Timelines and actions for creation of current prescribing information

	Medical Affairs – Communications/Action(s)
18 July 2016	Medical affairs manager briefed medical affairs team including, *inter alia*,: • Fostair SPCs would be updated with information on pneumonia following the PRAC review. • Significant changes in Section 4.4 and 4.8 would impact the Fostair prescribing information. • Update the prescribing information for Fostair. • Note in the job summary that the updated prescribing information would be embargoed until formal approval received from the MHRA (anticipated early September 2016). • Once approved the old prescribing information would be withdrawn and archived.
18 July 2016	Medical affairs manager informed the marketing department, *inter alia*, that: • Fostair SPCs for both NEXThaler and pMDI would be updated with information on pneumonia following the PRAC review. • The medical affairs team will subsequently prepare the updated prescribing information. • Prescribing information will be embargoed for use until approval received from the MHRA.
8 August 2016	Internal approval of updated prescribing information by two Chiesi signatories. Consequently, the date of preparation was July 2016.
9 August 2016	Medical affairs team informed the marketing department, *inter alia*, that: • Updating of Fostair prescribing information was complete. • Updated prescribing information was embargoed until confirmation of MHRA approval which was expected in September. • The prescribing information would be added to the server for use only after the embargo was lifted.
7 September 2016	Medical affairs manager informed the marketing department, *inter alia*, that: • The pneumonia variation for Fostair pMDI 100/6 and Fostair NEXThaler 100/6 were both now approved. • Fostair prescribing information was no longer embargoed.

Chiesi submitted that given the actions undertaken, the Fostair NEXThaler 100/6 prescribing information was not out-of-date as alleged and therefore not in breach of the Code.

The Code stated that the prescribing information consisted of, *inter alia*, a succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement.

It was not clear why the complainant concluded that a warning related to pneumonia had been omitted other than he/she had incorrectly assumed that the prescribing information could not reflect the updated Fostair NEXThaler 100/6 SPC dated 7 September 2016, because this prescribing information was prepared in July 2016 and did indeed include the pneumonia warning.

Failure to acknowledge the statements related to pneumonia in the prescribing information by the complainant thus appeared to be an oversight and invalidated the related allegation. Chiesi noted that the PMCPA specifically requested the complainant to set out what in his/her opinion, was missing from the prescribing information.

Furthermore, Chiesi submitted that the proactive risk mitigating measures implemented by the medical affairs team (tabulated above) following the release of the April 2016 PMCPA guidance on keeping prescribing information up-to-date, meant Chiesi was actually enhancing the high standards expected and strengthening the image of the pharmaceutical industry, contrary to alleged implications of Clauses 9.1 and 2. Therefore there was no breach of Clauses 4.1, 9.1 and 2.

In response to a request for further information in relation to the delay in using updated prescribing information on the Chiesi respiratory website, Chiesi submitted that an update to the prescribing information for Fostair pMDI and Fostair NEXThaler 100/6 was prepared in July 2016 following an update to the SPC with the pneumonia warning. The prescribing information was examined and approved by two Chiesi signatories on 8 August 2016, ahead of the formal approval of the SPC variation by the MHRA on 5 September 2016. The Chiesi respiratory website was not developed or live at the time of approval of the SPC variation by the MHRA. The Chiesi respiratory website was certified on 22 November 2016 and went live for the first time on 25 November 2016.

2 Alleged misleading claim

Chiesi stated that the claim '3 steps per inhalation –

open, inhale, close' appeared part way through the running of the digital banner advertisement once the gradually building image of the Fostair NEXThaler 100/6 device was fully formed and the claim in question appeared over the top of the fully formed device image.

The primary reference supporting the claim was the Fostair NEXThaler 100/6 SPC to which the complainant did not refer. The Fostair NEXThaler 100/6 SPC included a section entitled 'E. How to use your NEXThaler inhaler'. Directly underneath this were three of four sub-section titles that clearly related to the operational sequence of the Fostair NEXThaler 100/6 device, namely E2 – Open; E3 – Inhale and E4 – Close. E1 – Visual Check, would not ordinarily be considered as part of the operational sequence. These sub-section headings were aligned to the operational sequence of an inhaler device, and supported the claim '3 steps per inhalation – open, inhale, close'. Chiesi submitted that the statement was not misleading and therefore there was no breach of the Code.

Chiesi submitted that the claim was supported by other literature including Corradi *et al* 2014 which described the inhalation steps as '3 Open Inhale Close'.

Voshaar T *et al* 2014 undertook a usability study involving the NEXThaler device and noted that '... NEXThaler was a DPI that had been designed to overcome some of the limitations of the currently marketed devices ... had a unique "open-inhale-close" operating sequence that was at least one inhalation step less than that of other existing DPIs and easy for patients to use ....'. In this study involving 66 adult asthma patients, NEXThaler was considered the easiest to use device when compared to two other devices assessed.

Chiesi therefore submitted that the claim '3 steps per inhalation – open, inhale, close', was therefore not misleading and not in breach of the Code.

Chiesi stated that sequences such as opening a device cap, priming/loading a device, inhaling from a device and finally, closing a device were generally well accepted overarching steps related to operational sequences of any inhaler device. Fully opening the inhaler cap of Fostair NEXThaler 100/6 automatically primed the device. So in the case of Fostair NEXThaler 100/6, the operational sequences were: Opening a device cap, inhaling from a device and closing the device cap ie excluding the necessity to prime the device separately.

The complainant alleged that the claim '3 steps per inhalation – open, inhale, close' was misleading because the Fostair PIL contained a section 'E3 – Inhale' where there were 5 sub-points, one of which the complainant stated was crucial.

Chiesi firmly believed it was self-evident that the '3 steps' referred to the operational sequence 'open-inhale-close' and not the sub-points directly underneath 'E3 – Inhale' as seen in the PIL and SPC.

Additionally, the fully formed Fostair NEXThaler 100/6 device image alone placed in the background behind the claim in question also helped with the context of the operational sequence. Chiesi submitted it was self-evident to health professionals that there would be specific actions related to each over-arching step such as holding breath immediately after inhalation, and therefore Chiesi did not accept that the claim was misleading as implied and therefore not in breach of Clauses 7.2, 9.1 and 2 of the Code.

PANEL RULING

The Panel noted that all promotional material must be accurate when it was used and include prescribing information that complied with the Code. The three month time limit that had been previously allowed for prescribing information to be updated was only in relation to changes in cost for a medicine as a result of new Pharmaceutical Price Regulation Scheme (PPRS) agreements.

The PMCPA had always advised that prescribing information had to be up-to-date at the time it was used. It appeared that some in the industry had, in error, interpreted this as three months.

The Panel noted Chiesi's submission about the timing of the update to the prescribing information for the advertisement in question to include the addition of pneumonia in patients with COPD to Section 4.4, Special warnings and precautions for use of the Fostair NEXThaler 100/6 SPC. The update to the prescribing information had been prepared in July 2016 ahead of the formal approval of the SPC variation by the MHRA on 5 September 2016. The Panel considered that the prescribing information for the online advertisement was up-to-date and therefore ruled no breach of Clause 4.1.

The Panel also ruled no breach of Clause 4.1 in relation to the Chiesi respiratory website which according to Chiesi was not available before the approval of the SPC variation. This website went live in November 2016 and included the updated prescribing information which was prepared in July 2016.

The Panel noted that the Fostair NEXThaler 100/6 SPC dated 7 September 2016 stated that correct use of the NEXThaler inhaler was essential in order for the treatment to be successful. The patient should be advised to read the PIL carefully and follow the instructions for use as given in the leaflet. It stated that optimal lung delivery was obtained if the patient inhaled by breathing in quickly and deeply through the inhaler. A breath holding period of 5-10 seconds, or as long as comfortable for the patient was suggested before breathing out. The PIL instructions which were also in the SPC referred to four steps, visual check, open, inhale, close. Each of these steps had a number of instructions. The 'open' section included an instruction 'before inhaling breathe out as far as is comfortable'.

The advertisement in question referred to 'Efficacy with only 3 steps per inhalation. See the features of

the Fostair NEXThaler device. The Panel accepted that as far as the device was concerned it had to be opened by the patient, used for an inhalation and closed by the patient. However to take the medicine correctly in order for the dose to be efficacious there were more than three steps. These were set out in full in the PIL. In addition as far as the device was concerned the PIL referred to four steps. The Panel decided that the advertisement was misleading as it was inconsistent with the SPC and the PIL. A breach of Clause 7.2 was ruled.

The Panel did not consider that the advertisement failed to meet high standards and thus no breach of Clause 9.1 was ruled. The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. It did not consider that the circumstances warranted a ruling of a breach of Clause 2 and ruled accordingly.

Complaint received **8 February 2017**

Case completed **2 May 2017**

CASE AUTH/2934/2/17

HEALTH PROFESSIONAL CONSULTANT TO A PHARMACEUTICAL COMPANY v JOHNSON & JOHNSON

Promotion of Nicorette

A complaint was received in a private capacity from a health professional who stated that he/she worked as a consultant to a pharmaceutical company.

The principles set out above were applied to this complaint. Consultancy status should not be used to circumvent the normal rules for inter-company complaints.

The complainant was advised that if he/she wished to proceed with the complaint in a private capacity Novartis would be named in the case report; and the respondent company would be informed of his/her professional status and the connection with pharmaceutical companies. The complainant so agreed.

The complaint concerned an online advertisement for Nicorette (nicotine) issued by Johnson & Johnson and was published in Pulse online. The advertisement was headed 'Nicorette Do Something Incredible' and referred to combination nicotine replacement therapy (NRT).

The complainant stated that there was no generic name on the advertisement nor any mention of where the prescribing information could be found (although if one clicked on the advertisement it was present). It appeared to be a 'teaser'.

The complainant explained that this style of advertisement might be acceptable for consumer advertising but not for healthcare professionals. The complainant was concerned that there were not adequate internal controls to ensure that it was not used in publications aimed at the wrong audience. The complainant stated that it was difficult to read the prescribing information as it had not been split into smaller columns and instead was in one large block.

The detailed response from Johnson & Johnson is given below.

As the non-proprietary name was included next to the brand name on the first banner the Panel ruled no breach of the Code.

The Panel noted that the first banner did not include a clear, prominent statement as to where the prescribing information could be found and therefore, ruled a breach of the Code.

The Panel did not consider the advertisement was a teaser. Information about Nicorette had been provided, including prescribing information, and thus the Panel ruled no breach of the Code.

The Panel considered that the advertisement was such that it was aimed at prescribers who would be the main audience of Pulse. The Panel therefore ruled no breach of the Code. It noted that the advertisement was for general sales list medicines and not prescription only medicines. The Code prohibited the promotion of prescription only medicines to the public. There could be no breach in that regard and the Panel ruled accordingly.

The Panel considered that although line length at around 140 characters was more than recommended this did not necessarily mean the prescribing information was not legible. The spacing between the lines and emboldening of the headings were helpful. The Panel decided that although on the limits of acceptability the prescribing information was legible and no breach of the Code was ruled.

A complainant stated at the time of submitting the complaint that he/she was a health professional who worked as a consultant to Novartis. It had previously been decided, following consideration by the then Code of Practice Committee and the ABPI Board of Management, that private complaints from pharmaceutical company employees had to be accepted. To avoid this becoming a means of circumventing the normal procedures for intercompany complaints, the employing company would be named in the report. The complainant would be advised that this would happen and be given an opportunity to withdraw the complaint.

The case preparation manager decided that the principles set out above would apply to consultants. Consultancy status should not be used to circumvent the normal rules for inter-company complaints.

The complainant was advised that if he/she wished to proceed with the complaint in a private capacity Novartis would be named in the case report; and the respondent company would be informed of his/her professional status and the connection with pharmaceutical companies. The complainant so agreed.

Novartis stated that it had no knowledge of, or involvement in, the complaint and did not know the complainant's identity.

The complaint concerned an online advertisement for Nicorette (nicotine) (ref UK/NI/16-7664) issued by Johnson & Johnson Limited and was published in Pulse online. The advertisement was headed 'Nicorette Do Something Incredible' and referred to combination nicotine replacement therapy (NRT).

COMPLAINT

The complainant stated that there was no generic name on the advertisement nor any mention of where the prescribing information could be found (although if one clicked on the advertisement it was present).

The complainant further stated that the content of the advertisement itself gave no information and appeared to be a 'teaser'.

The complainant explained that this style of advertisement might be acceptable for consumer advertising but not to be directed towards healthcare professionals. The complainant was concerned that there were not adequate internal controls to ensure that it was not used in publications aimed at the wrong audience.

The complainant stated that it was difficult to read the prescribing information as it had not been split into smaller columns and instead was in one large block.

In writing to Johnson & Johnson attention was drawn to the requirements of Clauses 4.3, 4.4, 9.1, 11.1 and 26.1.

RESPONSE

Johnson & Johnson explained that the advertisement at issue was a 'rolling banner' made up of four banners which flicked through automatically, one after the other over approximately 10 seconds and repeated constantly on a loop. Johnson & Johnson submitted that the reader would see each of the four rolling banners and the individual banners should not be considered in isolation.

1 Non-proprietary name

Johnson & Johnson submitted that the first banner in the advertisement clearly stated the non-proprietary name, 'nicotine', immediately adjacent to the brand name at its first appearance, fulfilling the requirements in Clause 4.3. The text on this was 'Nicorette nicotine Do something incredible'.

2 Prescribing information

Johnson & Johnson submitted that the link to the prescribing information was highlighted in bold writing at the bottom of both the second and third banners which included 'Click here for prescribing and adverse event reporting information and references'. The link took the reader directly to a copy of the prescribing information, as well as the required adverse event reporting statement and references for all the claims. The advertisement satisfied the requirements of Clause 4.4. The complainant confirmed that he/she could view the prescribing information by clicking on the advertisement.

Although not asked to address Clause 4.1 and the legibility of prescribing information Johnson & Johnson was happy to address the point. Johnson & Johnson submitted that the prescribing information fulfilled the requirements of Clause 4.1 as well as the recommendations given in supplementary information to Clause 4.1, that the prescribing information must be clear and legible. In this regard the prescribing information used type size such that a lower case 'x' was larger than 1mm on an A4 printed copy, with an easy to read font style and black lettering on a white background and had sufficient space between lines to assist with easy reading, with emboldened headings so prescriber could easily find the section they wish to read.

Although the prescribing information contained more than 100 characters per line, Johnson & Johnson noted that this was an online banner advertisement, and the prescribing information was provided as an electronic document. Thus, legibility was entirely dependent upon the size and quality of the screen that the reader was using. All devices were capable of 'zooming in' on documents, and it was assumed that the complainant was able to zoom in on the prescribing information in this instance.

Given that the requirement for legibility were fulfilled as the PDF version of the prescribing information was clearly legible, Johnson & Johnson submitted that the prescribing information was not in breach of the Code.

3 Content of advertisement

Johnson & Johnson noted the complainant's statement that the advertisement gave no information and appeared to be a teaser intended to elicit an interest in something which would be following or would be available at a later date, without providing any information about it. Johnson & Johnson stated that the advertisement in question scrolled through four different banners which posed the question to the healthcare professional, 'How do you empower them to quit for good?'

Healthcare professionals faced great challenges in helping patients to quit smoking, and large numbers of quit attempts failed. Patients might require support in terms of behavioural therapy and medicines might help them resist cravings to smoke and avoid some of the symptoms of nicotine withdrawal; healthcare professionals could therefore help empower patients to make a successful quit attempt. In this instance, the advertisement highlighted that prescribing combination nicotine replacement therapy (NRT) could be a more effective way to help patients quit smoking for good than prescribing nicotine patches alone. Nicorette was indicated to aid smokers wishing to quit and to relieve and/or prevent cravings and nicotine withdrawal symptoms associated with tobacco dependence. Johnson & Johnson therefore submitted that the advertisement was not a teaser and did not breach Clause 9.1.

4 Suitability of audience

Johnson & Johnson stated that the advertisement was aimed at healthcare professionals and had been

reviewed and certified as such under the ABPI Code. Pulse was widely read by general practitioners (GPs), and most would be interested in helping patients quit smoking, and might find it helpful to consider ways to support patients through a quit attempt. Thus the wording in the advertisement talked directly to the healthcare professional, asking, 'How do you empower them to quit for good?' where 'them' would be interpreted by healthcare professional's as meaning their patients who wished to quit smoking. A high proportion of Nicorette prescriptions came from general practice and hence displaying the Nicorette advertisement in Pulse was appropriate; it was the number 1 GP magazine in the UK. The media plan for Nicorette ABPI approved materials focused on GPs, nurses and pharmacists, with materials being adapted as appropriate to be suitable for the intended audience. Any Nicorette advertisements aimed at prescribers were reviewed and approved by Johnson & Johnson in accordance with the ABPI Code. The requirements for Clause 11.1 had been met as this advertisement, distributed via the Pulse website, would be of interest to and relevant for its audience.

5 Advertising to the public

Johnson & Johnson pointed out that Nicorette held a legal category of general sales list (GSL) and therefore any advertising aimed at consumers was subject to the Proprietary Association of Great Britain (PAGB) Code of Practice for Advertising Over-The-Counter medicines and was fully reviewed and approved by both Johnson and Johnson and the PAGB. Nicorette digital advertising for consumers targeted online spaces used by consumers. As described above, the media plan for ABPI materials targeted healthcare professional journals and websites. Johnson & Johnson submitted it had no reason to believe that the advertisement in question on the Pulse website had been seen by members of public. Therefore, Johnson & Johnson denied a breach of Clause 26.1.

In response to a request for further information Johnson & Johnson provided an electronic copy of the rolling banner advertisement.

PANEL RULING

The Panel noted that the advertisement, published in Pulse today online continuously revolved through four banners, one after the other, over 10 seconds. The Panel noted that the supplementary information to Clause 4.1, Electronic Journals, stated the first part of an advertisement in an electronic journal, such as the banner, is often the only part of the advertisement that is seen by readers. It must therefore include a clear, prominent statement as to where the prescribing information could be found. This should be in the form of a direct link. The first part was often linked to other parts and in such circumstances the linked parts would be considered as one advertisement. If the first part mentioned the product name then this was the most prominent display of the brand name and the non-proprietary name of the medicine or a list of the active ingredients using approved names where such existed must appear immediately adjacent to the most prominent display of the brand name. The Panel noted that the purpose of this supplementary information was to ensure that the prescribing information and other obligatory information were an integral part of the advertisement thus satisfying Clause 4.1 in that regard.

The Panel considered that there were differences between a static banner on which one proactively clicked to link to other material including the prescribing information, and a series of continuously revolving banners. The length of time that each banner was displayed within a revolving series would vary, could not be influenced by the reader and might be longer or shorter than those in the material at issue in this case where each banner was displayed for 2.5 seconds. The Panel considered that such cases should be considered individually in relation to the requirements of the Code.

The Panel noted that Clause 4.3 required the non-proprietary name or the list of active ingredients using approved names where such existed to appear immediately adjacent to the most prominent display of the brand name. As the non-proprietary name was included next to the brand name on the first banner the Panel ruled no breach of Clause 4.3.

The Panel noted that the first banner did not include a clear, prominent statement as to where the prescribing information could be found. The Panel noted the complainant's submission that although there was no mention of where the prescribing information could be found, if one clicked on the advertisement it was present. The Panel noted that the case preparation manager had not raised Clause 4.6 with Johnson & Johnson. Clause 4.6 required the statement as to where the prescribing information was found in the case of promotional material included on the internet which, as stated in the supplementary information to Clause 4.1 and noted above, should appear on the first banner rather than on the second or third. The Panel was thus unable to make a ruling in that regard. The Panel noted that Clause 4.4 was raised which required that in the case of digital material such as advertisements in electronic journals, emails, electronic detail aids and suchlike, the prescribing information as required by Clause 4.1 might be provided either by inclusion in the digital material itself, or by way of a clear and prominent direct single click link. Although the prescribing information was provided, if the reader clicked on the advertisement, the link was not clear and prominent on the first banner and the Panel, therefore, ruled a breach of Clause 4.4.

The Panel did not consider the advertisement was a teaser as set out in the supplementary information to Clause 9.1. Information about Nicorette had been provided, including prescribing information, and thus the Panel ruled no breach of Clause 9.1.

Clause 11.1 required that promotional material should only be sent or distributed to those categories of persons whose need for, or interest in, the particular information could reasonably be assumed. The supplementary information to Clause 11.1 stated

that promotional material should be tailored to the audience to whom it was directed.

The Panel considered whether the content of the advertisement was suitable for the readership of the journal. The Panel noted Johnson & Johnson's submission that Pulse was widely read by GPs and that a high proportion of Nicorette prescriptions came from GPs. The Panel further noted Johnson & Johnson's submission that materials were adapted to be suitable for the intended audience. The Panel considered that the advertisement was such that it was aimed at prescribers who would be the main audience of Pulse. The Panel therefore ruled no breach of Clause 11.1. It noted that the advertisement was for general sales list medicines and not prescription only medicines. Clause 26.1 prohibited the promotion of prescription only medicines to the public. There could be no breach of Clause 26.1 and the Panel ruled accordingly.

The Panel noted that Johnson & Johnson had not been asked to comment on the legibility of the prescribing information and Clause 4.1 by the case preparation manager. However, this was the relevant clause in relation to the allegation that it was difficult to read the prescribing information. Johnson & Johnson had responded to the allegation. In these unusual circumstances, the Panel decided to consider the matter. The Panel noted the line length used in the prescribing information was longer than 100 characters. The supplementary information to Clause 4.1, Legibility of Prescribing Information gave recommendations to assist legibility. The Panel considered that although line length at around 140 characters was more than recommended this did not necessarily mean the prescribing information was not legible. The spacing between the lines and emboldening of the headings were helpful. The Panel decided that although on the limits of acceptability the prescribing information was legible and no breach of Clause 4.1 was ruled.

Complaint received **8 February 2017**

Case completed **10 May 2017**

HEALTH PROFESSIONAL CONSULTANT TO A PHARMACEUTICAL COMPANY v JOHNSON & JOHNSON

Online Nicorette advertisement

A complaint was received in a private capacity from a health professional who stated that he/she worked as a consultant to a pharmaceutical company.

The complaint concerned an online advertisement for Nicorette (nicotine) issued by Johnson & Johnson and was published in Pulse magazine February.

The advertisement was headed 'How do you empower them to quit for good?' followed by the claims 'Combination NRT [nicotine replacement therapy] is 43% more effective than patch alone. This was followed by a photograph of one Nicorette patch pack with a Nicorette Quick mist mouth spray. Under which was the claim 'nothing beats Nicorette dual support'. The advertisement included a photograph of a man on the beach throwing and catching a young child in the air.

The complainant alleged that the child in the advertisement was an inappropriate age. The complainant was also concerned that the claim '...43% more effective than patch alone' gave no absolute data. Given there was no absolute values, the heading 'how do you empower them to quit for good' could be taken to mean this always worked which was highly unlikely.

The detailed response from Johnson & Johnson is given below.

The Panel considered that the claim 'combination NRT is 43% more effective than patch alone' was a comparison of efficacy of the two. There was no mention of relative risk as such. The odds ratio was provided in small type above the details of reference 1 in the bottom left hand part of the advertisement.

The Panel did not accept that the heading 'How do you empower them to quit for good?' and the content of the advertisement including the claim 'Nothing beats Nicorette dual support' implied that Nicorette dual support always worked as alleged. The Panel considered that the difficulty smokers had in quitting would be well understood by the audience and that success would be likely to be due to a number of factors. The Panel did not consider that the advertisement was misleading and ruled no breach of the Code.

The Panel did not consider that the inclusion of a photograph of an infant in the advertisement for NRT was such that health professionals would consider that the product should be prescribed for that infant. The Panel noted that the photograph also included an adult for whom the product could be used. It was not unreasonable to use the photograph, particularly given the impact an adult's smoking could have on children. The health of children appeared to be a reason for adults to try to stop smoking. The Panel thus ruled no breach of the Code in this regard.

The complainant stated at the time of submitting the complaint that he/she was a health professional who worked as a consultant to Novartis. It had previously been decided, following consideration by the then Code of Practice Committee and the ABPI Board of Management, that private complaints from pharmaceutical company employees had to be accepted. To avoid this becoming a means of circumventing the normal procedures for intercompany complaints, the employing company would be named in the report. The complainant would be advised that this would happen and be given an opportunity to withdraw the complaint.

This issue came to the fore many years ago when an employee of a pharmaceutical research company complained in a private capacity about a journal advertisement issued by GlaxoSmithKline UK Ltd (Case AUTH/1498/7/03). In Case AUTH/1498/7/03 it was decided that the pharmaceutical research company would be named in the case report whilst making it clear that the complaint was made in a private capacity.

The case preparation manager decided that the principles set out above would apply to consultants. Consultancy status should not be used to circumvent the normal rules for inter-company complaints.

The complainant was advised that if he/she wished to proceed with the complaint in a private capacity Novartis would be named in the case report; and the respondent company would be informed of his/her professional status and the connection with pharmaceutical companies. The complainant so agreed.

Novartis stated that it had no knowledge of, or involvement in, the complaint and did not know the complainant's identity.

The complaint concerned an online advertisement for Nicorette (nicotine) issued by Johnson & Johnson Limited and was published in Pulse magazine February (ref UK/NI/16-7093(1).

The advertisement was headed 'How do you empower them to quit for good?' followed by the claims 'Combination NRT [nicotine replacement therapy] is 43% more effective than patch alone (referenced to Cahill *et al* Cochrane summaries 2013). This was followed by a photograph of one Nicorette patch pack with a Nicorette Quick mist mouth spray.

Under which was the claim 'nothing beats Nicorette dual support' which was also referenced to Cahill *et al*. The advertisement included a photograph of a man on the beach throwing and catching a young child in the air.

COMPLAINT

The complainant alleged that the child in the advertisement was an inappropriate age. The complainant was also concerned that the claim '...43% more effective than patch alone' gave no absolute data. Given there was no absolute values, the heading 'how do you empower them to quit for good' could be taken to mean this always worked which was highly unlikely.

In writing to Johnson & Johnson attention was drawn to the requirements of Clauses 7.2 and 9.1.

RESPONSE

6 Combination NRT claim

Johnson & Johnson submitted that the odds ratio related to the claim 'Combination NRT is 43% more effective than patch alone' ('Odds ratio 1.43 (95%CI 1.08 to 1.91)') was contained within the advertisement, above the reference list. As the claim was not referring to relative risk there was no requirement to provide the absolute risk and the 2013 Cochrane review reference contained no information regarding absolute risk. Johnson & Johnson disagreed with the complainant that the call out 'How do you empower them to quit for good?' could be interpreted as a guarantee of effect or that using odds ratio without absolute values breached Clauses 7.2 or 9.1. However, it acknowledged that it could be difficult to communicate odds ratio values such that a healthcare professional could interpret the clinical impact. Johnson & Johnson was, therefore, reviewing how best to address this issue in order to increase clarity, and consequently would amend this claim in future materials.

7 Imagery of child

Johnson & Johnson submitted that the picture of a man with his child on the beach was a lifestyle image and reflected the motivations of some people who might ask health professional's for help in quitting smoking. It showed the lifestyle benefits of quitting for good and being smoke free, ie the freedom and health to lead a happy and active family life.

The Office for National Statistics report on smoking related behaviour and attitudes 2008/9 reported that 22% of smokers who wanted to quit said they wanted to give up because of the effect of smoking on children, and 16% said it was because of family pressure. Children were especially vulnerable to second hand smoke, resulting in 300,000 GP visits and 9,500 hospital admissions every year. A healthcare professional would be likely to see adult smokers in their day-to-day practice who were citing their children as a reason for wanting to quit smoking. Healthcare professionals might also use the impact of smoking on children's health as a motivational tool to initiate a discussion around quitting smoking with parents. Therefore, Johnson & Johnson submitted that the imagery of a parent with a child was appropriate in this context. The use of the word "them" in this context would be interpreted by a prescribing healthcare professional as meaning their patients who were smokers, and would not be interpreted as referring to the man and the infant pictured.

Johnson & Johnson did not accept that any healthcare professional reading the advertisement would think that the imagery implied that Nicorette was suitable for infants. Smoking was not prevalent amongst toddlers, and it was highly unlikely that a GP would be helping a child of this age to make a successful quit attempt or would consider the advertisement in the context of a child of this age. Consequently, it did not believe that any healthcare professional would interpret the advertisement as implying that Nicorette could be used in this age group or that the advertisement breached Clauses 7.2 or 9.1. Nicorette was indicated to aid adult or adolescent smokers from the age of 12 wishing to quit and should any healthcare professional wish to confirm the licensed age indication, this was clear on the prescribing information which was positioned immediately below the image. This advertisement was not in breach of the Code in this regard.

PANEL RULING

The Panel examined the advertisement and considered that it used the example of combination NRT as one of a number of ways of empowering smokers to quit. The photograph of an adult and child was, in the Panel's view, another example of something that might empower smokers to quit for good.

The Panel noted that the supplementary information to Clause 7.2 stated that referring only to relative risk, especially with regard to risk reduction could make a medicine appear more effective than it actually was. In order to assess the clinical impact of an outcome, the reader also needed to know the absolute risk involved. In that regard relative risk should never be referred to without also referring to the absolute risk. Absolute risk could be referred to in isolation. The claim 'combination NRT is 43% more effective than patch alone' was a comparison of efficacy of the two. There was no mention of relative risk as such. The odds ratio was provided in small type above the details of reference 1 in the bottom left hand part of the advertisement.

The Panel did not accept that the heading 'How do you empower them to quit for good?' and the content of the advertisement including the claim 'Nothing beats Nicorette dual support' implied that Nicorette dual support always worked as alleged. The Panel considered that the difficulty smokers had in quitting would be well understood by the audience and that success would be likely to be due to a number of factors. The Panel did not consider that the advertisement was misleading and ruled no breach of Clause 7.2.

The Panel noted that the supplementary information to Clause 7.8 of the Code stated that care must be taken to ensure that artwork did not mislead as to the nature of a medicine or any claim or comparison. Depictions of children should not be used in relation to products not authorized for use in children in any way which might encourage such use.

The Panel did not consider that the inclusion of a photograph of an infant in the advertisement for NRT was such that health professionals would consider that the product should be prescribed for that infant. The Panel noted that the photograph also included an adult for whom the product could be used. It was not unreasonable to use the photograph, particularly given the impact an adult's smoking could have on children. The health of children appeared to be a reason for adults to try to stop smoking. The Panel thus ruled no breach of Clauses 7.2 and 9.1 of the Code in this regard.

Complaint received **15 February 2017**

Case completed **27 April 2017**

CASE AUTH/2938/2/17

SANOFI v NOVO NORDISK

Tresiba leavepiece

Sanofi UK complained about a Tresiba (insulin degludec) leavepiece issued by Novo Nordisk. Tresiba was for the treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.

The claim 'Tresiba provides 75% less variability in glucose-lowering effect over 24 hours versus insulin glargine U100' appeared as a heading to page 3 above a bar chart titled 'Within-patient variation in glucose-lowering effect over 24 hours, calculated at two-hourly intervals in patients with type 1 diabetes'. A bold and prominent claim adjacent to the bar chart read '75% Less Variability'. Text beneath discussed within-patient day-to-day variability and the benefits of lower variability. These being 'A potentially lower risk of hypo- and hyperglycaemia' and 'Potentially aids titration to glycaemia targets'.

Sanofi stated that this page did not clearly indicate that the information provided related specifically to a pharmacodynamic clamp study. The only indirect reference to a clamp study was along the small font sized title alongside the Y axis of the bar chart. Hence the claim 'Tresiba provided 75% less variability in glucose lowering effect over 24 hours vs insulin glargin U100' was misleading without sufficient qualification that this related to the results from an experimental clamp study as it strongly suggested that the outcomes shown related to real life clinical practice which had yet to be proven with clinical studies.

Sanofi stated that, in addition, the disproportionate very large font size used on the page for '75% Less Variability' compared with the font size used beneath it distorted the perceived impact of such outcomes derived from the clamp study. Sanofi noted that the page at issue also included claims of the potential clinical benefits of lower variability based on the results of the clamp study and alleged that the claims 'A potentially lower risk of hypo- and hyperglycaemia' and 'Potentially aids titration to glycaemic targets' were misleading and not fully substantiated by Heise *et al*.

The detailed response from Novo Nordisk appears below.

The Panel noted that Heise *et al* stated that 'a limitation of this study was the difficulty in transferring the results from an experimental clamp setting to clinical reality. As noted, clinical studies show a lower rate in (nocturnal) hypoglycaemia with [Tresiba] compared with [insulin glargine] but it is not possible to attribute this clinical difference solely to the difference in variability between the two insulins'. The authors concluded that the results showed that, at steady state, Tresiba had a significantly more predictable glucose-lowering effect from day-to-day compared to insulin glargine. The Panel noted that the front page of the leavepiece featured clinical claims for Tresiba and referred to a lower risk of nocturnal hypoglycaemia vs insulin glargine U100. The second page introduced three patients that might be suitable for treatment. Page 4 presented nocturnal hypoglycaemia data, Bode *et al*, which compared Tresiba and insulin glargine U100 and highlighted a significantly lower risk of nocturnal hypoglycaemic events with Tresiba. The gate-folded design of the leavepiece was such that the page in question, page 3, could only be viewed when the leavepiece was fully open such that it was the central page in a triple page spread to be read alongside pages 2 and 4 and was an integral part of the clinical story presented across the triple page spread.

The Panel noted Novo Nordisk's submission that the informed audience would understand that there was no way to assess the variability and pharmacodynamic properties of insulins other than by a euglycaemic clamp study. The Panel noted Novo Nordisk's submission regarding the reference in the SPC to the lower day-to-day variability of the glucose-lowering action of Tresiba. The Panel also noted Novo Nordisk's submission that the labelling of the Y axis of the bar chart which stated 'Day-to-day variability (coefficient of variation (CV*) %) Area under the glucose infusion rate (GIR) curve' showed that the data was from a clamp study. The Panel noted that page 3 had to be turned to read the labelling which was in a small typeface and in its view was not sufficiently prominent. This was especially so given the design of the page which drew the reader's eye to other highlighted text. The Panel accepted that part of the audience might be well-informed and thus aware that variability of glucose lowering response was assessed using euglycaemic clamp studies. Some might be aware of the nature of the data but not aware of the study authors' caveats regarding its clinical application. The immediate impression was of paramount importance.

In the particular circumstances of this case the Panel considered that given the caveats in Heise *et al* and the presentation of the data as an integral part of a clinical story leading inexorably to those clinical benefits (lower risk of nocturnal hypoglycaemia) outlined, *inter alia*, on page 4 it should have been made clearer that the data on page 3 derived from a clamp study and that a degree of caution ought to be exercised in the application of the results to the clinical situation. The Y axis labelling was insufficient in this regard. On balance the Panel considered that the failure to do so implied that the data derived from Heise *et al* had definitive clinical benefit and so meant that the page was misleading in this regard. Breaches of the Code were ruled.

The Panel noted its comments above about Heise *et al* and the study's limitations and the impression created by the page in question. The Panel considered that within the context of the page in question the claim of benefits of lower variability would be seen as a claim for Tresiba as would the two bullet points, 'A potentially lower risk of hypo- and glycaemic attacks' and 'Potentially aids titration to glycaemic targets' which were misleading. A breach of the Code was ruled.

The Panel noted that the safety section of Heise *et al* stated that 'In total 100 confirmed hypoglycaemic episodes were observed with [Tresiba] compared with 95 episodes with [insulin glargine]' and 'fewer confirmed nocturnal hypoglycaemic episodes were reported for [Tresiba] (16 episodes in 9 subjects) than iGlar (26 episodes in 13 subjects)' and that 'The observed number of hypoglycaemic episodes might be artificially high due to the fixed dosing level of 0.4U/kg of [Tresiba] and [insulin glargine]'. The Panel noted its comments above about the misleading impression given by the page including the two bullet points in question. The Panel did not consider that the primary impression given by the bullet points in question could be substantiated by Heise *et al* as alleged and a breach was ruled.

Sanofi alleged that the claim '142 Fewer Nocturnal Hypoglycaemic Events' on page 4 was misleading and exaggerated the effect of Tresiba vs glargine U100. The very large font size and undue emphasis of the large sized number in contrast to the much smaller font size used below 'for every 100 patients ...' was misleading and exaggerated the reported hypoglycaemic event difference between the two insulins. There was no significant difference in the rate of confirmed overall hypoglycaemic episodes for Tresiba vs insulin glargine U100 in patients with type 1 diabetes as detailed in the small font sized statement at the bottom right-hand side of the page at issue.

The Panel noted that the bold and prominent claim in question '142 Fewer Nocturnal Hypoglycaemic Events' appeared adjacent to the graph and in the same green font as the prominent page heading. The qualification 'for every 100 patients treated with Tresiba per year versus insulin glargine U100' appeared in much smaller black font, as a distinct and separate paragraph below and did not immediately appear to be part of the claim in question. This was compounded by the fact that the font colour and prominence of the claim in question and the page heading visually linked the two drawing the reader's eye away from the qualification to the claim in question. In the Panel's view it would not be immediately obvious that the separate paragraph beneath was in fact a continuation of the claim above and formed part of the same sentence.

The Panel noted that the statement that there was 'no significant difference in the rate of confirmed overall hypoglycaemic episodes for Tresiba versus insulin glargine U100 in patients with type 1 diabetes (p=ns)' was the third paragraph below the claim in question again in black smaller font.

The Panel considered that the claim '142 Fewer Nocturnal Hypoglycaemic Events' exaggerated the reported hypoglycaemic event difference between the two insulins. The Panel disagreed with Novo Nordisk's submission that the statement regarding no significant difference in the rate of confirmed hypoglycaemic episodes was sufficiently prominent and considered that it did not negate the overall impression of the page. Nor in the Panel's view and for the reasons stated above was the claim in question suitably qualified by the paragraph immediately beneath. The Panel considered that the comparison was misleading in that regard and potentially exaggerated the effect of Tresiba and a breach of the Code was ruled.

Sanofi UK complained about a Tresiba (insulin degludec) leavepiece (ref UK/TB/1214/0302(4)) issued by Novo Nordisk Ltd. Tresiba was for the treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.

Novo Nordisk submitted that the aim of the leavepiece was to provide information about the pharmacodynamic variability of Tresiba vs insulin glargine U100 which was reflected in Bode *et al* (2013), a large scale clinical trial. The leavepiece also provided details relating to the two available Tresiba preparations and dosing, and suggested some patient types for which Tresiba might be suitable.

The front page referred to the duration of action, reductions in HbA1c and price reductions. It also claimed that Tresiba had a lower risk of nocturnal hypoglycaemia vs insulin glargine U100 referenced to Rodbard *et al* (2013) and Bode *et al*.

1 Claim 'Tresiba provides 75% less variability in glucose-lowering effect over 24 hours versus insulin glargine U100'

This claim appeared as a heading to page 3 above a bar chart titled 'Within-patient variation in glucose-lowering effect over 24 hours, calculated at two-hourly intervals in patients with type 1 diabetes'. A bold and prominent claim adjacent to the bar chart read '75% Less Variability'. Text beneath discussed within-patient day-to-day variability and the benefits of lower variability. These being 'A potentially lower risk of hypo- and hyperglycaemia' and 'Potentially aids titration to glycaemia targets'. Claims and data on the page were referenced to Heise *et al* (2012).

COMPLAINT

Sanofi stated that this page illustrated the outcomes of a comparative pharmacodynamic euglycaemic glucose clamp study between Tresiba and insulin glargine U100, manufactured by Sanofi (Heise *et al*). The clamp study was conducted to assess day-to-day variability in glucose-lowering effect in 54 subjects with type 1 diabetes. Clamp studies were commonly conducted to assess the pharmacodynamic properties of insulins to measure parameters such as the duration of action and variability of glucose lowering response in an artificial experimental environment. As outlined by Heise *et al*, 'Care needs to be taken when extrapolating results from

experimental situations to clinical practice'. In addition, the discussion stated that 'A limitation of this study is the difficulty in transferring the results from an experimental clamp setting to clinical reality. As noted, clinical studies show a lower rate in (nocturnal) hypoglycaemia with [Tresiba] compared with [insulin glargine], but it is not possible to attribute this clinical difference solely to the difference in variability between the two insulins'.

Sanofi stated that page 3 of the leavepiece did not clearly indicate to the reader that the information provided related specifically to a pharmacodynamic clamp study. There was no mention in the title of the page that the information was derived from such an experimental clamp study. The only indirect reference to a clamp study was along the small font sized title alongside the Y axis of the bar chart. Hence the claim 'Tresiba provided 75% less variability in glucose lowering effect over 24 hours vs insulin glargin U100' was misleading without sufficient qualification that this related to the results from an experimental clamp study. Without sufficient and prominent qualification, the claim strongly suggested that the outcomes shown related to real life clinical practice which had yet to be proven with robust clinical studies. Sanofi believed that particular care was needed when making claims in promotional material based upon an experimental pharmacodynamic clamp study, particularly when its main author indicated that caution was required in extrapolating such data to a real clinical setting. Sanofi alleged that the claim was misleading in breach of Clauses 7.2 and 7.3.

Sanofi stated that, in addition, the disproportionate very large font size used on the page to illustrate '75% Less Variability' compared with the font size used beneath this statement distorted the perceived impact of such outcomes derived from the clamp study. Such distortion created the impression that less 'within-patient variability' would have definitive clinical benefit relevant for Tresiba vs insulin glargine U100. This was not the case as the outcomes from such an experimental clamp study could not be made definitively generalisable to a real life clinical setting due to the experimental nature of pharmacodynamic euglycaemic clamp studies. Sanofi alleged breaches of Clauses 7.2 and 7.8.

Sanofi noted that the page at issue also included claims of the potential clinical benefits of lower variability based on the results of the clamp study. Sanofi believed that the claims 'A potentially lower risk of hypo- and hyperglycaemia' and 'Potentially aids titration to glycaemic targets' were misleading and not fully substantiated by Heise *et al*. The reported study safety outcomes indicated that 'In total, 100 confirmed hypoglycaemic episodes observed with iDeg (Tresiba) compared with 95 episodes with iGlar. Fewer confirmed nocturnal hypoglycaemic episodes were reported for iDeg (16 episodes in 9 subjects) than iGlar (26 episodes in 13 subjects). The observed number of hypoglycaemic episodes might be artificially high due to the fixed dosing level of 0.4U/kg of iDeg and iGlar'.

Sanofi alleged that claims relating to the potential benefits of lower variability were misleading and could not be substantiated in breach of Clauses 7.2 and 7.4.

RESPONSE

Novo Nordisk agreed that euglycaemic clamp studies were conducted to assess the pharmacodynamic properties of insulins to measure parameters such as variability of glucose lowering response. These studies had been conducted since 1979 and were regarded as the gold standard for investigation of insulins by agencies such as the European Medicines Agency (EMA). In its guidance for clinical investigation for medicinal products for the treatment of type 2 diabetes, the EMA Committee for Proprietary Medicinal Products (CPMP) stated 'data on time-action profiles using the euglycaemic clamp technique should be available, providing data based on the glucose infusion rate'. Novo Nordisk submitted that for an informed audience, such as would be reading a promotional leavepiece for a diabetes treatment, it would be understood that there was no other way to assess the variability and pharmacodynamic properties of insulins.

Novo Nordisk submitted that the claim, '75% Less Variability' was supported by the bar chart. The Y-axis of the chart clearly stated 'Area under the glucose infusion rate (GIR) curve' which showed that it was from a clamp-study. The claim of '75% Less Variability' was quantified and substantiated based on the results of Heise *et al* and therefore was not misleading. Novo Nordisk thus denied breaches of Clauses 7.2 and 7.3.

Novo Nordisk further submitted that Section 5.1 of the Tresiba summary of product characteristics (SPC) also substantiated the lower day-to-day variability of the glucose-lowering action of insulin degludec:

> 'The insulin degludec glucose-lowering action at steady state shows four times lower day-to-day variability in terms of Coefficients of Variation (CV) for the glucose-lowering effect during 0-24 hours (AUC GIR, SS) and 2–24 hours (AUC GIR2-24h, SS) as compared to insulin glargine.'

Therefore the claim was further substantiated.

Novo Nordisk stated that the font size used for the claim '75% Less Variability' was reasonable and not disproportionate to the size of the chart which illustrated this difference. The statements below the claim regarding potential clinical benefits were not in the same font size and therefore did not create the impression that less within-patient variability would have 'definitive clinical benefit ...' as alleged. Novo Nordisk submitted that the requirements of Clauses 7.2 and 7.8 had been met.

With reference to the benefits of lower variability, both claims stated the potential of lower variability, not definitive effects. Heise *et al* stated:

> 'The difference in within-subject variability is expected to be of clinical relevance and to have an impact upon the risk of both hyper- and hypoglycaemia for the individual patient .... Although caution should be taken when

> extrapolating from experimental situation to clinical practice, it is worth noting that the predicted hypoglycaemia risks are qualitatively consistent with the results of clinical trials ….'

and

> 'A lower variability of effect would be a major advantage when titrating the individual insulin dose and might provide a mechanistic explanation of the differences in the hypoglycaemic incidence observed in the clinical trials.'

The clinical relevance of less variability had also been documented in other publications including Bekker *et al* (2015) a Sanofi supported paper which stated:

> 'low diurnal fluctuation in insulin exposure was expected to be of clinical relevance by reducing an individual's risk of hyperglycaemia and hypoglycaemia'

and

> 'In a clinical setting, high reproducibility would be a major advantage when titrating an individual's insulin dose, owing to a more predictable insulin exposure'.

Novo Nordisk thus submitted that the claims made about the potential benefits of lower variability could be supported by Heise *et al* and other published studies. The company denied any breaches of Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that it was an established principle under the Code that all claims related to the clinical situation unless otherwise stated. The supplementary information to Clause 7.2 stated that care must be taken with the use of data derived from *in vitro* studies and the like so as to not mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance.

The Panel noted that the entire page at issue (page 3) was referenced to Heise *et al* which in the discussion section stated that 'a limitation of this study was the difficulty in transferring the results from an experimental clamp setting to clinical reality. As noted, clinical studies show a lower rate in (nocturnal) hypoglycaemia with [Tresiba] compared with [insulin glargine] but it is not possible to attribute this clinical difference solely to the difference in variability between the two insulins'. The authors concluded that the results showed that, at steady state, Tresiba had a significantly more predictable glucose-lowering effect from day-to-day compared to insulin glargine.

The Panel noted that the front page of the leavepiece featured clinical claims for Tresiba and referred to a lower risk of nocturnal hypoglycaemia vs insulin glargine U100. The second page introduced three patients that might be suitable for treatment. One patient had a fear of nocturnal hypoglycaemia, another found it hard to keep to a strict treatment regimen and the third found it difficult to take twice daily doses of insulin. Directly after the third page (the page at issue) page 4 presented nocturnal hypoglycaemia data from a randomised control trial, Bode *et al*, which compared Tresiba and insulin glargine U100 and highlighted a significantly lower risk of nocturnal hypoglycaemic events with Tresiba. The gate-folded design of the leavepiece was such that the page in question, page 3 could only be viewed when the leavepiece was fully open such that it was the central page in a triple page spread to be read alongside pages 2 and 4. Whilst page 3 had to be capable of standing alone in relation to the requirements of the Code, context was relevant. The Panel considered that the design of the leavepiece was such that the page in question was an integral part of the clinical story presented across the triple page spread.

The Panel noted Novo Nordisk's submission that the informed audience would understand that there was no way to assess the variability and pharmacodynamic properties of insulins other than by a euglycaemic clamp study. The Panel noted Novo Nordisk's submission regarding the reference in the SPC to the lower day-to-day variability of the glucose-lowering action of Tresiba. The Panel also noted Novo Nordisk's submission that the labelling of the Y axis of the bar chart which stated 'Day-to-day variability (coefficient of variation (CV*) %) Area under the glucose infusion rate (GIR) curve' showed that the data was from a clamp study. The Panel noted that page 3 had to be turned to read the labelling which was in a small typeface and in its view was not sufficiently prominent. This was especially so given the design of the page which drew the reader's eye to other highlighted text. The Panel accepted that part of the audience might be well-informed and thus aware that variability of glucose lowering response was assessed using euglycaemic clamp studies. Some might be aware of the nature of the data but not aware of the study authors' caveats regarding its clinical application. The immediate impression was of paramount importance particularly for those that might not study it in detail.

The Panel considered that whether the presentation of data derived from a clamp study was acceptable under the Code in relation to implied clinical benefit depended on the individual circumstances of each case: the nature of the material, the potential extrapolation to the clinical situation and the audience would be relevant. The Panel noted the caveats in the study in question as set out above. The Panel also noted the strong visual link between the prominent claim '75% Less Variability' on the page in question and the prominent clinical claims on page 4. The Panel noted that page 3 did not state that Heise *et al* used a fixed dose of 0.4U/kg. In the particular circumstances of this case the Panel considered that given the caveats in Heise *et al* and the presentation of the data as an integral part of a clinical story leading inexorably to those clinical

benefits (lower risk of nocturnal hypoglycaemia) outlined, *inter alia*, on page 4 it should have been made clearer that the data on page 3 derived from a clamp study and that a degree of caution ought to be exercised in the application of the results to the clinical situation. The Y axis labelling was insufficient in this regard. On balance the Panel considered that the failure to do so implied that the data derived from Heise *et al* had definitive clinical benefit and so meant that the page was misleading in this regard. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel further noted Sanofi's allegation that the disproportionate large font size of the claim '75% less variability' distorted the perceived impact of the clamp study outcomes and implied that less 'within-patient variability' would have definitive clinical benefit. The Panel considered that this matter was inextricably linked to its rulings of breaches of the Code immediately above. A breach of Clause 7.2 was ruled. The Panel noted that the alleged breach of Clause 7.8 related to the visual prominence of the claim '75% Less Variability'. The Panel noted that Clause 7.8 stated that all artwork including illustrations, graphs and tables must conform to the letter and spirit of the Code and, when taken from published studies, a reference must be given. Graphs and tables must be presented in such a way as to give a clear, fair, balanced view of the matters with which they dealt, and must not be included unless they were relevant to the claims or comparisons being made. The Panel noted its comments above and considered that in the context of the page in question, the prominence of the claim in question and the Y axis labelling of the bar chart did not give a fair and balanced view of matters nor did it enable the nature of the data presented to be readily understood. A breach of Clause 7.8 was ruled.

The Panel noted that beneath the claim '75% Less Variability' in green font followed, in smaller black font:

> 'Tresiba was associated with **four-times lower within-patient day-to-day variability** in total glucose-lowering effect compared with insulin glargine U100.'
>
> This was followed by **'Benefits of lower variability:**
>
> - A potentially lower risk of hypo- and hyperglycaemia
> - Potentially aids titration to glycaemic targets'.

The Panel noted its comments above about Heise *et al* and the study's limitations. The Panel also noted its comments above about the impression created by the page in question. The Panel considered that use of the word 'potentially' in each of the bullet points did not negate the primary unequivocal impression given by the page and triple page spread including the unqualified bold subheading to the bullet points 'Benefits of lower variability'. The Panel considered that within the context of the page in question the claim of benefits of lower variability would be seen as a claim for Tresiba as would the two bullet points. The two claims 'A potentially lower risk of hypo- and glycaemic attacks' and 'Potentially aids titration to glycaemic targets' were misleading. A breach of Clause 7.2 was ruled.

The Panel noted that the safety section of Heise *et al* stated that 'In total 100 confirmed hypoglycaemic episodes were observed with [Tresiba] compared with 95 episodes with [insulin glargine]' and 'fewer confirmed nocturnal hypoglycaemic episodes were reported for [Tresiba] (16 episodes in 9 subjects) than iGlar (26 episodes in 13 subjects)' and that 'The observed number of hypoglycaemic episodes might be artificially high due to the fixed dosing level of 0.4U/kg of [Tresiba] and [insulin glargine]'. The Panel noted its comments above about the misleading impression given by the page including the two bullet points in question. The Panel did not consider that the primary impression given by the bullet points in question could be substantiated by Heise *et al* as alleged and a breach of Clause 7.4 was ruled.

2 Claim '142 Fewer Nocturnal Hypoglycaemic Events'

This claim appeared on page 4 of the leavepiece which was headed 'Tresiba achieves similar reductions in HbA1c versus insulin glargine U100 but with a significantly lower risk of nocturnal hypoglycaemia'. It was followed by a graph titled 'Nocturnal confirmed hypoglycaemia in patients on basal-bolus, with type 1 diabetes over 105 weeks'. Both were referenced to Bode *et al*. The graph included a box stating '25% lower risk (p=0.02)'. To the right of the graph appeared the claim in question '142 Fewer Nocturnal Hypoglycaemic Events' in large green font followed, in smaller black font, by 'for every 100 patients treated with Tresiba per year versus insulin glargine U100' which was referenced to Bode *et al*, Data on file and Ratner *et al* (2013). Directly beneath, in the same size font were the absolute rates per patient-year of exposure (Tresiba 3.9 episodes vs 5.3 episodes for glargine U100) followed by the statement 'There was no significant difference in the rate of confirmed overall hypoglycaemic episodes for Tresiba versus insulin glargine U100 in patients with type 1 diabetes *(p=ns)*'.

COMPLAINT

Sanofi alleged that the claim '142 Fewer Nocturnal Hypoglycaemic Events' was misleading and exaggerated the effect of Tresiba vs glargine U100. The very large font size and undue emphasis of the large sized number in contrast to the much smaller font size used below 'for every 100 patients ...' was misleading as it was not clear at first sight that this number was relevant specifically to 100 patients. The illustration using disproportionate font sizes, exaggerated the reported hypoglycaemic event difference between the two insulins. This was especially pertinent as there was no significant difference in the rate of confirmed overall hypoglycaemic episodes for Tresiba vs insulin glargine U100 in patients with type 1 diabetes as detailed in the small font sized statement at the bottom right-hand side of the page at issue. Sanofi alleged a breach of Clause 7.2.

RESPONSE

Novo Nordisk noted that page 4 of the leavepiece presented hypoglycaemia data from a randomised controlled clinical trial (Bode *et al*, Heller *et al* 2012 and Ratner *et al*). The company stated that the font size used for the claim '142 Fewer Nocturnal Hypoglycaemic Events' was reasonable and not disproportionate to the size of the graph which illustrated this difference. The statement '... for every 100 patients' was sufficiently prominent to be clear to the reader despite a difference in font size since the 'per 100 patients' was directly beneath and had also been enlarged and in black font to make it prominent to the reader. In addition, the statement '142 Fewer Nocturnal Hypoglycaemic Events ...' did not make sense in isolation without a denominator, therefore readers would naturally be drawn to read on to make scientific sense of the information in front of them. Directly below, in the same size font were the absolute rates which again were clear for the reader to interpret for additional information. This gave a fully balanced set of statistics for the reader to interpret the results.

Novo Nordisk submitted that the statement regarding no significant difference in the rate of confirmed hypoglycaemic episodes was also sufficiently prominent and in a black font and therefore was not misleading. The company denied a breach of Clause 7.2.

Novo Nordisk submitted that the leavepiece was accurate, not misleading and was sufficiently complete to enable readers to form their own opinion of the therapeutic value of Tresiba.

PANEL RULING

The Panel noted that the graph showed a 25% lower risk of nocturnal hypoglycaemia with Tresiba compared with insulin glargine U100; a prominent downward arrow bore the claim ' 25% lower risk', p=0.02. The graph, and the claim in question '142 Fewer Nocturnal Hypoglycaemic Events' were each referenced to Bode *et al* which concluded that patients with type 1 diabetes who continued Tresiba therapy experienced similar long-term fasting plasma glucose and HbA1c to that of patients treated with insulin glargine but with a lower risk of nocturnal hypoglycaemia. The study authors noted that the similarity in overall confirmed hypoglycaemic episodes between groups suggested that the hypoglycaemic benefit of Tresiba was not observed during the day. The study showed that rates of nocturnal hypoglycaemia were 25% lower with Tresiba than insulin glargine U100.

The bold and prominent claim in question '142 Fewer Nocturnal Hypoglycaemic Events' appeared adjacent to the graph and in the same green font as the prominent page heading. The qualification 'for every 100 patients treated with Tresiba per year versus insulin glargine U100' appeared in much smaller black font, as a distinct and separate paragraph below and did not immediately appear to be part of the claim in question. This was compounded by the fact that the font colour and prominence of the claim in question and the page heading visually linked the two drawing the reader's eye away from the qualification to the claim in question. In the Panel's view it would not be immediately obvious that the separate paragraph beneath was in fact a continuation of the claim above and formed part of the same sentence.

The Panel noted that the statement that there was 'no significant difference in the rate of confirmed overall hypoglycaemic episodes for Tresiba versus insulin glargine U100 in patients with type 1 diabetes (p=ns)' was the third paragraph below the claim in question again in black smaller font.

The Panel considered that the claim '142 Fewer Nocturnal Hypoglycaemic Events' exaggerated the reported hypoglycaemic event difference between the two insulins. The Panel disagreed with Novo Nordisk's submission that the statement regarding no significant difference in the rate of confirmed hypoglycaemic episodes was sufficiently prominent and considered that it did not negate the overall impression of the page. Nor in the Panel's view and for the reasons stated above was the claim in question suitably qualified by the paragraph immediately beneath. The Panel considered that the comparison was misleading in that regard and potentially exaggerated the effect of Tresiba and a breach of Clauses 7.2 was ruled.

Complaint received **20 February 2017**

Case completed **7 July 2017**

HEALTH PROFESSIONAL CONSULTANT TO A PHARMACEUTICAL COMPANY v MERCK SHARP & DOHME

Invitation to webcast

A complaint was received in a private capacity from a health professional who stated that he/she worked as a consultant to a pharmaceutical company.

The complaint concerned an invitation from Merck Sharp & Dohme to a live webcast. The subject line of the mail stated 'MSD Promotional Email; Cardiovascular Matters Part 1 – Online webcast register today'. This was followed by 'This email contains promotional information and is sent to you as you have opted into receiving third-party information from Pulse' followed by the Merck Sharp & Dohme logo and 'This event is organised and fully funded by MSD'. The webcast was entitled 'Cardiovascular matters Improving the CV health of Britain'. It was the first of three webcasts.

The complainant stated that he/she received a promotional email from Pulse on 16 February which stated that it was promotional without stating what it was promoting, nor was prescribing information present.

A second email from the complainant referred to another email from Pulse he/she received on 28 February which was apparently certified but did not include prescribing information, so the complainant had no idea what it was promoting.

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

The Panel considered that whilst it might be prudent to provide prescribing information for such medicines with the invitation, as the invitation did not promote any specific Merck Sharp & Dohme medicines it was not a breach of the Code not to. Thus the Panel ruled no breach of the Code.

The complainant stated at the time of submitting the complaint that he/she was a health professional who worked as a consultant to Novartis. It had previously been decided, following consideration by the then Code of Practice Committee and the ABPI Board of Management, that private complaints from pharmaceutical company employees had to be accepted. To avoid this becoming a means of circumventing the normal procedures for intercompany complaints, the employing company would be named in the report. The complainant would be advised that this would happen and be given an opportunity to withdraw the complaint.

The case preparation manager decided that the principles set out above would apply to consultants. Consultancy status should not be used to circumvent the normal rules for inter-company complaints.

The complainant was advised that if he/she wished to proceed with the complaint in a private capacity Novartis would be named in the case report; and the respondent company would be informed of his/her professional status and the connection with pharmaceutical companies. The complainant so agreed.

Novartis stated that it had no knowledge of, or involvement in, the complaint and did not know the complainant's identity.

The complaint concerned an invitation from Merck Sharp & Dohme to a live webcast. The subject line of the mail stated 'MSD Promotional Email; Cardiovascular Matters Part 1 – Online webcast register today'. This was followed by 'This email contains promotional information and is sent to you as you have opted into receiving third-party information from Pulse' followed by the Merck Sharp & Dohme logo and 'This event is organised and fully funded by MSD'. The webcast was entitled 'Cardiovascular matters Improving the CV health of Britain'. It was the first of three webcasts.

COMPLAINT

The complainant stated that he/she received a promotional email from Pulse on 16 February which stated that it was promotional without stating what it was promoting, nor was prescribing information present.

A second email from the complainant referred to another email from Pulse he/she received on 28 February which was apparently certified but did not include prescribing information either in the email or as a link, so the complainant had no idea what it was promoting.

In writing to Merck Sharp & Dohme attention was drawn to the requirements of Clauses 4.1 and 9.1 of the Code.

RESPONSE

Merck Sharp & Dohme stated that it took the requirements of both the letter and the spirit of the Code very seriously and was keen to reassure both the PMCPA and the complainant about the nature of this invitation and the rationale for it not containing prescribing information for a product.

The purpose of the invitation was to invite health professionals to an educational webcast on strategies to lower cardiovascular risk, presented by two external experts in this field. As the complainant noted, the invitation clearly stated that it was a promotional meeting within the email subject

heading and within the body of the email invitation itself and that the meeting was organised and funded by Merck Sharp & Dohme.

Health professionals were invited via a number of different routes, and included emails from five different providers (named) and sales representatives handing a similar invitation (in hard copy format) to health professionals. Health professionals could then decide whether they dialled into a local webcast or attended a local hub meeting in person, organised and facilitated by the Merck Sharp & Dohme marketing team.

The email invitation in question was sent by a third party (Pulse) which held a list of health professionals who had consented to receive promotional information. All health professionals on this list were sent the invitation.

Merck Sharp & Dohme noted that Clause 1.2 defined promotion as 'any activity undertaken by a pharmaceutical company or with its authority which promotes the administration, consumption, prescription, purchase, recommendation, sale or supply or use of its medicines'. Furthermore, Clause 1.2 explicitly included both '… the activities of representatives including any electronic or printed materials used by them …' and '… the sponsorship of promotional meetings …' in the definition of promotion.

As the content of the webcast included content in therapy areas where Merck Sharp & Dohme had products with a marketing authorisation and the activity was organised and facilitated by the marketing team with some involvement of sales representatives in the delivery of the meeting at some venues, Merck Sharp & Dohme decided to classify this webcast and the invitation to attend the webcast as promotional.

Clause 4.1 of the Code stated that 'the prescribing information listed in Clause 4.2 must be provided in a clear and legible manner in all promotional material **for a medicine** except for abbreviated advertisements' (emphasis added). Merck Sharp & Dohme pointed out that the invitation made no mention of a specific medicine and as such, the invitation was not promotional material for a medicine. Therefore, although the invitation pertained to a promotional activity and had been openly flagged to recipients as promotional; Merck Sharp & Dohme submitted that in and of itself, it did not require the inclusion of prescribing information and denied a breach of Clause 4.1.

Merck Sharp & Dohme submitted that in ensuring the invitation was flagged to recipients as a promotional item, high standards had been maintained at all times in the organisation and facilitation of this meeting and therefore it was not in breach of Clause 9.1.

Merck Sharp & Dohme referred to Case AUTH/1800/2/06 – Primary Care Trust Head of Prescribing v AstraZeneca which supported the fact that an invitation to a speaker meeting with no mention of a medicine would not require prescribing information to be included but should be clear as to the type of meeting it was, so as not to be disguised promotion.

To conclude, Merck Sharp & Dohme submitted that it had maintained high standards in flagging to recipients that the email invitation was promotional in nature; and as it did not believe the invitation required prescribing information and denied breaches of Clauses 4.1 and 9.1.

PANEL RULING

The Panel examined the invitation at issue. The subject heading was clear that the email was promotional and the complainant's version was headed 'This email contains promotional information and is sent to you as you have opted into receiving third-party information from Pulse'. The invitation was headed 'This event is organised and fully funded by MSD' and the MSD logo was included in the top right hand corner. This was followed by 'Cardiovascular Matters Improving the CV Health of Britain' and the details of the live webcast. This was the first of three webcasts. The first speaker was to discuss the scale of high CV risk and the evidence that could help inform treatment strategies and the other speaker would then highlight the opportunities within primary care that could make a difference to the high risk patient during every day clinical practice. Details about the two speakers were provided. The agenda stated that one was to speak on the 'Rationale for maintaining CV risk reduction as a key health priority' and the other on 'Strategies for action – opportunities to lower risk post CV Event'.

The Panel noted that there was no direct or implied mention of any medicine in the invitation. Recipients of the invitation would be clear that the webcast would include treatment strategies and was from a company, Merck Sharp & Dohme, which had medicines for use in cardiovascular disease. The company had made it clear that the invitation was promotional. The Panel considered that whilst it might be prudent to provide prescribing information for such medicines with the invitation, as the invitation did not promote any specific Merck Sharp and Dohme medicines it was not a breach of the Code not to. Thus the Panel ruled no breach of Clause 4.1. The Panel did not consider that high standards had not been maintained and therefore ruled no breach of Clause 9.1.

Complaint received **23 February 2017**

Case completed **9 May 2017**

CASE AUTH/2942/2/17 *NO BREACH OF THE CODE*

HEALTH PROFESSIONAL CONSULTANT TO A PHARMACEUTICAL COMPANY v BOEHRINGER INGELHEIM

Online Spiolto advertisement

A complaint was received in a private capacity from a health professional who stated that he/she worked as a consultant to a pharmaceutical company.

The complaint concerned an online advertisement for Spiolto (tiotropium and olodaterol) issued by Boehringer Ingelheim. Spiolto was indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The complainant stated that although Spiriva was a Boehringer Ingelheim product it had not mentioned the generic name. This was rather important as how else was one supposed to know what Spiolto was better than. The advertisement stated that prescribing information and references were available which, was only partially true as an out of date prescribing information was present, but references were not.

Spiriva was available as both a Respimat device as well as a dry powder inhaler (Handihaler). The complainant stated that he/she was not clear as to which formulation of Spiriva the comparison referred.

The complainant was interested to look at the references to see what the 'better outcomes' were since this was vague and could be anything from quality of life to length of life or number of exacerbations – or indeed something else entirely. But since the references were not present the complainant stated he/she was still none the wiser and did not see how such a vague claim could be substantiated.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that the advertisement published in Pulse, today online, continuously clicked through the five images one after the other, each of the first four images was shown for approximately four seconds before moving to finishing on the fifth image which was then static.

Each image was of a tree showing its roots and with what appeared to be a couple and their dog underneath the tree. The first stated 'SPIOLTO – an advance in COPD care built on the strong roots of Spiriva (tiotropium)'. The second stated 'Superior lung function and less breathlessness vs Spiriva'. The third stated 'Superior quality of life vs Spiriva'. The fourth stated 'Respimat – designed for effective lung delivery' and included an image of the device firing. The final static image stated 'SPIOLTO – from the start of COPD mainenance therapy for better outcomes early on compared to Spiriva' and included an image of the closed device.

As the first banner included the non-proprietary name, tiotropium, immediately adjacent to the first mention of Spiriva the Panel ruled no breach of the Code.

The Panel noted that all five images included a clear, prominent statement as to where the prescribing information, adverse event reporting and references could be found. The Panel noted the complainant's allegation that the prescribing information was out of date where as Boehringer Ingelheim submitted that it was up-to-date. The Panel noted that it was for the complainant to prove his/her complaint on the balance of probabilities. No detail had been provided by the complainant as to why the prescribing information was not up-to-date. The Panel therefore ruled no breach of the Code.

The Panel noted that the advertisement clearly promoted Spiolto Respimat and compared this with Spiriva which was available as a Respimat and Handihaler. The Panel noted Boehringer Ingelheim's submission that the Spiolto clinical trials programme compared Spiolto and Spiriva Respimat and that Spiolto demonstrated statistically significant improvements in lung function, breathlessness and quality of life as stated in the advertisement. The Panel noted that these features appeared in the second and third images with the final image referring to 'Spiolto - From the start of COPD maintenance therapy for better outcomes early on compared to Spiriva'. The fourth banner stated 'Respimat – designed for effective lung delivery'. The Panel noted that although there was no specific mention of the Spiriva device used for the comparison, the fact that the studies used the same device (Respimat) for both medicines meant that readers would not be misled regarding the devices. The Panel thus ruled no breach of the Code. The Panel considered that the claim for 'better outcomes' compared to Spiriva in the final image would be read in relation to the features compared in the advertisement and thus was not misleading. The comparisons were substantiated by the material provided by Boehringer Ingelheim including the Spiolto SPC. The Panel thus ruled no breaches of the Code.

The Panel noted its rulings above and did not consider that Boehringer Ingelheim had failed to maintain high standards. No breach was ruled.

The complainant stated at the time of submitting the complaint that he/she was a health professional who worked as a consultant to Novartis. It had previously been decided, following consideration

by the then Code of Practice Committee and the ABPI Board of Management, that private complaints from pharmaceutical company employees had to be accepted. To avoid this becoming a means of circumventing the normal procedures for intercompany complaints, the employing company would be named in the report. The complainant would be advised that this would happen and be given an opportunity to withdraw the complaint.

This issue came to the fore many years ago when an employee of a pharmaceutical research company complained in a private capacity about a journal advertisement issued by GlaxoSmithKline UK Ltd (Case AUTH/1498/7/03). In Case AUTH/1498/7/03 it was decided that the pharmaceutical research company would be named in the case report whilst making it clear that the complaint was made in a private capacity.

The case preparation manager decided that the principles set out above would apply to consultants. Consultancy status should not be used to circumvent the normal rules for inter-company complaints.

The complainant was advised that if he/she wished to proceed with the complaint in a private capacity Novartis would be named in the case report; and the respondent company would be informed of his/her professional status and the connection with pharmaceutical companies. The complainant so agreed.

Novartis stated that it had no knowledge of, or involvement in, the complaint and did not know the complainant's identity.

The complaint concerned an online advertisement for Spiolto (tiotropium and olodaterol) (ref UK/SPRES-161076) issued by Boehringer Ingelheim Limited and was published by Pulse online. Spiolto was indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

COMPLAINT

The complainant stated that although Spiriva was a Boehringer Ingelheim product it had not mentioned the generic name. This was rather important as how else was one supposed to know what Spiolto was better than. The advertisement stated that prescribing information and references were available using the link (http://spioltouk.cherrythinking.net/ps/), this was only partially true as an out of date prescribing information was present, but references were not.

Spiriva was available as both a Respimat device as well as a dry powder inhaler (Handihaler). The complainant stated that he/she was not clear as to which formulation of Spiriva the comparison referred.

The complainant was interested to look at the references to see what the 'better outcomes' were since this was vague and could be anything from quality of life to length of life or number of exacerbations – or indeed something else entirely. But since the references were not present the complainant stated he/she was still none the wiser and did not see how such a vague claim could be substantiated.

In writing to Boehringer Ingelheim attention was drawn to the requirements of Clauses 4.1, 4.3 7.2, 7.4 and 9.1 of the Code.

RESPONSE

Boehringer Ingelheim explained that the image of the advertisement provided by the complainant was one of a series of five which made up the whole of the advertisement (UK/SPRES-161076) within the website www.pulsetoday.co.uk. Each image was shown for approximately four seconds before ending on the fifth image, which was then static.

The generic name of Spiriva, tiotropium was mentioned within the advertisement. The name of the active ingredient clearly appeared immediately after the first mention of Spiriva. This could be seen in the first image of the advertisement that the complainant sent to the PMCPA and in the enclosed copies of the advertisement. Boehringer Ingelheim therefore submitted that there was no breach of Clause 4.3.

The prescribing information for Spiolto (tiotropium and olodaterol) and references were available from the link on the advertisement. The prescribing information available via the link was indeed the latest version and up-to-date.

For a brief period between 14 February and 2 March 2017, the website hosting the advertisement experienced a technical error where the link for the prescribing information and references had been routing to a version of the prescribing information which did not include the references. The version without references was designed for a static version of the advertisement that would only be displayed if there was a technical issue with the website. This had yet to be displayed if there was a technical issue with the website. This had yet to be displayed on this website. Despite this, all claims were capable of substantiation, as could be seen in the enclosed references. Boehringer Ingelheim therefore submitted there was no breach of Clauses 4.1 or 7.4.

The comparison drawn within the advertisement was between Spiolto and Spiriva. Both formulations of Spiriva, ie the Respimat device and the Handihaler (dry powder inhaler) contained only tiotropium as an active ingredient. In a very large study of more than 17,000 patients it had been unequivocally demonstrated that both formulations had a comparable efficacy and safety profile. In the Spiolto clinical trials programme, Spiolto was comparable to Spiriva Respimat and demonstrated statistically significant improvements in lung function, breathlessness and quality of life as stated in the advertisement. Boehringer Ingelheim therefore submitted that there was no breach of Clauses 7.2 or 7.4.

The claim of an improvement in the outcomes was on the fifth of five images displayed. The outcomes referred to could clearly be seen within images two, three and four of the five. When the whole advertisement was considered, the statement regarding an improvement in outcomes was not ambiguous. References had been provided to demonstrate that the claims were capable of substantiation. Boehringer Ingelheim therefore submitted there was no breach of Clauses 7.2 or 7.4.

As there were no breaches of any of the clauses stated, Boehringer Ingelheim also submitted that there was no breach of Clause 9.1.

In a response to a request for further information Boehringer Ingelheim provided an electronic copy of the rolling banner advertisement.

PANEL RULING

The Panel noted that the advertisement published in Pulse, today online, continuously clicked through the five images one after the other, each of the first four images was shown for approximately four seconds before moving to finishing on the fifth image which was then static. The Panel noted that the supplementary information to Clause 4.1 Electronic Journals stated that the first part of an advertisement in an electronic journal, such as the banner, was often the only part of the advertisement that was seen by readers. It must therefore include a clear, prominent statement as to where the prescribing information could be found. This should be in the form of a direct link. The first part was often linked to other parts and in such circumstances the linked parts would be considered as one advertisement. The Panel noted that the purpose of this supplementary information was, *inter alia*, to help ensure that the prescribing information and other obligatory information were an integral part of the advertisement thus satisfying the requirements of Clause 4.1. If the first part mentioned the product name then this was the most prominent display of the brand name and the non-proprietary name of the medicine or a list of the active ingredients using approved names where such existed must appear immediately adjacent to the most prominent display of the brand name.

The Panel considered that there were differences between a static banner on which one proactively clicked to link to other material including the prescribing information, and a series of images. The length of time that each image was displayed within a series would vary, could not be influenced by the reader and might be longer or shorter than those in the material at issue in this case where the first four images were displayed for approximately four seconds each before ending on the fifth image which was then static. The Panel considered that such cases should be considered individually in relation to the requirements of the Code.

Each image was of a tree showing its roots and with what appeared to be a couple and their dog underneath the tree. The first stated 'SPIOLTO – an advance in COPD care built on the strong roots of Spiriva (tiotropium)'. The second stated 'Superior lung function and less breathlessness vs Spiriva'. The third stated 'Superior quality of life vs Spiriva'. The fourth stated 'Respimat – designed for effective lung delivery' and included an image of the device firing. The final static image stated 'SPIOLTO – from the start of COPD mainenance therapy for better outcomes early on compared to Spiriva' and included an image of the closed device.

The Panel noted that Clause 4.3 required the non-proprietary name or the list of active ingredients using approved names where such existed to appear immediately adjacent to the most prominent display of the brand name. As the first banner included the non-proprietary name, tiotropium, immediately adjacent to the first mention of Spiriva the Panel ruled no breach of Clause 4.3.

The Panel noted that all five images included a clear, prominent statement as to where the prescribing information, adverse event reporting and references could be found. The Panel noted the complainant's allegation that the prescribing information was out of date. Boehringer Ingelheim submitted that the prescribing information was up-to-date. The Panel noted that it was for the complainant to prove his/her complaint on the balance of probabilities. No detail had been provided by the complainant as to why the prescribing information was not up-to-date. The Panel therefore ruled no breach of Clause 7.2 of the Code.

The Panel noted that from 14 February until 2 March the references had not been available via the link from the advertisement. The Panel noted that the case preparation manager had not raised Clause 7.6 with Boehringer Ingelheim. Clause 7.6 required that when promotional material referred to published studies clear references must be given. The Panel was therefore unable to make a ruling in that regard. Clauses 4.1 and 4.2 made no mention of the inclusion of references. Thus the Panel ruled no breach of Clause 4.1.

The Panel noted that the advertisement clearly promoted Spiolto Respimat and compared this with Spiriva. Spiriva was available as a Respimat and Handihaler. The Panel noted Boehringer Ingelheim's submission that the Spiolto clinical trials programme compared Spiolto and Spiriva Respimat and that Spiolto demonstrated statistically significant improvements in lung function, breathlessness and quality of life as stated in the advertisement. The Panel noted that these features appeared in the second and third images with the final image referring to 'Spiolto - From the start of COPD maintenance therapy for better outcomes early on compared to Spiriva'. The fourth banner stated 'Respimat – designed for effective lung delivery'. The Panel noted that although there was no specific mention of the Spiriva device used for the comparison, the fact that the studies used the same device (Respimat) for both medicines meant that readers would not be misled regarding the devices. The Panel thus ruled no breach of

Clause 7.2. The Panel considered that the claim for 'better outcomes' compared to Spiriva in the final image would be read in relation to the features compared in the advertisement and thus was not misleading. No breach of Clause 7.2 was ruled. The comparisons were substantiated by the material provided by Boehringer Ingelheim including the Spiolto SPC. The Panel thus ruled no breach of Clause 7.4.

The Panel noted its rulings above and did not consider that Boehringer Ingelheim had failed to maintain high standards. No breach of Clause 9.1 was ruled.

Complaint received **1 March 2017**

Case completed **15 May 2017**

COMMUNITY PHARMACIST v GLAXOSMITHKLINE

Resource booklet for Pharmacists

An anonymous, non contactable complainant who stated he/she was a community pharmacist submitted a complaint about a National Pharmacy Association (NPA) booklet 'Managing COPD [chronic obstructive pulmonary disease] in the community, Resources for pharmacists', which had the GlaxoSmithKline and NPA logo printed on the front page. The booklet was written and developed by the NPA and GlaxoSmithKline had provided funding and checked it for scientific accuracy in respect to any GlaxoSmithKline products. The booklet mentioned the Evohaler and Accuhaler devices which were GlaxoSmithKline devices for various GlaxoSmithKline medicines.

The complainant referred to a table on page 28 under a heading 'COPD inhaler devices' which referred to the Evohaler Device as an example of a standard MDI. The complainant was concerned that the reference to the 'Evohaler' device could refer not only to the Ventolin Evohaler, which was licensed for COPD, but also to the Seretide Evohaler which was not so licensed. The 'Evohaler' trade name could therefore cause confusion and acceptance that Seretide Evohaler was licensed for COPD which it was not. This was something that should be highlighted during a medicine use reviews (MUR) and (NMS) intervention which was not referenced in any of the MUR and new medicines services NMS documentation within the booklet.

The complainant questioned the bias towards some inhaler devices that had been listed and others which had higher prescribing within his/her locality and not been referenced.

The detailed response from GlaxoSmithKline is given below.

The Panel noted GlaxoSmithKline's role in relation to supporting the booklet was limited to funding and checking it for factual accuracy with respect to its own products; its content was otherwise a matter for the NPA. However GlaxoSmithKline submitted it would make the booklet available for a promotional purpose which meant that it was subject to the Code. The Panel noted GlaxoSmithKline's submission that it had not proactively distributed the booklets.

The Panel noted GlaxoSmithKline's submission that Evohaler products; Ventolin Evohaler and Seretide Evohaler, were not licensed for COPD whereas Serevent Evohaler was. The Panel noted the complainant's statement that Ventolin Evohaler was so licensed. In this regard the summary of product characteristics (SPC) for the Ventolin Evohaler stated at section 4.1, that Ventolin provided short-acting (4-6 hour) bronchodilation with fast onset (within 5 minutes) in reversible airways obstruction. The SPC then stated that it was 'particularly suitable for the relief and prevention of asthma symptoms' and that it was 'particularly valuable as relief medication in mild, moderate or severe asthma'. There was no mention of COPD in the indication section of the SPC.

The Panel noted that pages 26-38 were headed 'COPD inhaler devices', the table in question started on page 28 and was headed 'The different types of inhaler devices available and instructions for their use*'. This table listed 7 types of device providing information about the device type, examples of devices and instructions for their use. The heading to the table bore an asterisk which related to a footnote to the table which appeared as five bullet points on page 34. One bullet point stated, *inter alia*, that the licensed indications varied, and that some might only be licensed for use in asthma and not COPD – individual products' SPCs should be referred to for more information. The Panel noted that GlaxoSmithKline had requested this footnote be inserted as a correction to the draft booklet.

The Panel did not consider that it was necessarily misleading to refer simply to 'Evohaler' in Table 8 as an example of a standard MDI device. The Panel noted that this was clearly an area of potential difficulty as demonstrated by the complainant's confusion.

The booklet included a number of loose insert 'crib sheets' for MUR or an NMS. Neither specifically mentioned the need to check that medicines were licensed for COPD, nor did the crib sheet for a NMS. However, the Panel considered that this in itself was not necessarily inappropriate given that a MUR would look at all medicines prescribed. If concerned after a MUR or NMS consultation, pharmacists could query which medicines had been prescribed and why and take further action as appropriate.

The Panel did not consider that the references to Evohaler in the booklet meant that GlaxoSmithKline had promoted Seretide Evohaler for an unlicensed indication as alleged. On balance the Panel did not consider that the reference to Evohaler as an example of a device for use in COPD was misleading as alleged. The Panel considered that it would have been helpful if the relevant footnote had appeared at the outset rather than 6 pages later where it might be read as the heading to table 9 rather than the footnote to table 8. However, the intended audience would know that not all medicines licensed for asthma were licensed for COPD. No breaches of the Code were ruled.

With regard to the lack of mention of other devices the Panel noted GlaxoSmithKline's submission that three more recent DPIs were not used as examples. The foreword which included 'Details of available COPD inhaler devices and other equipment' and

the heading to pages 26-38 'COPD inhaler devices' could be seen as implying all devices would be listed. However, table 8 was clear that 'Examples of devices' were listed. The Panel considered, that, on balance, table 8 was not an unfair comparison or misleading as alleged and ruled no breach of the Code.

The Panel noted its rulings above and considered that GlaxoSmithKline had not failed to maintain high standards and no breach of the Code was ruled.

An anonymous, non contactable complainant who stated he/she was a community pharmacist submitted a complaint about a National Pharmacy Association (NPA) booklet 'Managing COPD [chronic obstructive pulmonary disease] in the community, Resources for pharmacists', (Ref UK/RET/0007/16) which had the GlaxoSmithKline and NPA logo printed on the front page. A statement on the front page indicated that the booklet was written and developed by the NPA and that GlaxoSmithKline had provided funding and checked it for scientific accuracy in respect to any GlaxoSmithKline products. The booklet was designed to help community pharmacists and their teams improve the diagnosis, care and management of patients with COPD. The booklet also mentioned the Evohaler and Accuhaler devices which were GlaxoSmithKline devices for various GlaxoSmithKline medicines.

COMPLAINT

The complainant alleged that the booklet was misleading and biased when pharmacists conducted medicine use reviews (MURs) and new medicines services (NMS) with COPD patients.

The complainant referred to the statement on page 26 that:

'There are a variety of different inhaler devices available on the market for the treatment of chronic obstructive pulmonary disease (COPD) and these include: Pressurised metered dose inhalers (MDIs), Standard 'press and breathe' MDIs, Breath-activated MDIs, Dry powder inhalers (DPIs) and Soft Mist MDIs.'

The complainant also referred to a table on page 28 under a heading 'COPD inhaler devices' which referred to the Evohaler Device as an example of a standard MDI. The complainant was concerned that the reference to the 'Evohaler' device could refer not only to the Ventolin Evohaler, which was licensed for COPD, but also to the Seretide Evohaler which was not so licensed. The 'Evohaler' trade name could therefore cause confusion and acceptance that Seretide Evohaler was licensed for COPD which it was not. Community pharmacists had come across patients prescribed Seretide Evohaler off-label by both primary and secondary clinicians. This was something that should be highlighted during a MUR and NMS intervention which was not referenced in any of the MUR and NMS documentation within the booklet. It was a term that should be referenced and not freely listed as 'Evohaler' which could be linked to both Ventolin and Seretide as the device was a standard metered dose inhaler (MDI) device.

The Elipta device was not referenced in the booklet but neither were the Spiromax, NEXThaler and Forspiro devices which were all licensed for COPD. The complainant questioned the bias towards some inhaler devices that had been listed and others which had a higher % prescribing within his/her locality and not been referenced.

The complainant stated that he/she would also be writing to the NPA.

In writing to GlaxoSmithKline attention was drawn to the requirements of Clauses 3.2, 7.2, 7.3 and 9.1 of the Code.

RESPONSE

GlaxoSmithKline stated that as of 29 March 2017 the NPA confirmed that no such letter had been received.

Background, history and nature of the arrangement

The 54-page document at issue was written by the NPA for pharmacists and their teams in the community to 'Improve the diagnosis, care and management of patients with chronic obstructive pulmonary disease (COPD)'. The concept for the booklet was suggested by the NPA at a meeting with GlaxoSmithKline at the end of 2014 as the association had had experience in developing a similar booklet in diabetes which had proved to be very popular with its members.

The NPA selected one of its pharmacist writers as the 'Supplier Contact Person' as named in the contract with specific responsibility for drafting the booklet. GlaxoSmithKline agreed to fund the service. The contract also specified that the bulk of the booklets (>7,000 copies) would be sent by the NPA to its members and that GlaxoSmithKline would only take around 1000 to be given to member pharmacists of the Company Chemists' Association. GlaxoSmithKline's role in the development of the booklet was to ensure that it was in line with the requirements of the Code and more specifically to check for the scientific and medical accuracy of any GlaxoSmithKline product mentioned in the booklet. As required by the Code, the exact nature of GlaxoSmithKline's involvement was made clear on the front page of the booklet.

The booklet was reviewed and approved by the NPA's chief pharmacist who wrote the Foreword as well as certified by GlaxoSmithKline, before being sent to print. Payment for the booklet was made directly to the NPA and not to the author.

Non-promotional nature of the COPD booklet

GlaxoSmithKline submitted that the booklet was non-promotional in nature, design and content and did not refer to any GlaxoSmithKline product, nor indeed to any other pharmaceutical company's products by brand name. Where there was any mention of medicines in the booklet, they were referred to by generic name only.

As noted by the complainant, there was no mention of the Ellipta device, the respiratory device used to

deliver the majority of GlaxoSmithKline's actively promoted branded products; namely Relvar, Anoro and Incruse, as the NPA decided not to include it.

Even though the item was non-promotional in its own right it had been certified as 'Promotional' as it formed part of a suite of services which pharmacists might select to have as part of the GlaxoSmithKline Partnership Programme Agreement which provided discounts on some of the GlaxoSmithKline products. The booklets had not been proactively distributed by GlaxoSmithKline personnel and as of 29 March only the NPA had distributed them.

Alleged promotion of Seretide Evohaler in COPD

GlaxoSmithKline submitted that Seretide was not mentioned anywhere in the booklet. Its non-proprietary constituents, salmeterol and fluticasone propionate, only appeared on page 19 where they were mentioned as an example of a combined inhaled corticosteroid and then, only as the second example after formoterol plus budesonide.

The complainant correctly stated that the MDI delivery system for Seretide, Seretide Evohaler, was not licensed for use in COPD even though the dry powder (DP) delivery system, Seretide Accuhaler, was licensed (50/500mg dose only). However, the complainant incorrectly stated that Ventolin Evohaler was licensed for use in COPD, which was not so and the complainant failed to mention that Serevent Evohaler (salmeterol xinofoate) was licensed for use in patients with COPD. The choice of the Evohaler (the original inhaler device) as an example of a MDI for use in patients with COPD was therefore validated, as the Serevent Evohaler was available for use in patients with COPD since 2005.

Furthermore, the Evohaler was only mentioned in the document once, (page 29), in the third column of Table 8 entitled 'The different types of inhaler devices and instructions for their use*' and was given as an example of an MDI. The complainant failed to mention that explanation for the asterisk appeared at the end of the table on page 34, as follows:

Please note:

- ***The instructions for use in Table 8 are generic and may not be applicable to every type of inhaler listed – therefore please refer to the individual product's Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL) for detailed guidance on how to use the inhaler.***
- ***The full NICE guideline "Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care, CG101" states that patients should receive training on the use of their prescribed devices and be able to demonstrate adequate technique before being prescribed the devices.***
- ***The full NICE guideline indicates that patients using inhalers should be reassessed regularly as inhaler technique can deteriorate over time***
- ***The licensed indications for inhalers vary and some may only be licensed for use in asthma and not COPD – individual product's SPCs should be referred to for more information.***
- ***If patients are unable to use their inhaler device adequately, an alternative device should be prescribed.***

GlaxoSmithKline stated that at no time was the Evohaler mentioned with Seretide nor indeed with any other GlaxoSmithKline product, nor was it referred to in the introductory section on standard metered dose inhalers (page 26).

GlaxoSmithKline therefore denied any promotion of the Seretide Evohaler for use in COPD and thus any breach of Clauses 3.2, 7.2, 7.3 and 9.1.

The choice of examples of devices

GlaxoSmithKline stated that the booklet simply gave some examples of the different types of devices and never claimed to be comprehensive in its list of all available inhalers in the UK, as a large number with new ones were introduced on a regular basis. The choice of examples was at the discretion of the NPA, which in the chapter on inhaler devices listed the following: Accuhaler, Breezhaler, Easyhaler, Handihaler, Novolizer and Turbohaler (page 26) Evohaler, Respimat (page 28), Autohaler, Easibreathe (page 29), Accuhaler, Breezhaler, Easyhaler, Handihaler, Novolizer, Turbohaler (page 30-33). The fact that these were examples was made quite clear in both the text and the table.

DuoResp Spiromax (Teva) 2014, Fostair NEXThaler (Chiesi) 2014 and Forspiro AirFluSal (Sanofi) 2015 were all more recently introduced breath actuated dry powdered inhalers (DPIs) and if included would be three more additions to the six examples already included in the booklet. The decision not to add these more recently introduced devices was not deliberate. The NPA had no specific policy to either include or exclude any specific medicines or inhalers and certainly did not have one based on the prescription/sales of inhalers at a 'local level' as cited as a criticism by the complainant. The NPA just included as examples those devices which it considered would be of most relevance to members. As the complainant correctly observed, GlaxoSmithKline's Ellipta inhaler was not mentioned in the booklet.

GlaxoSmithKline therefore denied any breach of Clauses 3.2, 7.2, 7.3 and 9.1.

GlaxoSmithKline has shared the complaint with the NPA together with its response. GlaxoSmithKline provided the NPA perspective.

Finally, GlaxoSmithKline stated that the feedback to the NPA had been extremely favourable where the booklet was being widely used by pharmacists for the benefit of patients in the community.

PANEL RULING

The Panel noted that it was possible for a company to sponsor material, produced by a third party which mentioned its own product, and not be liable under

the Code for its contents, but only if, *inter alia*, there had been a strictly arm's length arrangement between the parties. The arrangements must be such that there could be no possibility that the pharmaceutical company had been able to exert any influence or control over the final content of the material. Use of such material for a promotional purpose would mean that it was subject to the Code.

The Panel noted GlaxoSmithKline's role in relation to supporting the booklet was limited to funding and checking it for factual accuracy with respect to its own products; its content was otherwise a matter for the NPA. However GlaxoSmithKline submitted it would make the booklet available for a promotional purpose which meant that it was subject to the Code. The Panel noted GlaxoSmithKline's submission that it had not proactively distributed the booklets.

The Panel noted GlaxoSmithKline's submission that Evohaler products; Ventolin Evohaler and Seretide Evohaler, were not licensed for COPD whereas Serevent Evohaler was. The Panel noted the complainant's statement that Ventolin Evohaler was so licensed. In this regard the summary of product characteristics (SPC) for the Ventolin Evohaler stated at section 4.1, that Ventolin provided short-acting (4-6 hour) bronchodilation with fast onset (within 5 minutes) in reversible airways obstruction. The SPC then stated that it was 'particularly suitable for the relief and prevention of asthma symptoms' and that it was 'particularly valuable as relief medication in mild, moderate or severe asthma' provided that reliance on it did not delay the introduction and use of inhaled corticosteroid therapy. There was no mention of COPD in the indication section of the SPC.

The Panel noted that pages 26-38 were headed 'COPD inhaler devices', the table in question started on page 28 and was headed 'The different types of inhaler devices available and instructions for their use*'. This table listed 7 types of device providing information about the device type, examples of devices and instructions for their use. The heading to the table bore an asterisk which related to a footnote to the table which appeared as five bullet points on page 34. One bullet point stated, *inter alia*, that the licensed indications varied, and that some might only be licensed for use in asthma and not COPD – individual products' SPCs should be referred to for more information. The Panel noted that GlaxoSmithKline had requested this footnote be inserted as a correction to the draft booklet.

The Panel did not consider that it was necessarily misleading to refer simply to 'Evohaler' in Table 8 (page 28) as an example of a standard MDI device. The Panel noted that this was clearly an area of potential difficulty as demonstrated by the complainant's confusion.

The booklet included a number of loose insert 'crib sheets'. The crib sheet for a MUR in COPD did not specifically mention the need to check that medicines were licensed for COPD, nor did the crib sheet for a NMS. However, the Panel considered that this in itself was not necessarily inappropriate given that a MUR would look at all medicines prescribed. If concerned after a MUR or NMS consultation, pharmacists could query which medicines had been prescribed and why and take further action as appropriate.

The Panel did not consider that the references to Evohaler in the booklet meant that GlaxoSmithKline had promoted Seretide Evohaler for an unlicensed indication as alleged. No breach of Clause 3.2 of the Code was ruled. On balance the Panel did not consider that the reference to Evohaler as an example of a device for use in COPD was misleading as alleged. The Panel considered that it would have been helpful if the relevant footnote had appeared at the outset rather than 6 pages later where it might be read as the heading to table 9 rather than the footnote to table 8. However, the intended audience would know that not all medicines licensed for asthma were licensed for COPD. No breach of Clause 7.2 was ruled.

With regard to the lack of mention of other devices the Panel noted GlaxoSmithKline's submission that three more recent DPIs were not used as examples. The foreword which included 'Details of available COPD inhaler devices and other equipment' and the heading to pages 26-38 'COPD inhaler devices' could be seen as implying all devices would be listed. However, table 8 was clear that 'Examples of devices' were listed. The Panel considered, that, on balance, table 8 was not an unfair comparison or misleading as alleged. The Panel ruled no breach of Clauses 7.2 and 7.3.

The Panel noted its rulings above and consider that GlaxoSmithKline had not failed to maintain high standards. No breach of Clause 9.1 was ruled.

Complaint received **13 March 2017**

Case completed **28 June 2017**

ANONYMOUS CONSULTANT ONCOLOGIST v MERCK SERONO

Conduct of representative

An anonymous, non-contactable complainant who described themselves as a consultant oncologist complained about the conduct of a representative from Merck Serono with regard to the promotion of Erbitux (cetuximab).

The complainant's concerns were frequent email contact, frequent requests for appointment, often monthly, representatives arriving in the day unit or out-patients clinic, without an appointment or prior permission which was against trust policy and wasted valuable clinic time. The complainant also referred to presentation of old data when the appointment was granted on the understanding that new data would be discussed. As cetuximab was a well-established medicine, it was not necessary to meet frequently to discuss established data that offered no new clinical value. The final concern was a failure to provide paper copies of information presented during appointments, despite requests.

The detailed response from Merck Serono is given below.

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure for the Prescription Medicines Code of Practice Authority stated that anonymous complaints would be accepted but that like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities.

The Panel was concerned about the allegations made by the anonymous complainant but he/she had provided no supporting detail such as the relevant hospital location. The company was unable to properly investigate the allegations.

The Panel examined the materials provided by Merck Serono. The representatives' training (dated August 2015) reflected the restrictions in the Code on calls. The representatives' briefing materials provided made no mention of the number of calls/contacts. The company had received recent NICE guidance for use of Erbitux in a particular type of patient. This was likely to be of interest to health professionals but it was unlikely that this related to new clinical data. The job description for a key account manager stated that they should act with integrity to ensure compliance with company and industry guidelines and requirements.

The Panel noted that the complainant bore the burden of proof and considered that he/she had failed to prove any of the allegations on the balance of probabilities. The Panel therefore ruled no breaches of the Code.

An anonymous, non-contactable complainant who described themselves as a consultant oncologist complained about the conduct of a representative from Merck Serono Limited with regard to the promotion of Erbitux (cetuximab). Erbitux was for the treatment of certain forms of metastatic colorectal cancer and for the treatment of squamous cell cancer of the head and neck.

COMPLAINT

The complainant stated that he/she had enjoyed a cordial relationship with the pharmaceutical industry over many years, and had valued the support provided to his/her clinic and patients. However, he/she had recently become concerned by the conduct of Merck Serono. The complainant stated that, in summary, his/her concerns were:

- Frequent email contact. While he/she had given the representative permission to contact him/her via email, the rate of contact was more than could be viewed as reasonable.
- Frequent requests for appointment, often monthly, with him/herself, junior doctors and nursing staff.
- Representatives arriving in the day unit or out-patients clinic, without an appointment or prior permission, in the anticipation that they might be able to see someone. This practice was against trust policy and wasted valuable clinic time.
- Presentation of old data when the appointment was granted on the understanding that new data would be discussed.
- Cetuximab was a well-established medicine; the complainant did not consider it necessary to meet frequently to discuss established data that offered no new clinical value.
- Failure to provide paper copies of information presented during appointments, despite requests.

The complainant firmly believed that this behaviour was unprofessional and not of the standard that he/she had come to expect from the pharmaceutical industry. The complainant stated that on several occasions he/she had made his/her concerns clear to the representative, but they claimed that Merck expected them to see clinicians frequently and present their data in this way, regardless of clinicians' individual preferences.

When writing to Merck Serono, the Authority asked it to consider the requirements of Clauses 7.1, 7.5, 9.1, 11.2, 15.2, 15.4 and 15.9 of the Code.

RESPONSE

Merck Serono stated that it took any allegation of inappropriate conduct of its staff very seriously.

On being advised of the complaint, it immediately launched an internal investigation into the allegations.

Merck Serono noted that according to the introduction of the PMCPA Constitution and Procedure, the complainant had the burden of proving his/her complaint on the balance of probabilities. As the complainant had not identified a specific representative or location, the investigation was challenging and the company could not investigate the specific representative involved.

Merck Serono submitted that all of its representatives were trained on the requirements of the Code regarding calls. The training also covered frequency and manner of calls on doctors and other prescribers which outlined that calls must not be inconvenient in terms of frequency, duration, interval between calls, timing, nature and that calls must be in line with individuals' wishes and with local requirements/ procedures. Merck Serono provided a copy of relevant guidance for its customer-facing employees and submitted that through its investigation it did not find any evidence that it had breached Clause 15.4 or 11.2.

As detailed in the guidance, representatives were responsible for complying with hospital requirements. With regard to trusts which did not allow cold calling, Merck Serono emailed its representatives to ask them if any hospital trusts had policies which prohibited representatives from going to the day unit or out-patients without a specific appointment or which restricted representative activity in other ways.

A sample of some of the responses from the oncology sales team showed that there were many hospitals that had restrictions to prohibit representatives from entering different parts of the hospitals. Some trusts prohibited representatives from calling without an appointment. Many trusts had introduced the Medical Industry Accredited (MIA) card which representatives must carry if they had an appointment. One trust required sign in via the procurement department, a badge was then issued and the appointment confirmed with the relevant health professional etc. If representatives were seen anywhere in the hospital without the lanyard they were required to leave the hospital and banned for six months.

Merck Serono submitted 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 Serono submitted that its investigation had found no evidence that any of its representatives had not acted in line with their job description or had been in breach of Clause 15.2.

Merck Serono submitted that its representatives were not rewarded nor did they receive bonuses related to number of calls or contacts. A copy of the key account manager (KAM) Incentive Plan was provided which Merck Serono stated demonstrated the lack of such rewards/bonuses.

Merck Serono submitted that its promotional material was accurate and relevant and frequently updated to ensure it was current.

The data to support the use of cetuximab had evolved over recent years with, for example, further understanding of how biomarkers could be better used to target metastatic colorectal cancer patients who were the most likely to benefit; such data had led to changes in the marketing authorisation. Further new data were presented at major congresses, such as the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) each year. In order to reflect the most relevant and up-to-date evidence, the marketing campaigns were updated, to provide the sales teams and therefore customers with the most relevant data. In December 2016 the detail aid was updated to include data on tumour location which were initially presented at the ASCO and ESMO conferences. A briefing document was approved in December for the sales team, Tumour Location Data KAM Briefing. This was the latest certified briefing on the technical aspects of Erbitux. Merck Serono believed this demonstrated that there could be no breach of Clause 15.9.

In addition to the latest clinical data, in the first quarter of 2017, the National Institute for Health and Care Excellence (NICE) issued a final appraisal determination related to Erbitux, which was important information about funding and practice in the UK. This had also been communicated and briefed to the KAMs and marketing materials provided. Merck Serono submitted that this further demonstrated that KAM material, and subsequently the content of their visits to customers, was up-to-date and relevant. Merck Serono provided an agenda for the meeting in March where this was communicated. Additionally, a leavepiece was approved to communicate this to health professionals.

Merck Serono stated that it made great efforts to tailor its interactions to the preferences of individual clinicians. Its electronic detail aid contained 178 pages, and was configured into several sections so that representatives could flexibly tailor the conversation to customers' individual needs. The use and functionalities of the electronic detail were most recently demonstrated to representatives in April 2016. KAMs were clearly directed that the content of their calls should be tailored to customer needs and that there was no pre-specified or mandated call flow. As noted above, customer-facing employees were given guidance on interactions, and in addition, the latest guidance around motivational customer messaging was trained in January 2017.

Merck Serono thus considered that the information it provided was relevant and accurate and therefore not in breach of Clause 7.1.

Merck Serono stated that it was unable to comment about the complainant's concern about the presentation of old data as no specific information had been provided about the data itself or the timeframe which the complainant believed constituted old data.

With regard to the provision of information, Merck Serono stated that if a health professional requested information that had been presented electronically then the representative would contact the medical information department as the content of a digital sales aid could not be provided by the representative to a customer.

If a written response was received by the medical information department, it would email the health professional to confirm his/her question by the next working day. If no response was provided within 10 working days the request would be closed. Health professionals were routinely advised that they needed to respond for the information to be sent. The email response from the health professional provided further evidence of an unsolicited request for information; the information would be sent by medical information in 5 days. Merck Serono provided a copy of a standard operating procedure (SOP) which outlined this process.

Merck Serono noted that the complainant stated that it had not provided information when requested to do so, however, without specifics the company was unable to investigate this further and it refuted a breach of Clauses 7.1 or 7.5.

Merck Serono reiterated that compliance with the Code was taken very seriously across the organisation. The company hoped that its explanation and supporting documentation provided clear reasons as to why it had not breached Clauses 7.1, 7.5, 11.2, 15.2, 15.4, 15.9 or 9.1.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure for the Prescription Medicines Code of Practice Authority stated that anonymous complaints would be accepted but that like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant had provided no evidence to support his/her allegations and could not be contacted for more information.

The Panel was concerned about the allegations made by the anonymous complainant but he/she had provided no supporting detail such as the relevant hospital location. The company was unable to properly investigate the allegations.

The Panel examined the materials provided by Merck Serono. The representatives' training (dated August 2015) reflected the restrictions in the Code on calls as set out in Clause 15.4 and its supplementary information. The company defined calls and contacts. The incentive plan (August 2016) had both quantitive and qualitive elements. In relation to one element of the incentive, the sales commitment, there was no benefit from under or over commitment. The representatives' briefing materials provided made no mention of the number of calls/contacts. The company had received recent NICE guidance for use of Erbitux in a particular type of patient. This was likely to be of interest to health professionals but it was unlikely that this related to new clinical data. The job description for a key account manager stated that they should act with integrity to ensure compliance with company and industry guidelines and requirements.

The Panel noted that the complainant bore the burden of proof and considered that he/she had failed to prove any of the allegations on the balance of probabilities. The Panel therefore ruled no breach of Clauses 7.1, 7.5, 11.2, 15.4 and 15.9 of the Code. Neither the representatives nor the company had failed to maintain high standards. No breach of Clauses 15.2 and 9.1 were ruled.

Complaint received **21 March 2017**

Case completed **28 June 2017**

CASE AUTH/2950/4/17

HEALTH PROFESSIONAL v TOR GENERICS

Advertisement in The Big Issue

A health professional complained that a Tor Generics advertisement which included a pack shot of, *inter alia*, Tor-Bac 5ml in The Big Issue magazine, advertised an injection, and thus a prescription only medicine (POM) to the public in breach of the Code.

The detailed response from Tor Generics is given below.

The Panel noted the company's submission that once licensed Tor-Bac saline solution for injection would be a POM; the licence was pending. The Code prohibited the promotion of POMs to the public. Although the company was aware of its likely classification pending grant of Tor-Bac's marketing authorisation the product was not classified as a POM when the advertisement at issue was published. On this narrow technical point the Panel ruled no breach of the Code.

The Panel, however, considered that the inclusion of the Tor-Bac product pack in an advertisement aimed at the general public prior to the grant of its marketing authorization and when the company knew that it would be classified as a POM meant that high standards had not been maintained; a breach of the Code was ruled.

The Panel considered that the advertisement in The Big Issue in March 2017 promoted Tor-Bac to the public prior to the grant of its marketing authorization which was expected in June 2017. The Panel noted the company's explanation that the packshot had been provided by mistake. In the Panel's view the publication of the advertisement demonstrated a lack of care and awareness of the Code on matters that reflected UK law. The Panel considered that Tor Generics had thus brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

A health professional complained about an advertisement issued by Tor Generics Ltd and published in The Big Issue, 20-26 March 2017. The advertisement provided by the complainant included pack shots of Vitamin D3 capsules, Vitamin A capsules and Tor-Bac 5ml which was described as 'Bacteriostatic saline solution for injection'.

COMPLAINT

The complainant explained that there were no general sale or over-the-counter injectable medicines in the UK. Hence normal saline for injection must be a prescription only product. As The Big Issue magazine was sold by street vendors to the public, the complainant alleged that an advertisement in it for injectable saline was an advertisement for a prescription only medicine to the public, in breach of Clause 26.1.

When writing to Tor Generics the Authority asked it to consider the requirements of Clauses 26.1, 9.1 and 2 of the Code.

RESPONSE

Tor Generics confirmed that Tor-Bac would be a prescription only medicine; the licence was pending with the Medicines and Healthcare products Regulatory Agency (MHRA). Tor Generics submitted that Tor-Bac was manufactured in the EU and was due to launch in June 2017. Due to an oversight on Tor Generics' part, it was included ahead of launch in error, when jpegs for other products were sent for the advertisement compilation and the advertisement was placed in The Big Issue. Tor-Generics stated that it would withdraw the advertisement or 'public information' from The Big Issue from the next edition (end of April) and provided assurance that it would not include the product going forward until all terms via the ABPI had been adhered to. According to Tor-Generics, Tor-Bac was a saline solution aimed at the dental market and was not generally perceived as a generic for generic sale.

Tor Generics confirmed that the jpeg had been taken off any future advertisements in The Big Issue and would not be advertised anywhere in the public press until a licence was obtained and even then only in suitable medical journals.

The company provided a copy of its revised advertisement which referred to Tor Generics and its website. This advertisement did not mention by name or refer to any products.

It appeared from correspondence with a third party that the jpeg for the advertisement at issue was placed by mistake and that Tor Generics currently wanted to keep the advertisement just as a picture of Glastonbury Tor with the company's website address. The company stated that it was happy to support The Big Issue with advertising until its contract finished shortly, but it would be wiser to show no pictures of its products at all.

The company confirmed that the advertisement was sent in error and had been withdrawn as indicated in emails provided. A copy of an email dated 4 April was provided in which the typesetter for The Big Issue was asked to remove the 3 pack shots from the advertisement. In addition, Tor Generics stated that having thought again it might be wise to remove all pack shots for the remaining 2/3 advertisements left in the 12 month agreement.

In a further email to the ABPI, Tor Generics stated that Tor-Bac was not on the market yet. The company submitted that there was not much of a case to answer as Tor Generics was a tiny company and the

product was not available in the UK. A jpeg was loaded incorrectly, and the advertisement was picked up in The Big Issue.

PANEL RULING

The Panel noted Tor Generic's submission that Tor-Bac saline solution for injection would be a prescription only medicine, the licence was pending with the MHRA and the product was due to launch in June 2017. Clause 26.1 prohibited the promotion of prescription only medicines to the public. Although the company was aware of its likely classification pending grant of its marketing authorisation the product was not classified as a prescription only medicine when the advertisement at issue was published. On this narrow technical point the Panel ruled no breach of Clause 26.1 of the Code.

The Panel noted that Clause 3.1 which required that a medicine must not be promoted prior to the grant of the marketing authorization which permits its sale or supply had not been raised with the company as on receipt of the complaint it had not been apparent that the medicine was unlicensed. The Panel therefore made no rulings in that regard.

The Panel noted the requirements of Clauses 3.1 and 26.1. The Panel considered that the inclusion of the Tor-Bac product pack in an advertisement aimed at the general public prior to the grant of its marketing authorization and when the company knew that it would be classified as a prescription only medicine meant that high standards had not been maintained; a breach of Clause 9.1 was ruled.

The Panel considered that the advertisement in The Big Issue in March 2017 promoted Tor-Bac to the public prior to the grant of its marketing authorization which was expected in June 2017. The Panel noted the company's explanation that this matter had arisen as a jpeg file had been provided to the journal by mistake. In the Panel's view the publication of the advertisement demonstrated a lack of care, and awareness of the Code on matters that reflected UK law. The Panel noted that the supplementary information to Clause 2 included promotion prior to the grant of a marketing authorization as an example of an activity that was likely to be in breach of that Clause. The Panel considered that Tor Generics had thus brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

Complaint received **1 April 2017**

Case completed **9 June 2017**

CODE OF PRACTICE REVIEW – August 2017

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

AUTH/2884/10/16	**Clinical Commissioning Group member v Intrapharm**	**Letter to GP practices**	**Breaches Clauses 7.2, 7.4 and 9.1**	**No appeal**	**Page 3**
AUTH/2903/11/16	Director v Novo Nordisk	Clinical trial disclosure (Ryzodeg)	No Breach	No appeal	Page 5
AUTH/2928/1/17 And AUTH/2929/1/17	**Anonymous v Pfizer and Novartis**	**Pharmacovigilance compliance, promotion of an unlicensed indication and breach of undertaking**	**Breaches Clauses 2, 3.2, 7.2, 9.1, 15.9 and 29**	**No appeal**	**Page 13**
AUTH/2930/1/17	**Health professional consultant to a pharmaceutical company v Johnson & Johnson**	**Nicorette advertisement**	**Breaches Clauses 7.2 and 7.10**	**No appeal**	**Page 31**
AUTH/2931/1/17	**Health professional consultant to a pharmaceutical company/Director v Pfizer**	**Online advertisement for a meeting**	**Breach Clause 9.2**	**No appeal**	**Page 34**
AUTH/2933/2/17	**Health professional consultant to a pharmaceutical company v Chiesi**	**Promotion of Fostair**	**Breach Clause 7.2**	**No appeal**	**Page 39**
AUTH/2934/2/17	**Health professional consultant to a pharmaceutical company v Johnson & Johnson**	**Promotion of Nicorette**	**Breach Clause 4.4**	**No appeal**	**Page 44**
AUTH/2936/2/17	Health professional consultant to a pharmaceutical company v Johnson & Johnson	Online Nicorette advertisement	No Breach	No appeal	Page 48
AUTH/2938/2/17	**Sanofi v Novo Nordisk**	**Tresiba leavepiece**	**Four Breaches Clauses 7.2** **Breaches Clause 7.3, 7.4 and 7.8**	**No appeal**	**Page 51**
AUTH/2941/2/17	Health professional consultant to a pharmaceutical company v Merck Sharp & Dohme	Invitation to a web cast	No breach	No appeal	Page 57

AUTH/2942/2/17	Health professional consultant to a pharmaceutical company v Boehringer Ingelheim	Online Spiolto advertisement	No Breach	No appeal	Page 59
AUTH/2945/3/17	Community Pharmacist v GlaxoSmithKline	Resource booklet for pharmacists	No Breach	No appeal	Page 63
AUTH/2946/3/17	Anonymous non contactable v Merck Serono	Conduct of representatives	No Breach	No appeal	Page 67
AUTH/2950/4/17	**Health Professional v Tor Generics**	**Advertisment in the Big Issue**	**Breaches Clauses 2 and 9.1**	**No appeal**	**Page 70**

PMCPA | Prescription Medicines Code of Practice Authority

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

The Code covers the advertising of medicines to health professionals and other relevant decision makers and also covers information about prescription only medicines made available to the public.

It covers:

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

It also covers:

- the provision of information on prescription only medicines to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations
- disclosure of tranfers of value to health professionals and organisations
- joint working between the NHS and pharmaceutical companies
- the use of consultants
- non-interventional studies of marketed medicines
- the provision of items for patients
- the provision of medical and educational goods and services
- grants, donations and benefits in kind to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of three of the four members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. One member of the Panel acts as case preparation manager for a particular case and that member does not participate and is not present when the Panel considers it.

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

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Further information about the Authority and the Code can be found at www.pmcpa.org.uk

Complaints under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 7th Floor, Southside, 105 Victoria St, London SW1E 6QT

telephone 020 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.