NUMBER 91 February 2016

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.

HEAD OF COMMUNICATIONS

The PMCPA is delighted to announce that it has appointed as Head of Communications, Elly Button, who first joined on a short term contract in January 2015. Her previous role was in Strategic Communications at NHS London and before that she worked for the BBC, Shelter and the Audit Commission. Elly can be contacted at ebutton@pmcpa.org.uk or 0207 747 8884.

MHRA HOT TOPICS MEETINGS AND ANNUAL REPORT

The Medicines and Healthcare products Regulatory Agency has published its annual report for 2015. There were five upheld complaints about prescription medicines. This was a decrease from 2014 when twelve complaints were upheld. Two of the 2015 complaints related to unlicensed medicines in development and two concerned misleading claims in advertising for generic medicines. One of these led to the issue of a corrective statement.

The report notes that most companies in this sector use the self-regulatory regime to resolve their concerns. The MHRA fully supports use of the self-regulatory system and inter-company dialogue as a first step in resolving medicines advertising issues where this is appropriate.

The MHRA will continue to work proactively with self-regulatory bodies and others to support self-regulation and ensure consistent high standards. At its annual meeting the MHRA strongly supported self-regulation which had been shown time and again to be effective.

The MHRA also welcomed the forthcoming publication of more information about transfers of value to health professionals and others.

DISCLOSURE DEADLINE – 31 MARCH 2016

In 2016 pharmaceutical companies will disclose details of certain transfers of value made to healthcare professionals (HCPs), other relevant decision makers (ORDMs) and healthcare organisations (HCOs) during 2015 on the ABPI central platform. Further details can be found in the Code (see Clause 24 and others) and on the ABPI website. The disclosure template (available from the PMCPA website) needs to be completed by companies and uploaded by 31 March 2016.

CONTACT THE CASE PREPARATION MANAGER

When a complaint is received by the Authority the papers for that case are prepared by the case preparation manger. The case preparation manager will write to the complainant to acknowledge receipt of the complaint and to the respondent company to inform it of the complaint and request a response. The role of the case preparation manager was established in 2011 to separate the preparation of a complaint from the subsequent adjudication upon it. Paragraph 5.1 of the Constitution and Procedure states that the case preparation manager must not divulge to any other members of the Authority details of matters being processed until formal case papers are provided to the Code of Practice Panel for consideration.

It is important, therefore, if you have any queries about a complaint you have submitted or received, and you have not been informed that the papers have been sent to the Panel, that you contact the case preparation manager for help and not any other member of the Authority.

NEW INDEPENDENT MEMBERS OF THE APPEAL BOARD

Dr Anne Hawkridge and Mrs Natasha Duke have recently been appointed to the Code of Practice Appeal Board as independent members. Both are welcomed by the Authority. Dr Hawkridge joins as a medical member. Dr Hawkridge is currently a general practitioner (GP) principal in Bolton. Dr Hawkridge is also involved with the Royal College of General Practitioners Examination (MRCGP) as a Clinical Skills Assessment Examiner and tutors doctors training to become GPs for Health Education North West. Mrs Duke is an Advanced Nurse Practitioner (ANP) and Independent Non-Medical Prescriber on the Health Sciences Faculty Ethics Committee at the University of Southampton. She is presently a Triage Nurse and ANP at a GP surgery.

CODE OF PRACTICE TRAINING

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

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

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

Thursday 17 May
Tuesday 14 June

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

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

HOW TO CONTACT THE AUTHORITY

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

www.pmcpa.org.uk

Telephone:	020 7747 8880
Facsimile:	020 7747 8881

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or 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.

ROCHE/DIRECTOR v MERCK SERONO

Alleged breach of undertaking

Roche alleged that Merck Serono had breached its undertaking given in Case AUTH/2705/3/14 with regard to a presentation in July 2015 of clinical trial data for Erbitux (cetuximab) to a meeting of the Cancer Drugs Fund (CDF). Roche submitted that, as in the material at issue in Case AUTH/2705/3/14, a September 2013 press release, clinical data had not been presented in context of other data or its (lack of) statistical significance. Roche alleged a breach of Clause 2.

The licence for Erbitux changed in December 2013 such that it was now indicated, *inter alia*, for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer (mCRC). When the press release was issued in September 2013, the licence was wider in that Erbitux was for use in patients with EGFR-expressing, KRAS wild-type mCRC.

Roche marketed Avastin (bevacizumab) which was indicated, *inter alia*, in combination with chemotherapy for the treatment of adults with metastatic carcinoma of the colon or rectum.

As the complaint was about an alleged breach of undertaking, it was taken up by the Authority in the name of the Director as the Authority was responsible for ensuring compliance with undertakings.

Roche stated that Merck Serono's presentation in an open forum of other companies, lay members of cancer charities and clinicians, began with an overview of the data it proposed to cover. This included its two registration studies for cetuximab in combination chemotherapy (CRYSTAL and OPUS) and data from the FIRE-3 and CALGB studies.

FIRE-3 was presented first and one slide showed the overall survival but did not explain that this was an exploratory secondary endpoint nor that the study failed to meet its primary endpoint. There were no other slides presented for this study to better understand how the patients in this analysis were arrived at, including whether the analysis was appropriately powered, and whether the correct statistical analysis was used.

Roche stated that as previously ruled in breach of the Code, not providing this study specific information was misleading for the audience regarding the significance of the data. In contrast to Case AUTH/2705/3/14, where the press release included a clarifying statement that the data was exploratory, the presentation did not make this clear.

The FIRE-3 data was also not placed in context of the CALGB data which was designed to look at the specific question regarding the comparison [of cetuximab vs bevacizumab]. Regarding the Merck Serono defence at appeal of the significance of data included in the summary of product characteristics (SPC), Roche noted that the CALGB data was included in the cetuximab SPC immediately below and juxtaposed to the FIRE-3 data: this served to represent the FIRE-3 data in the full context of all clinical data available for cetuximab in this indication.

Roche noted that the CALGB data was included later in the presentation but the scientifically important aspect of discordant results with FIRE-3 was again omitted. The original registration data for cetuximab for this indication was presented later.

At the end of the presentation the chairman of the CDF panel asked the rest of the panel to disregard the portion that focused on the head-to-head studies between Avastin and cetuximab because of the discordant results between FIRE-3 and CALGB data. The chairman also stated that the presentation of the data in comparison to Avastin was not necessary, since this was no longer funded in England for the patient population being discussed. This comment, and the inclusion in the presentation, implied that the CDF panel believed Merck Serono had included an unsubstantiated comparison to a Roche medicine, and misled as to the correct clinical context for the use of cetuximab.

Roche noted that whereas the press release at issue in Case AUTH/2705/3/14 was targeted towards a medical audience and the broader press, the presence of lay observers from cancer charities ought to be considered, this had again occurred in an intentionally non-promotional context, high standards needed to be maintained. In any context, and at the heart of Case AUTH/2705/3/14, all data wherever used or presented had to be fair, balanced, accurate, in context, and not misleading.

The detailed response from Merck Serono is given below.

With regard to Case AUTH/2705/3/14 the Panel considered that the press release heading, 'Merck Serono's Erbitux Significantly Extends Survival to 7.5 Months in mCRC Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study', was not a fair reflection of the overall data; it had not been placed within context of the study's primary outcome. The reference to the study's failure to meet its primary endpoint appeared in the third paragraph on page 2 and was insufficient to counter the heading. Insufficient information had been provided to enable the reader to properly assess how much weight to attach to the secondary endpoint findings. The heading was therefore misleading as alleged and the Panel ruled a breach of the Code which was upheld on appeal.

In relation to the bullet point in the press release which read, 'New data from a pre-planned analysis

of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 months to 33.1 months (p=0.011) …' the Panel considered that its general comments above in relation to the heading of the press release were relevant. The sub-group analyses had not been placed in context of the study's failure to achieve its primary endpoint. In addition, it was not clear at the outset that the data was from a pre-planned exploratory analysis. The only reference to this was on the second page and there was no explanation that no confirmatory clinical conclusions could be drawn from such an analysis. In the Panel's view the press release invited the reader to draw such conclusions. Exploratory analyses should not be used as the basis for a robust comparison of medicines. The material should be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. The Panel considered that the bullet point was misleading as alleged and ruled a breach of the Code which was upheld on appeal.

Turning to the present case, Case AUTH/2789/8/15, the Panel noted Merck Serono's submission about the differences between the press release and the material now at issue ie a presentation made to the CDF panel to support the continued use in England of Erbitux in the treatment of mCRC. A copy of the presentation, together with a much larger body of material, had to be submitted to the CDF panel ahead of the meeting. Merck Serono had 15 minutes on the day to make its presentation which, in the Panel's view, it would do on the assumption that the CDF panel members had read the material previously submitted. Although Roche submitted that others including lay members of cancer charities were present at the meeting, the Panel considered that the presentation was, nonetheless, directed solely at the CDF panel.

The Panel noted that slide 2 of the presentation set out the therapeutic indication for Erbitux and highlighted that it was for use in patients with RAS wild-type mCRC. Slide 4 illustrated how the Erbitux licence had evolved over time. Up until 2008, Erbitux was licensed for use in all mCRC patients based on the results from the CRYSTAL and OPUS studies. From 2008 until January 2014 Erbitux was licensed for use in patients with KRAS wild-type mCRC (approximately 55% of all mCRC patients) based on the results from, *inter alia*, FIRE-3. From January 2014 the licence was further restricted to patients with RAS wild-type mCRC (approximately 45% of all mCRC patients) and it was clearly stated on the slide that this was as a result of, *inter alia*, a subgroup analysis of the FIRE-3 study.

The Panel noted that Roche referred in particular to slide 10 headed 'FIRE-3: median Overall survival: RAS wild-type patients' which depicted the probability of overall survival over time. The data showed a benefit for FOLFIRI plus Erbitux vs FOLFIRI plus Avastin. It was made clear that overall survival was a secondary endpoint and hazard ratios and confidence intervals were given. Two separate footnotes in very small print stated that the data was in 'KRAS and NRAS exon 2, 3 and 4 wild-type' and that 'Erbitux (cetuximab) is only indicated in RAS wild-type mCRC (KRAS & NRAS wild-type)'. The Panel noted that the data for the RAS wild-type subgroup from the FIRE-3 study was now included in the Erbitux SPC. In that regard the data had been accepted by the regulatory authorities. In the Panel's view, the patient population suitable for treatment with Erbitux was clearly defined at the outset of the presentation together with an explanation of the clinical data which supported its use in successively restricted populations over time. Subsequent slides which referred to the results of FIRE-3 referred to 'RAS wild-type patients' which in the Panel's view, the audience to whom the presentation was addressed ie the CDF panel, would realise was a subset of FIRE-3. Slide 20 clearly stated the primary endpoint of the FIRE-3 study showed no statistical difference between Erbitux plus FOLFIRI vs Avastin plus FOLFIRI in the intention to treat (ITT) population of KRAS wild-type mCRC patients. The Panel considered it would have been helpful if this information appeared earlier in the presentation.

The Panel considered that there were important differences between the press release and the materials currently at issue and the audiences to whom they were directed. The Panel noted that since the press release had been issued (September 2013), the marketing authorization for Erbitux had changed significantly in that the licensed indication was now restricted for use in patients with RAS wild-type mCRC. As the FIRE-3 study had progressed it became clear that patients with RAS wild-type mCRC responded better to therapy than those with RAS mutations. To support the restricted licence, the Erbitux SPC (last revised June 2014) now included results from the FIRE-3 study with regard to the RAS wild-type population (n=342) and not the ITT group (n=592). In that regard the Panel did not consider it unreasonable for Merck Serono only to refer to the smaller group; indeed to have referred to the ITT group might have been misleading as many of those patients would now not be suitable for Erbitux treatment.

The Panel noted the change in the marketing authorization for Erbitux in December 2013 and overall considered that the content of the presentation at issue, the context in which it was used and the audience to whom it was directed were all significantly different to the press release considered in Case AUTH/2705/3/14 such that it was not closely similar and thus the presentation was not caught by the undertaking previously given. No breaches of the Code were ruled including Clause 2.

Roche Products Ltd alleged that Merck Serono Limited had breached its undertaking given in Case AUTH/2705/3/14 with regard to the presentation of clinical trial data for Erbitux (cetuximab). The material at issue in Case AUTH/2705/3/14 was a press release; the material now at issue was a presentation given to the Cancer Drugs Fund (CDF).

The licence for Erbitux changed in December 2013 such that it was now indicated, *inter alia*, for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer (mCRC). When the press release was issued in September 2013, the licence

was wider in that Erbitux was for use in patients with EGFR-expressing, KRAS wild-type mCRC.

Roche marketed Avastin (bevacizumab) which was indicated, *inter alia*, in combination with chemotherapy for the treatment of adults with metastatic carcinoma of the colon or rectum.

As the complaint was about an alleged breach of undertaking, it was taken up by the Authority in the name of the Director as the Authority was responsible for ensuring compliance with undertakings.

COMPLAINT

Roche explained that as part of the CDF's review of a number of medicines that were available for funding in England, the CDF panel held two days of meetings, 29 and 30 July, during which pharmaceutical companies could present clinical data to support the continued use of the medicine. This was the second such panel meeting and the pharmaceutical company engagement process was the same both times. Merck Serono presented the same clinical case at the original meeting in December and therefore knew the format of the meeting and the appropriateness of data for inclusion in the presentation.

To facilitate this meeting, companies were invited to submit supporting clinical data by 16 July; such data would subsequently be presented at the meeting. It was not mandatory to submit a presentation or to present, and not all companies took up this opportunity.

The presentations, which were to last approximately five minutes, were made in an open forum consisting of other companies, lay members of cancer charities, and clinicians (the full attendee list was not publicly available). The CDF panel consisted of a sub-committee of Clinical Reference Group members. Following the presentation, the panel could ask questions and the company could respond to those. The panel members took notes to help to inform their decision making in a subsequent closed meeting, where a clinical score would be attributed to each medicine per specific indication. The clinical score was critical in determining whether a medicine would stay funded for use in England beyond around December 2015. Therefore, the presentation of the clinical data was of the highest importance given the public scrutiny; it must of course be factually accurate, not misleading, able to be substantiated and placed within the correct clinical context of treatment within the UK and England.

Roche noted that Merck Serono provided evidence for cetuximab in accordance with its CDF listing.

Since companies could not provide their presentation on the day, and to follow process, Merck Serono sent its slides to the CDF panel before the presentation. Printed copies of the presentation were provided for the panel before the meeting opened, and separate from the verbal presentation.

Roche noted that a member of Merck Serono medical team presented the cetuximab data and began by discussing the first-line mCRC data in combination with chemotherapy.

Roche alleged a breach of Clause 29 with regard to the undertaking given in Case AUTH/2705/3/14 in respect of the content of the pre-submitted slides and the omission of context, the omission of either the CALGB interim analysis (no statistical significance) or the subsequent final analysis (still no statistical difference), and the misleading over-emphasis of the clinical data during the presentation.

Roche noted that in Case AUTH/2705/3/14 a breach of Clause 2 was ruled, upheld at appeal, given the nature of the multiple breaches relating to the presentation of the FIRE-3 data in a press release. Roche asserted that the same actions and omissions had occurred in an exceptionally high profile forum which could only reduce confidence in the pharmaceutical industry.

Roche stated that Merck Serono opened its presentation with an overview of the data it proposed to cover. This included its two registration studies for cetuximab in combination with irinotecan and oxaliplatin-based combination chemotherapy respectively (CRYSTAL and OPUS). Merck Serono also stated that it was going to include data from the FIRE-3 and CALGB studies.

The first study presented was FIRE-3 (rather than the registration study, CRYSTAL) and one slide showed the overall survival Kaplan-Meier curve without any qualification either on the slide, or verbally, that this was an exploratory secondary endpoint for a study, nor that it did not meet its primary endpoint. There were no other slides presented for this study to better understand how the patients in this analysis were arrived at, including whether the analysis was appropriately powered, and whether the correct statistical analysis was used, since the primary endpoint was negative.

As previously ruled in breach of Clause 7.2, not providing this study specific information was misleading for the audience regarding the significance of the data. An important additional contrast to Case AUTH/2705/3/14, where the press release included a statement to clarify that the data was exploratory, albeit significantly distant from the prominent statement, in this presentation neither verbally nor on the slides was this contextualizing point made clear.

The FIRE-3 data was also not placed in context of the CALGB data which was designed to look at the specific question regarding the comparison [of cetuximab vs bevacizumab]. Regarding the Merck Serono defence at appeal of the significance of data included in summary of product characteristics (SPC), Roche noted that the CALGB data was included in the cetuximab SPC immediately below and juxtaposed to the FIRE-3 data: this served to represent the FIRE-3 data in the full context of all clinical data available for cetuximab in this indication.

Roche noted that the CALGB data was included later in the presentation but the scientifically important aspect of discordant results with FIRE-3 was a second time omitted and not highlighted. The original registration data for cetuximab for this indication was presented later.

At the end of the presentation for first-line mCRC, the chairman of the CDF panel, an oncologist, asked the rest of the panel to disregard the portion that focused on the head-to-head studies between Avastin and cetuximab because of the discordant results between FIRE-3 and CALGB data.

The chairman also stated that the presentation of the data in comparison to Avastin was not necessary, since this was no longer funded in England for the patient population being discussed. The impression left by this comment, and the inclusion in the presentation, was that the panel believed Merck Serono had included this to make an unsubstantiated comparison to a Roche medicine, and to mislead as to the correct clinical context for the use of cetuximab.

In Case AUTH/2705/14 breaches were ruled. Roche was concerned once again that high standards were not upheld with regard to this presentation in an area where Merck Serono had previously been found in breach and as the chairman had to request the CDF panel to disregard information this brought discredit to and reduced confidence in the pharmaceutical industry.

Roche submitted that someone from another pharmaceutical company who was present, and very closely aware and following the therapy area and science, spoke to a Roche individual at the meeting, to state that it was clear that Merck Serono's actions were exactly those described in Case AUTH/2705/3/14 as related to misleading and over-emphasising the clinical significance of FIRE-3, and not placing it in context for the audience. The individual also highlighted that a breach of Clause 2 was ruled, and he/she were extremely surprised to see the same actions happening in this high-profile setting.

Roche noted that whereas the press release at issue in Case AUTH/2705/3/14 was targeted towards a medical audience and the broader press, the presence of lay observers from cancer charities ought to be considered, this had again occurred in an intentionally non-promotional context, but the high standards required by Clause 9.1 still needed to apply. In any context, and at the heart of Case AUTH/2705/3/14, all data wherever used or presented had to be fair, balanced, accurate, in context, and not able to mislead.

Roche stated that in conclusion, a pharmaceutical company's presentation of data, when relied upon by national public organisations, must be able to withstand the highest level of public scrutiny and scientific rigor. This required maintaining the highest standards as set out in Clause 9.1, identified as a Code breach relating to the presentation of the FIRE-3 data, and here the undertaking to maintain high standards Roche asserted was a breach of Clause 29. It was both disappointing and fortuitous that the chairman of the panel publicly asked panel members to disregard this aspect of data presentation.

RESPONSE

Merck Serono stated that it took compliance with the Code extremely seriously and understood the importance of complying with undertakings given under the Code. The company provided details of the actions it took to comply with the undertaking in Case AUTH/2705/3/14. This included, without limitations, withdrawing all materials in breach of the Code as a result of the rulings in that case, ensuring all subsequent promotional materials provided enough information to ensure the reader could form a rational opinion of the use of the medicine, by training personnel on the details of the case and issuing guidance to reduce the risk of anything similar occurring in the future.

Merck Serono did not believe that the presentation it gave at the CDF or any of the materials and submissions sent to the CDF in preparation for the meeting breached the undertaking given in Case AUTH/2705/3/14 or Clauses 2 and 9.1 of the Code as outlined below.

1 The licence for Erbitux had changed materially since Case AUTH/2705/3/14

When the press release was published, Erbitux's marketing authorization was not restricted to patients with RAS wild-type mCRC. The Appeal Board noted in its ruling that 'The analysis at issue in the press release involved only the RAS wild-type patients (n=342) and not the original ITT populations (n=592). Although the Erbitux marketing authorization had been restricted to patients with RAS wild-type mCRC, this was not the case when the press release was issued on 28 September 2013'. The rulings in Case AUTH/2705/3/14 were therefore made in that context.

Merck Serono stated that the current complaint must been seen in light of the marketing authorization in place in July 2015 when the submission and presentation was made to the CDF.

In December 2013, the indication was restricted to patients who had RAS wild-type mCRC as new safety information had become available from a retrospective subset analysis of data from a randomised, multicentre phase II study (OPUS) of cetuximab plus (oxaliplatin-containing) FOLFOX4 chemotherapy vs FOLFOX4 alone in people with previously untreated mCRC. In the OPUS study, patients with RAS mutations who were randomly assigned cetuximab plus FOLFOX4 had inferior survival, progression-free survival and objective response rates than did those assigned FOLFOX4 alone. As a consequence of this information, in February 2014 the CDF reimbursement for Erbitux in the treatment of mCRC was restricted to RAS wild-type patients only.

Further post-hoc analyses of the interaction between RAS mutation status and treatment outcome in the pivotal first-line phase III cetuximab trials CRYSTAL and FIRE-3 (the study at issue in the press release) were still ongoing when the indication was amended in December 2013. When completed, these analyses were included in the Erbitux SPC in July

2014, demonstrating that their validity and clinical relevance was *de facto* accepted by the regulators. Section 5.1 of the SPC did not present the intention to treat (ITT) population results for these studies including FIRE-3 (the study at issue), but summarised the efficacy results in tables which compared only the RAS wild-type population (as per indication) with the RAS mutant population (not indicated). The tables started with overall survival, then progression free survival and then objective response rate and displayed duration (months), hazard ratios, their confidence intervals and associated p values. There was no discussion of the failed primary endpoint in the ITT population of FIRE-3.

As such, the results of the ITT population were not directly relevant as many of the ITT population were no longer within the licensed indication for Erbitux. Merck Serono believed that the data it presented at the CDF meeting was not misleading as it was aligned with the Erbitux SPC and the specific CDF reimbursement indication that Merck Serono had been invited to defend. ITT results were simply not under consideration by the CDF.

Merck Serono thus refuted the alleged breach of undertaking (Clause 29) as the licensed indication for Erbitux and the data to support it as described in the SPC was materially different to that which was in place when the press release at issue in Case AUTH/2705/3/14 was issued. For the same reason, Merck Serono did not believe that the presentation given to the CDF or any of the materials submitted to the CDF breached Clauses 2 or 9.1 as high standards were maintained and therefore they did not bring discredit upon, or reduce confidence in, the pharmaceutical industry.

2 Meaningful difference in the materials at issue

Merck Serono noted that the press release at issue in Case AUTH/2705/3/14 was distributed through usual channels to health journalists interested in oncology with the expectation they would share this news story with their readership, many of whom would be the general public.

The presentation now at issue was part of a submission to a national public health organisation, the Chemotherapy Clinical Reference Group, which was an NHS England committee responsible for administering and recommending which medicines were funded via the CDF and made available to NHS patients in England. This body, which occupied a health technology assessment (HTA) role for cancer medicines, assessed cancer medicines if they had been rejected or not yet reviewed by NICE. It did so via a formal process, and its decisions were published. It did not procure medicines. The CDF current standard operating procedures were provided. Merck Serono submitted that as such, the CDF was analogous to bodies described in Clause 1.2 of the Code and both the presentation and the submission to the CDF fell outside the scope of the Code. For this reason the presentation was not considered promotional and was not certified.

The CDF panel meeting was part of an ongoing process designed to refine the list of medicines authorised for reimbursement through the CDF in England. The CDF panel members had been selected by NHS England for their expertise, judgment and competence in defining criteria and evaluating the available clinical evidence to judge which oncology medicines best met those criteria and warranted investment of NHS expenditure to improve patient outcomes. Companies were invited to defend their current listed status through the submission of an extensive dossier of evidence, with a form aligned to a scoring system designed by the CDF and supported by clinical studies and a full reference pack (a copy was provided). The panel was familiar with the evidence for Erbitux in first-line treatment of mCRC in RAS wild-type patients as it had last assessed it in December 2014, with comparable data being used to support the clinical review.

Following the written submission each company was invited to defend its indications. The presentation time was limited to 5 minutes per indication approved. In the case of Erbitux, 15 minutes were allocated to defend the three CDF approved mCRC indications. Thus the presentation itself formed a limited part of the extensive submission and assessment process. Content of the presentation was focused on efficacy criteria determined by the CDF as of critical importance to determine their score of clinical effectiveness, notably median overall survival, median progression free survival endpoints, safety and quality of life.

Merck Serono submitted that meeting attendees were restricted to CDF panel members, who were the intended audience for the presentation, expert pharmaceutical company personnel and their representatives eg physicians or patient groups who were expert in the field to present their data or add expert opinion. Companies had to register their attendees and staff outside the meeting room ensured only those authorised to attend could do so. A list of CDF panel members who attended the meeting was provided.

Additionally, unlike the press release in Case AUTH/2705/3/14, the presentation now at issue was delivered by a company expert who could talk through the data, clarify any issues and answer the panel's questions. The panel members were all versed in evidence review and familiar with the data as they last reviewed it in December 2014. The panel had received all clinical trial data in advance and were provided with the current Erbitux SPC.

Merck Serono stated that in its view, the presentation and submission provided were appropriate and not misleading given the purpose and context of the meeting, and the knowledge of the members of the CDF panel and other attendees at the meeting, and given that the information presented or provided by Merck Serono was in line with the Erbitux SPC and the CDF listing under discussion. Therefore Merck Serono believed it had complied with Clauses 2, 9.1 and 29.

3 Content of the presentation

Merck Serono stated that the language used in the press release and its tone were substantially different

from the content of the presentation now at issue. The content of the CDF presentation was factual, accurate and not misleading. The presentation also formed part of a larger written submission to defend Erbitux's listing in the CDF for first-line use in RAS wild-type mCRC, in combination with either irinotecan-based therapy or FOLFOX.

Merck Serono noted Roche's assertion that Merck Serono had breached its undertaking because of the content of the slides, the omission of context, the omission of either the CALGB interim analysis (no statistical significance) or final analysis (still no statistical difference) and the misleading over-emphasis of the clinical data during the presentation.

As discussed above, the licensed indications for Erbitux when the CDF submission took place and the context and purpose in which the presentation at issue was made, were materially different from those at the time of the press release. The presentation explicitly focused on treatment of RAS wild-type mCRC patients in line with the licensed indication for Erbitux. This was made clear in the first slide of the presentation, and reinforced in subsequent slides.

The next slide summarised the CDF score applied to the evidence, and made clear exactly which population was being discussed (column headed 'biomarker defined population' with clear RAS wild-type against all first-line studies, and KRAS wild-type against third or fourth). The application of a score by the CDF panel was done in January 2015 which confirmed that the panel had already considered these data. The CDF panel was therefore not only versed in oncology data assessment, but also already familiar with these particular data and all the other evidence submitted in the dossier from the previous submission.

Several studies were discussed in the presentation. For each of them, relevant data in the licensed, RAS wild-type patient population had been achieved through retrospective sub-analyses of studies originally conducted in a wider patient population. Slide 4 highlighted this limitation of the data and explained the relevance of biomarkers and how they informed the interpretation of Erbitux data and its progressively restricted indication. Using the phrase 'subpopulation' made it clear that this was not the ITT population, the results of which were no longer relevant as they included patients who were not within the licensed indication and not being considered by the CDF. Slide 5 highlighted the extent to which this restriction of patient population consistently improved hazard ratios across a number of studies of EGFR inhibitors while also showing that original ITT patient populations were in broader patient sets.

As discussed above, these subgroup analyses had been in the SPC without the need to include the ITT results, which was not the case when the press release was issued in September 2013. This meant that information which could have been construed as misleading at the time should not be construed in the same way today.

Merck Serono submitted that a considerable proportion of the limited time available to present the data was devoted to ensuring a clear understanding that the clinical data subsequently discussed was derived from subgroup analyses of larger studies. In discussion at the end of the presentation, it was confirmed that the RAS wild-type population analyses were retrospective and FIRE-3 was highlighted in this context.

In contrast to Roche's assertion that FIRE-3 was the first study presented, data from the pivotal CRYSTAL study was the first data presented in slide 6. It was used to exemplify the progressive restriction of the Erbitux indication and its concomitant positive effect on risk benefit for the target patient population.

When endpoints for the FIRE-3 study were introduced, all relevant efficacy measures, and their degree of significance were shown (slide 8). When discussing the study design (slide 9), the original patient population, and protocol amendment, primary and secondary endpoints were all listed. After these two slides, the overall survival data in the RAS wild-type subset of patients was then discussed (slide 10) as overall survival was a particularly important endpoint to the CDF, and this subset was the licensed and reimbursed patient population in the UK.

FIRE-3 was subsequently mentioned in slide 20 with the intent to support a consistency of overall survival for Erbitux in combination with chemotherapy in the RAS wild-type subset across a range of studies. In this summary slide, the initial patient population, the primary endpoint and lack of a statistically significant difference were clearly referenced.

Merck Serono noted that Roche asserted that FIRE-3 data were not placed in context of the CALGB data yet it was presented on slide 4, slide 8 (combination with FOLFIRI), slides 15, 17, 18 (combination with FOLFOX) and in the summary slide 20. In each slide, the data were presented factually with appropriate endpoints and statistical analyses represented to allow relevant assessment. Roche's submission that this data was not present was inaccurate.

Merck Serono further noted that Roche asserted that the chairman of the CDF panel asked the panel to disregard the portion that focused on the head-to-head studies between Erbitux-based treatment and bevacizumab-based treatment because of the discordant results between FIRE-3 and CALGB data; Roche believed the impression was that Merck Serono had included this to make an unsubstantiated comparison with a Roche medicine and to mislead as to the correct clinical context for the use of cetuximab although it had provided no evidence for this assertion.

Merck Serono stated that it had a very different impression of commentary and discussion at the end of the presentation. The initial comment from the panel chairman reminded the panel of the limitations of the data which had been openly discussed in the presentation, and highlighted the heightened relevance of direct comparisons with

chemotherapy alone rather than to bevacizumab, as first-line regimens that included bevacizumab in combination with chemotherapy were no longer treatment options in this patient population as they had been removed by the CDF in the December 2014 prioritisation exercise. Finally, the discussion then gave Merck Serono the opportunity to reinforce that data analyses presented were retrospective (including, but not limited to FIRE-3) and to clarify the ongoing NICE assessment of these data and the relevance of Erbitux in other lines of therapy.

Merck Serono submitted that in summary the presentation focused on data which supported the CDF score for the listing under review and took a factual, balanced tone. That the RAS wild-type population analyses for all presented studies was retrospective, was discussed. CRYSTAL, rather than FIRE-3 was the first study for which data was presented. Relevant endpoints, statistical analysis and study design features for the licensed population were included to allow appropriate assessment of the data. CALGB/SWOG data was featured throughout the presentation, with appropriate endpoints and statistical analyses represented to allow relevant assessment. Limitations of the data were appropriately highlighted, both during the presentation and in the discussion. Any comparison made was evidence based and supported by clinical data. Similarly, Merck Serono could see no evidence of misleading the CDF panel as to the correct clinical context for the use of cetuximab as the presentation clearly focused on the licensed indication which was repeatedly listed on the slides.

4 Conclusion

Merck Serono denied the alleged breach of the undertaking given in Case AUTH2705/3/14. It believed it had maintained the high standards set out in Clause 9.1. In the context of a non-promotional meeting, which had a clearly defined format and purpose as set out and solicited by the CDF, the content of the presentation at issue was appropriate, factual, accurate and not misleading. The CDF panel was versed in its field and able to fully understand the data as presented. The presentation ensured the specific subpopulation of mCRC patients for whom Erbitux was indicated was clear and also how that subpopulation was derived though RAS testing on the original trial populations. The presentation, which formed part of a wider submission, was in line with the Erbitux SPC and the CDF listing.

Further, Merck Serono submitted that it approached its obligations under the Code with the utmost seriousness, as demonstrated by its remedial actions following the previous breach.

Merck Serono refuted Roche's allegations that it had acted in breach of Clauses 2, 9.1 and 29 of the Code.

PANEL RULING

The Panel noted that an undertaking was an important document. Companies had to give an undertaking that the material in question and any similar material, if not already discontinued or no longer in use, would cease forthwith and give an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the material previously at issue in Case AUTH/2705/3/14 was a press release which had been sent to medical and pharmaceutical titles, health journalists at national print and online titles and freelance health journalists. The Panel considered that the heading, 'Merck Serono's Erbitux Significantly Extends Survival to 7.5 Months in mCRC Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study', was not a fair reflection of the overall data; it had not been placed within context of the study's primary outcome. The reference to the study's failure to meet its primary endpoint of objective response rate based on investigators' read in patients with KRAS EXON 2 wild-type tumours appeared in the third paragraph on page 2 and was insufficient to counter the heading. Insufficient information had been provided to enable the reader to properly assess how much weight to attach to the secondary endpoint findings. The heading was therefore misleading as alleged and the Panel ruled a breach of the Code which was upheld on appeal.

In relation to the bullet point in the press release which read, 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 months to 33.1 months (p=0.011) …' the Panel considered that its general comments above in relation to the heading of the press release were relevant. The sub-group analyses had not been placed in context of the study's failure to achieve its primary endpoint. In addition, it was not clear at the outset that the data was from a pre-planned exploratory analysis. The only reference to this was on the second page and there was no explanation that no confirmatory clinical conclusions could be drawn from such an analysis. In the Panel's view the press release invited the reader to draw such conclusions. Exploratory analyses should not be used as the basis for a robust comparison of medicines. The material should be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. The Panel considered that the bullet point was misleading as alleged and ruled a breach of the Code which was upheld on appeal.

Turning to the present case, Case AUTH/2789/8/15, the Panel noted Merck Serono's submission about the meaningful differences between the press release and the material now at issue in Case AUTH/2789/8/15 ie a presentation made to the CDF panel to support the continued use in England of Erbitux in the treatment of mCRC. A copy of the presentation, together with a much larger body of material, had to be submitted to the CDF panel ahead of the meeting. Merck Serono had 15 minutes on the day to make its presentation which, in the Panel's view, it would do on the assumption that the panel members had read the material previously submitted. Although Roche submitted that others including lay members of cancer charities were present at the meeting, the Panel considered that the

presentation was, nonetheless, directed solely at the CDF panel.

The Panel noted that slide 2 of the presentation set out the therapeutic indication for Erbitux and highlighted that it was for use in patients with RAS wild-type mCRC. Slide 4 illustrated how the Erbitux licence had evolved over time. Up until 2008, Erbitux was licensed for use in all mCRC patients based on the results from the CRYSTAL and OPUS studies. From 2008 until January 2014 Erbitux was licensed for use in patients with KRAS wild-type mCRC (approximately 55% of all mCRC patients) based on the results from, *inter alia*, FIRE-3. From January 2014 the licence was further restricted to patients with RAS wild-type mCRC (approximately 45% of all mCRC patients) and it was clearly stated on the slide that this was as a result of, *inter alia*, a subgroup analysis of the FIRE-3 study.

The Panel noted that Roche referred in particular to slide 10 headed 'FIRE-3: median Overall survival: RAS wild-type patients' which depicted the probability of overall survival over time. The data showed a benefit for FOLFIRI plus Erbitux vs FOLFIRI plus Avastin. It was made clear that overall survival was a secondary endpoint and hazard ratios and confidence intervals were given. Two separate footnotes in very small print stated that the data was in 'KRAS and NRAS exon 2, 3 and 4 wild-type' and that 'Erbitux (cetuximab) is only indicated in RAS wild-type mCRC (KRAS & NRAS wild-type)'. The Panel noted that the data for the RAS wild-type subgroup from the FIRE-3 study was now included in the Erbitux SPC. In that regard the data had been accepted by the regulatory authorities. In the Panel's view, the patient population suitable for treatment with Erbitux was clearly defined at the outset of the presentation together with an explanation of the clinical data which supported its use in successively restricted populations over time. Subsequent slides which referred to the results of FIRE-3 referred to 'RAS wild-type patients' which in the Panel's view, the audience to whom the presentation was addressed ie the CDF panel, would realise was a subset of FIRE-3. Slide 20 clearly stated the primary endpoint of the FIRE-3 study showed no statistical difference between Erbitux plus FOLFIRI vs Avastin plus FOLFIRI in the ITT population of KRAS wild-type mCRC patients. The Panel considered it would have been helpful if this information appeared earlier in the presentation.

The Panel considered that there were important differences between the press release and the materials currently at issue and the audiences to whom they were directed. The Panel noted that since the press release had been issued (September 2013), the marketing authorization for Erbitux had changed significantly in that the licensed indication was now restricted for use in patients with RAS wild-type mCRC. As the FIRE-3 study had progressed it became clear that patients with RAS wild-type mCRC responded better to therapy than those with RAS mutations. To support the restricted licence, the Erbitux SPC (last revised June 2014) now included results from the FIRE-3 study with regard to the RAS wild-type population (n=342) and not the ITT group (n=592). In that regard the Panel did not consider it unreasonable for Merck Serono only to refer to the smaller group; indeed to have referred to the ITT group might have been misleading as many of those patients would now not be suitable for Erbitux treatment.

The Panel noted the change in the marketing authorization for Erbitux in December 2013 and overall considered that the content of the presentation at issue, the context in which it was used and the audience to whom it was directed were all significantly different to the press release considered in Case AUTH/2705/3/14 such that it was not closely similar and thus the presentation was not caught by the undertaking previously given. No breach of Clause 29 was ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2 of the Code.

During its consideration of this case the Panel noted Merck Serono's submission that the CDF was analogous to bodies listed in an exemption to Clause 1.2 (NICE, the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC)) and as such the presentation and the submission to the CDF fell outside the scope of the Code; the presentation was not considered promotional and was not certified. The Panel noted that Clause 1.2 of the Code provided that information supplied by pharmaceutical companies to national public organisations, such as NICE, the AWMSG and the SMC was exempt from the Code provided it was factual, accurate and not misleading. The Panel noted that the CDF panel was a subgroup of the Chemotherapy Clinical Reference Group; neither was listed in the exemption to Clause 1.2. Although the list was not exhaustive and other closely similar bodies might be recognised as national public bodies, in the Panel's view the exemption should be narrowly construed. The Panel noted Merck Serono's submission that the Chemotherapy Clinical Reference Group did not procure medicines. The Panel noted, however, that according to the CDF standard operating procedures, the role of the CDF panel was to manage the CDF on behalf of the Chemotherapy Clinical Reference Group. The CDF was intended to pay for the procurement of medicines. The CDF panel would monitor expenditure and support the management of the CDF budget to maximise overall clinical value to NHS patients and value for money to NHS England. Given its role, the Panel queried whether the CDF panel was a national public organisation similar to those listed in the exemption to Clause 1.2 and thus whether the presentation and submission ought to have been certified. The Panel requested that Merck Serono be advised of its concerns in this regard.

Complaint received **14 August 2015**

Case completed **3 November 2015**

CASE AUTH/2793/9/15

CLINICAL PHARMACIST v ASTRAZENECA

Identifying patients suitable for Forxiga treatment

A clinical pharmacist complained about an AstraZeneca leavepiece about how to create a clinical system search to identify patients suitable for treatment with Forxiga (dapagliflozin).

Forxiga was indicated in adults with type 2 diabetes to improve glycaemic control as monotherapy when diet and exercise alone did not provide adequate glycaemic control in patients for whom use of metformin was considered inappropriate due to intolerance. It was also indicated in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, did not provide adequate glycaemic control.

The leavepiece was entitled '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. The front page included 'FORXIGA is not indicated for weight loss and is not recommended for use in patients with an [eGFR] < 60 mL/min/1.73m^2. FORXIGA is not licensed for use with thiazolidinedione or GLP-1 agonists'.

The complainant alleged that the search instructions were potentially misleading and could easily identify patients who would not be suitable for treatment. The instructions showed how to add criteria for body mass index (BMI), glomerular filtration rate (GFR) and glycosylated haemoglobin (HbA1c). In all cases a clinical code was added with a qualifying value. However, no time restriction was added to qualify these values. The complainant explained the flaw. Patients were supposed to have an uncontrolled HbA1c to be suitable for treatment so those with an HbA1c above 58 should be identified. However, the value should also be the most recently recorded. A patient with an HbA1c of 48 now who had previously had an HbA1c of 63 should not be included in the final search. However, by applying the instruction as specified they would be included for consideration.

The complainant alleged that whilst he/she hoped that a clinical review would subsequently deem the patient as inappropriate for treatment, the search instructions could be construed as misleading by including such patients. By creating a sub-optimal search the usual high standards demonstrated by the pharmaceutical industry had not been maintained.

The detailed response from AstraZeneca is given below.

The Panel noted that the search was described in 9 steps: Setup initial search; Add Age Range to Search; Add Read Code to Search; Add Medication to Search; Add BMI to Search; Add HbA1c to search; Add GFR to search; Save and Run Report; and Build Report Output. Each step included detailed instructions and some included screenshot examples.

The Panel noted the order of the search criteria, age, read code, and medication were followed by BMI before selecting HbA1c and GFR. The report was then run (Step 8). Step 9, Build Report Output, instructed users to add BMI (22K) and value ≥ 25 before adding columns for HbA1c and GFR but unlike BMI no values were listed for these two criteria at this step in the description in the leavepiece. In the example screenshot of the completed report which appeared below step 9, the column of BMI values was fully populated for each identified patient and appeared before the HbA1c column. Neither the HbA1c nor GFR columns were fully populated. The Panel noted AstraZeneca's submission that the example report was generated using dummy patients in a test system and a report generated using real-life data in a live system would only include patient records that met all the search criteria and would have all the data values populated. The Panel considered that this was not clear from the leavepiece and was compounded by the screenshot heading 'The completed report should resemble this screenshot'. The Panel accepted AstraZeneca's submission regarding the responsibility of prescribers to make clinically reasoned prescribing decisions but considered that it was important that both the instructions and information on the nature and interpretation of the data retrieved was abundantly clear and otherwise complied with the Code. In this regard the Panel was concerned that nowhere in the leavepiece was there any mention of carrying out a clinical review nor was it referred to in the verbal briefing to the diabetes sales leadership team. In the Panel's view, the leavepiece implied that following the 9 step guide would generate a list of uncontrolled patients with a BMI≥ 25 who were suitable for Forxiga. This would include patients who currently had an HbA1c value of less than 58 but who previously had a value of more than 58 being identified as 'uncontrolled'. This impression was compounded by the title '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. In the Panel's view it might lead to controlled patients (based on HbA1c) being identified as uncontrolled and being prescribed Forxiga. The Panel considered that the leavepiece was misleading and a breach was ruled.

Whilst the Panel noted that BMI was relevant to this therapeutic area, the emphasis on BMI in the title, search criteria and the example completed report screenshot which omitted HbA1c values and the failure to refer to the need to carry out a clinical review meant that Forxiga had been promoted for some patients based solely on their weight. Forxiga was not indicated for weight loss. A breach was ruled.

The Panel however did not consider that the instructions were misleading on the narrow point that no time restrictions were included in the search criteria for BMI, GFR and HbA1c as alleged. No breach was ruled.

The Panel considered that high standards had not been maintained and a breach was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure.

A clinical pharmacist complained about instructions produced by AstraZeneca UK Limited about how to create an EMIS Web clinical system search to identify patients suitable for treatment with Forxiga (dapagliflozin) (ref 716.131.011).

Forxiga was indicated in adults aged 18 years and older with type 2 diabetes to improve glycaemic control as monotherapy when diet and exercise alone did not provide adequate glycaemic control in patients for whom use of metformin was considered inappropriate due to intolerance. It was also indicated in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, did not provide adequate glycaemic control.

The item was a leavepiece entitled '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. Above this on the front page was a container with a tap releasing sugar. Below the title was a description in smaller bold text of where the prescribing information and adverse event reporting could be found followed by 'FORXIGA is not indicated for weight loss and is not recommended for use in patients with an [eGFR] < 60 mL/min/1.73m^2. FORXIGA is not licensed for use with thiazolidinedione or GLP-1 agonists'. The leavepiece gave detailed instructions for the search including six search criteria.

COMPLAINT

The complainant alleged that the search instructions were potentially misleading and could easily identify patients who would not be suitable for treatment. The instructions showed how to add criteria for body mass index (BMI), glomerular filtration rate (GFR) and glycosylated haemoglobin (HbA1c). In all cases a clinical code was added with a qualifying value. However, no time restriction was added to qualify these values.

The complainant explained the flaw as follows: patients were supposed to have an uncontrolled HbA1c to be suitable for treatment so those with an HbA1c above 58 should be identified. However, the value should also be the most recent recorded on the system. This meant a patient with an HbA1c of 48 now who had previously had an HbA1c of 63 should not be included in the final search. However, by applying the instruction as specified they would be included for consideration.

The complainant alleged that whilst he/she hoped that a clinical review would subsequently deem the patient as inappropriate for treatment, the search instructions could be construed as misleading by including such patients. By creating a sub-optimal search the usual high standards demonstrated by the pharmaceutical industry had not been maintained.

The complainant hoped that the instructions would be withdrawn from circulation and, if desired, replaced with some that were more robust and accurate.

When writing to AstraZeneca, the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2 and 9.1 of the Code.

RESPONSE

AstraZeneca explained that the Forxiga EMIS search instructions included in the leavepiece were intended to be used by health professionals who used the EMIS Web clinical system. The EMIS Web clinical system allowed primary, secondary and community health professionals to view and contribute to a patient's electronic healthcare record.

The Forxiga EMIS search instructions were intended to enable health professionals to identify type 2 diabetics who were uncontrolled and overweight and who might be suitable for Forxiga treatment. The instructions guided the selection of patients with records held in the EMIS Web system which fulfilled the following criteria:

- Patients aged ≥18 years and ≤75 years

  Forxiga was indicated for patients aged 18 years and over. Section 4.4 of the summary of product characteristics (SPC) stated that therapeutic experience in patients 75 years and older was limited and Forxiga was not recommended for patients in this population. Therefore, patients with a recorded age of 18 - 75 were included within the search results.

- Patients identified as having type 2 diabetes

  Forxiga was indicated for the treatment of type 2 diabetes. Therefore, patients with a recorded diagnosis of type 2 diabetes were included in the search results.

- Patients not prescribed a loop diuretic in the last 3 months

  Forxiga was not recommended for use in patients on loop diuretics (Section 4.4 of the SPC). Therefore, patients with a recorded prescription for a loop diuretic in the last 3 months were excluded from the search results.

- Patients with a body mass index (BMI) of ≥25 kg/m^2

  Treatment with Forxiga was not limited to those who were overweight or those with a particular BMI. However, given its known effect in reducing body weight (Section 5.1 of the SPC) it had the potential to particularly benefit patients in whom weight loss would be valuable. Patients with a BMI > 25 kg/m^2 were defined as being overweight

and as such might benefit from weight loss. Therefore, patients with a record indicating a BMI > 25 kg/m^2 were included in the search results.

- Patients with glycosylated haemoglobin (HbA1c) ≥58mmol/mol

  Forxiga was indicated for patients with type 2 diabetes mellitus to improve glycaemic control. No specific HbA1c values were stated in the SPC. Guidelines indicated that there was no single figure that defined adequate glycaemic control. Rather, HbA1c goals should be individually tailored. The decision as to what HbA1c threshold should trigger the decision to modify a patient's treatment was a matter of clinical judgement tailored to the needs of each patient.

  The 58mmol/mol criterion was selected on the basis of the value specified for treatment intensification in the National Institute of Health and Care Excellence's (NICE) Draft Guidelines for the Management of Type 2 Diabetes and was consistent with the value set in the Quality and Outcomes Framework (QOF) diabetes indicators. Therefore, patients with a recorded HbA1c >58mmol/mol were included in the search results.

- Patients with a recorded eGFR ≥ 60ml/min/ 1.73 m^2

  Forxiga was not recommended for use in patients with moderate to severe renal impairment (patients with CrCl (Creatine clearance) < 60ml/min or eGFR (estimated Glomerular Filtration Rate) < 60ml/ min/1.73 m^2), (Section 4.4 of the SPC). Therefore, patients with a recorded eGFR value ≥ 60 ml/ min/1.73 m^2 were included in the search results.

AstraZeneca submitted that no timeframe was specified for the selection criteria, with the exception of the loop diuretic exclusion. If a timeframe had been specified then patients currently uncontrolled and overweight might not be included in the search results. For example, if a 3 month timeframe had been specified for the HbA1c value then patients with no HbA1c value recorded within the last 3 months, who might potentially still be uncontrolled, would not be included. Not imposing a time restriction also recognised the importance of considering a patient's blood glucose and weight control over time, rather than looking at a single point in time. Importantly, the list generated would include the dates on which measurements were recorded.

Once the search criteria had been built the instructions then continued to describe how to produce the patient list. Health professionals were then to identify patients that might be suitable for Forxiga treatment after further clinical evaluation. Patients appearing on the list might not be suitable for treatment with Forxiga for any number of reasons such as allergy to an ingredient. To further support such clinical decision making the leavepiece provided information on important situations in which Forxiga should not be prescribed. Prescribing information, as well as adverse event information, was also included.

In line with standard UK clinical practice, and as specified in the General Medical Council's Good Medical Practice, AstraZeneca expected doctors and other health professionals to 'prescribe medicines only when they had adequate knowledge of the patient's health and were satisfied that the medicine or treatment served the patient's needs'. In AstraZeneca's view no health professional would ever prescribe solely on the contents of a computer generated list. Rather, they would always use clinical judgement and consider the patient's current health status when making prescribing decisions.

AstraZeneca stated that the instructions did not suggest that Forxiga was indicated or should be prescribed for all patients that appeared in the search results. Rather, the instructions clearly stated in the title that patients identified '**may** be suitable for treatment with dapagliflozin' (emphasis added). As detailed above the search criteria were designed to reflect the Forxiga SPC, along with values appearing in the NICE guidelines and QOF indicators for type 2 diabetes.

AstraZeneca submitted that Forxiga had been promoted in accordance with particulars in the SPC and denied a breach of Clause 3.2.

AstraZeneca stated that its intention in assembling the list of instructions was to provide health professionals who used the EMIS Web system, a way to generate a list of patients who might be suitable for treatment with Forxiga. AstraZeneca firmly believed that health professionals would not prescribe solely on the basis of a computer generated list but rather would consider individual patient's needs and reach clinically-reasoned prescribing decisions.

As such, AstraZeneca submitted that the leavepiece was not misleading and that Forxiga had been promoted in a transparent manner that encouraged rational prescribing and in accordance with its SPC. Consequently, AstraZeneca denied a breach of Clause 7.2.

AstraZeneca submitted that its intention with this leavepiece, as explained above, was in line with the letter and spirit of the Code. AstraZeneca believed that this would be appreciated by the majority of health professionals who saw the material. High standards had been maintained and AstraZeneca denied a breach of Clause 9.1.

For the reasons detailed above, AstraZeneca also denied a breach of Clause 2.

In conclusion AstraZeneca reiterated that its intention with the leavepiece was to provide a tool to support health professionals who wished to identify patients who might be suitable for treatment with Forxiga. Such a tool could not, and should not, be a substitute for a clinician's professional judgment which would consider the individual patients' needs to fully inform a prescribing decision.

In response to a request for further information AstraZeneca stated that the Diabetes Sales

Leadership Team (heads of regional business, regional sales managers, and regional account managers) was briefed on the use of the leavepiece on 20 and 26 May 2015 via a WebEx and teleconference. A copy of the leavepiece was shown and the following points were explained verbally:

- The leavepiece was to be offered to healthcare professionals who had an interest in identifying their diabetic patients who might be suitable for treatment with Forxiga
- Representatives could only provide the leavepiece and must not be involved in any other way beyond provision of the leavepiece
- The leavepiece was available for representatives to order via the usual internal process.

The leadership team was instructed to cascade this information to their sales teams in their upcoming meetings. Consequently there was no written briefing material.

With regard to the search criteria and screenshot, AstraZeneca submitted that EMIS Web was a clinical system that allowed health professionals to record and use information to support patient care. A component of EMIS Web's functionality was the ability to perform searches and reports from the patient database. Practices would commonly run reports from their clinical system to assist in identifying patients for review.

All six search criteria stated in the leavepiece must be fulfilled in order for a patient's details to appear in the list generated. The report generated was not affected by the order of the search criteria. The example report on page 5 of the leavepiece was included at the end of the step-by-step guide to indicate that a report should now be available for extraction and the report should resemble the example. The example report was generated using dummy patients in a test system. AstraZeneca consulted with the agency that produced the step-by-step guide which confirmed that a report generated using real-life data in a live system would only include patient records that met all the search criteria and would have all the data values populated.

With regard to applying a date range for the search, AstraZeneca stated that the agency that produced the step-by-step instructions confirmed that it was not possible to perform a search for only the latest HbA1c value on the EMIS Web clinical system.

Applying a date range for the search criteria was possible, however as stated previously this had certain limitations. For example, if a 3 month timeframe had been specified for the HbA1c value then patients with a latest HbA1c of 58mmol/mol or greater but not recorded within the last three months would not be included in the report. Also, applying a date range would not prevent patients with an HbA1c of less than 58mmol/mol being included in the report if they had a historical HbA1c of 58mmol/mol or greater also recorded in that timeframe.

Therefore, no date range was specified and patients who had ever had an HbA1c value of greater than or equal to 58mmol/mol and satisfied all the additional criteria would be included in the report even if their most recent HbA1c reading was less than 58mmol/mol. Not imposing a time restriction also recognised the importance of considering a patient's HbA1c over time. The report included the dates on which the measurements were recorded.

AstraZeneca submitted that an example might help to illustrate why the history might be clinically useful:

Patient John Smith had the following HbA1c history:

John Smith	Date	HbA1c (mmol/mol)
	December 2014	62
	June 2014	60
	December 2013	64
	June 2013	67
	December 2012	65

Such a history of hyperglycaemia would appear in the report and might prompt the clinician to undertake a detailed case review. Upon review it might, for example, become apparent that:

a) the patient had not had a more recent HbA1c value record – they might therefore warrant re-testing and further follow up
b) There was a more recent HbA1c value of 56mmol/mol available. This might prompt the HCP to carefully evaluate the patient's individual case based on the totality of data and make a clinical decision as to further management.

PANEL RULING

The Panel noted that the leavepiece was entitled '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. The leavepiece then described the EMIS Web search in 9 steps as follows:

1 Setup initial search
2 Add Age Range to Search
3 Add Read Code to Search
4 Add Medication to Search
5 Add BMI to Search
6 Add HbA1c to search
7 Add GFR to search
8 Save and Run Report
9 Build Report Output.

Each step included detailed instructions and some included screenshot examples.

The Panel noted that the complainant was particularly concerned that no time restriction was added to qualify BMI, GFR and HbA1c values which were used as search criteria. In the complainant's view the HbA1c value should be that most recently recorded on the system. The complainant explained that patients were supposed to have an uncontrolled HbA1c to be suitable for treatment so those with an HbA1c above 58 should be identified. By applying the instruction as specified, a patient with an HbA1c of 48 now who had previously had an HbA1c of

63 would be included for consideration when they should not be and the search instructions could be construed as misleading by including such patients.

The Panel noted the order of the search criteria, age, read code, and medication were followed by BMI before selecting HbA1c and GFR. The report was then run (Step 8). Step 9, Build Report Output, instructed users to add BMI (22K) and value ≥ 25 before adding columns for HbA1c and GFR but unlike BMI no values were listed for these two criteria at this step in the description in the leavepiece. In the example screenshot of the completed report which appeared below step 9, the column of BMI values was fully populated for each identified patient and appeared before the HbA1c column. Neither the HbA1c nor GFR columns were fully populated. The Panel noted AstraZeneca's submission that the example report was generated using dummy patients in a test system and the agency that produced the step-by-step guide confirmed that a report generated using real-life data in a live system would only include patient records that met all the search criteria and would have all the data values populated. The Panel considered that this was not clear from the leavepiece and was compounded by the screenshot heading 'The completed report should resemble this screenshot'. The Panel accepted AstraZeneca's submission regarding the responsibility of prescribers but considered that it was important that both the instructions and information on the nature and interpretation of the data retrieved was abundantly clear and otherwise complied with the Code. In this regard the Panel was concerned that nowhere in the leavepiece was there any mention of carrying out a clinical review nor was it referred to in the verbal briefing to the diabetes sales leadership team. In the Panel's view, the leavepiece implied that following the 9 step guide would generate a list of uncontrolled patients with a BMI≥ 25 who were suitable for Forxiga. This would include patients who currently had an HbA1c value of less than 58 but who previously had a value of more than 58 being identified as 'uncontrolled'. This impression was compounded by the title '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. In the Panel's view it might lead to controlled patients (based on HbA1c) being identified as uncontrolled and being prescribed Forxiga. The Panel considered that the leavepiece was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that Clause 3.2 stated that promotion of a medicine must be in accordance with its marketing authorization and must not be inconsistent with the SPC. The Panel noted its comments above about the identification of patients. Whilst the Panel noted that BMI was relevant to this therapeutic area, the emphasis on BMI in the title, search criteria and the example completed report screenshot which omitted HbA1c values and the failure to refer to the need to carry out a clinical review meant that Forxiga had been promoted for some patients based solely on their weight. Forxiga was not indicated for weight loss. A breach of Clause 3.2 was ruled.

The Panel however did not consider that the instructions were misleading on the narrow point that no time restrictions were included in the search criteria for BMI, GFR and HbA1c as alleged. No breach of Clause 7.2 was ruled.

The Panel considered that the arrangements were such that high standards had not been maintained; a breach of Clause 9.1 was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure; no breach of Clause 2 was ruled.

During its consideration of this case the Panel was concerned that only in response to a question from the Panel did AstraZeneca confirm that the example completed report screenshot did not represent the real-life situation as implied by the leavepiece. In the Panel's view this should have been addressed prior to certification. The Panel was further concerned about the lack of written briefing material and the limited verbal briefing that was to be cascaded by the leadership team to their sales teams. In the absence of any written briefing, the Panel queried whether all sales teams would have received the same message and whether there was a process for ensuring that all sales teams had been briefed on the leavepiece before it became available for order. The Panel requested that AstraZeneca's attention be drawn to these concerns.

Complaint received **10 September 2015**

Case completed **16 November 2015**

CASE AUTH/2796/9/15

HEALTH PROFESSIONAL v BAUSCH & LOMB

Pulse Quick Guide

A general practitioner (GP) who was a GP trainer with an interest in allergy complained about an article published in Pulse as a Pulse Quick Guide. The article was entitled 'New approaches in management and treatment of anaphylaxis' and discussed adrenaline auto injectors (AAI) in relation to administration needle length, skin to muscle depth, and dosage cost. The named author was a consultant allergist who had been commissioned to write the article. An advertisement for Emerade (adrenaline) marketed by Bausch & Lomb appeared on the reverse.

Emerade was indicated for the emergency treatment of severe acute allergic reactions (anaphylaxis) triggered by allergens in foods, medicines, insect stings or bites, and other allergens as well as for exercise-induced or idiopathic anaphylaxis.

The complainant noted that the item was presented as a Pulse article on anaphylaxis; whereas it was obviously promotional. The complainant was unaware that any 'New guidelines' were presented. The Emerade device had been in the UK for over 2 years. Many of the suggestions appeared to be unscientific and poorly referenced, with very broad assumptions presented as fact.

The complainant queried the claim '68% of the allergy population has a STMD [skin-to-muscle depth] greater than the most common AAI [adrenaline autoinjectors]' and if this was really so including children. Just giving the STMD did not allow for the compression of fat/skin when a needle was pressed into the thigh. He/she understood that the European Medicines Agency (EMA) recently (June 2015) gave a Committee for Medicinal Products for Human Use report on AAIs. It suggested that further data should be generated but that until then, proper educational material should be given to patients and carers.

The statement that the British National Formulary (BNF) recommended a 500mcg dose was not correct, unless the new anticipated BNF had changed this recommendation.

The dosage suggestions of the UK Resuscitation Council were for professionals, not for patients' self-administration. The complainant also queried what 'for some patients' actually meant in the bullet-point 'For some patients, The UK Resuscitation Council also recommends 500mcg of adrenaline and makes specific needle length recommendations for intramuscular delivery'. The complainant alleged that it was unclear and misleading. 'Some patients' might equally be overdosing on the 500mcg dose. The complainant found it hard to believe this was an error in the article and believed it was included as a deliberate attempt to confuse doctors.

The referenced article on accuracy in use of AAIs was written in part by a non-clinical psychologist and was funded in part by the UK distributor of Emerade. 100% success with their sponsor's device, was astonishing, at the very least.

The cost per annum savings were made on the assumption that the AAIs were not used at all. The complainant understood that the published shelf lives were not relevant to the actual surviving shelf life when the devices were actually dispensed.

The detailed response from Bausch & Lomb is given below.

The Panel noted that the Pulse Quick Guide was supplied with Pulse as an A4 laminated loose insert, a full page Emerade advertisement appeared on the reverse. The comparison of shelf life at production, cost to the NHS and cost per annum were included in a table comparing Emerade, EpiPen and Jext. The table also included doses and exposed needle length.

The Panel noted the origin of the Pulse Guide and Bausch & Lomb's submission that the Pulse Quick Guide was clearly identified as being 'Initiated, developed, and funded by Bausch & Lomb' as stated in the top right hand corner of the article. The Panel noted that it appeared adjacent to the heading 'Pulse Quick Guide'. However, it was in a very small font size compared to the heading and subheading, in a black type face and was not emboldened. In the Panel's view, this would be missed by many readers. The Panel did not consider that the statement was prominent enough to ensure awareness of the company's role at the outset. The Panel also noted that 'see reverse for prescribing information' appeared at the bottom of the article in black, unemboldened font and appeared, at first glance, to be part of the article itself. The Panel considered that the nature of the material and role of the company was not clear. This misleading impression was compounded by the prominence of the Pulse and Nursing in Practice logos. Some readers might assume that the article was independent editorial matter. The material was disguised in that regard and a breach of the Code was ruled.

The Panel noted that the Quick Guide referred to new approaches rather than new guidelines as alleged by the complainant. Whilst the Panel noted that Emerade was first authorized in January 2013 it queried whether there were in fact new approaches in the management of treatment of anaphylaxis considering the length of time Emerade had been available. However, the allegations related to 'new guidelines' and as neither this phrase nor a closely similar phrase had been used or implied, the Panel ruled no breach of the Code on this narrow ground.

With regard to the claim '… 68% of the allergy population having a STMD greater than the most common AAI …' the Panel noted that Johnstone *et*

***al* reported STMDs >15mm in 68% of adults. The two other references quoted lower percentages in children, namely 60% and 30%. The Panel considered that the claim implied that 68% of the entire allergy population had an STMD greater than that of the most common AAIs. This was not so. The Panel considered that the statement was misleading and could not be substantiated. Breaches of the Code were ruled.**

In the Panel's view the reference to the BNF dose in the Guide was misleading. The Guide did not refer to severe anaphylaxis as mentioned in the BNF and neither the Guide nor the BNF reflected the dose recommended in the summary of product characteristics (SPC). A breach of the Code was ruled.

The Panel considered that it would be helpful if the Guide was clear that the UK Resuscitation Council guidelines were for health professionals considering that elsewhere the Guide was concerned with self administration. However, it did not consider that in the circumstances it was misleading and on this narrow ground ruled no breach of the Code. In the Panel's view, the Guide should be clearer about both the licensed dose of Emerade and the patients for whom 500mcg adrenaline was recommended. The SPC stated that 500mcg was not recommended for use in children. The UK Resuscitation Council guidelines recommended 500mcg for patients aged 12 and over except for those that were small or prepubertal. The Panel considered that the Guide was not sufficiently clear regarding the licensed doses. There was a possibility that it might lead to some patients being inappropriately prescribed a dose of 500mcg. This was clearly contraindicated in children. The Panel considered that the Guide was misleading and did not promote the rational use of the medicine. Breaches of the Code were ruled. Such material could potentially have an impact on patient safety. The Panel ruled a breach of the Code as high standards had not been maintained. The Panel noted that prejudicing patient safety was an activity likely to be ruled in breach of Clause 2. The Panel noted that there was no evidence to show that patient safety had been adversely affected but considered that to provide misleading information about licensed doses was a serious matter particularly given that the 500mcg dose was contraindicated in children and on balance a breach of Clause 2 was ruled.

With regard to the allegation about cost per annum savings, the Panel noted Bausch & Lomb's submission that as the bulk of all AAI's in circulation were never used, a longer shelf life was a beneficial factor as the requirement to replace the pen would be less frequent. The Panel noted that Emerade had a shelf life at production of 30 months compared to EpiPen and Jext with 18 months each. The Panel examined the table comparing the products. The costs were given and the final column gave the cost per annum; the cheapest being Emerade at £10.78 (150 and 300mcg). The column detailing shelf-life was headed 'Shelf life at production (months)'. In addition the bullet point in the conclusion read 'Emerade reduces cost, with the longest shelf life at production (30 months) compared to Jext /EpiPen (18 months). The Panel considered that it was clear that the longer shelf life referred to the maximum shelf life from the date of production. Whilst the supply chain was relevant the Panel considered that the Guide was sufficiently clear that it was referring to the shelf life at production. The Panel did not consider that readers would be misled in this regard and ruled no breach of the Code. The Panel considered that neither the table nor the bullet point 'Emerade reduces cost with the longest shelf-life at production …' were incapable of substantiation on this point and no breach of the Code was ruled.

A general practitioner (GP) and GP trainer with an interest in the allergy field complained about an article (ref EME-UK-1507-04, prepared July 2015) published in Pulse entitled 'New approaches in management and treatment of anaphylaxis'. The article discussed adrenaline auto injectors (AAI) in relation to administration needle length, skin to muscle depth, and dosage cost. The named author was a consultant allergist who had been commissioned to write the article.

Bausch & Lomb's product Emerade (adrenaline) was indicated for the emergency treatment of severe acute allergic reactions (anaphylaxis) triggered by allergens in foods, medicines, insect stings or bites, and other allergens as well as for exercise-induced or idiopathic anaphylaxis.

COMPLAINT

The complainant stated that the article was published as a laminated A4 sheet and was presented as a 'Pulse Quick Guide'.

The complainant's concerns were as follows:

1 The item was presented as a Pulse article on anaphylaxis; whereas it was obviously promotional. The complainant planned to write to Pulse about this and believed it should also take some responsibility, as it had a reputation to uphold.

2 The complainant was unaware that any 'New guidelines' were presented. The Emerade device had been in the UK for over 2 years.

3 Many of the suggestions appeared to be unscientific and poorly referenced, with very broad assumptions being made and presented as fact. For example:

   a) '68% of the allergy population has a STMD [skin-to-muscle depth] greater than the most common AAI [adrenaline autoinjectors]'. The complainant queried if this was really the case including children and alleged that just giving the STMD did not allow for the compression of fat/skin when a needle was pressed into the thigh. He understood that the European Medicines Agency (EMA) recently (June 2015) gave a Committee for Medicinal Products for Human Use report on AAIs. It suggested that further data should be generated but that until then, proper educational material should be given to patients and carers.

b) The statement that the BNF recommended a 500mcg dose was not correct, unless the new anticipated BNF had changed this recommendation; the complainant did not have this yet but noticed the article was prepared in July.

c) The dosage suggestions of the UK Resuscitation Council were for professionals, not for patients' self-administration. The complainant also queried what 'for some patients' actually meant when extracted into the presented bullet-point 'For some patients, The UK Resuscitation Council also recommends 500mcg of adrenaline and makes specific needle length recommendations for intramuscular delivery'. The complainant alleged that it was very unclear and misleading. 'Some patients' might equally be overdosing on the 500mcg dose. The complainant found it hard to believe this was an error in this article and believed it was included as a deliberate attempt to confuse doctors.

d) The referenced article on accuracy in use of AAIs was written in part by a non-clinical psychologist and was funded in part by the UK distributor of Emerade. 100% success with their sponsor's device, was astonishing, at the very least.

4 The cost per annum savings were made on the assumption that the AAIs were not used at all. The complainant understood that the published shelf lives were not relevant to the actual surviving shelf life when the devices were actually dispensed.

When writing to Bausch & Lomb, the Authority asked it to consider the requirements of Clauses 2, 7.2, 7.4, 7.10, 7.11, 9.1 and 12.1 of the Code.

RESPONSE

Bausch & Lomb stated that as members of the ABPI it took compliance with the Code seriously. It responded to each of the complainant's points in turn.

1 Bausch & Lomb submitted that the Pulse Quick Guide was clearly identified as being 'Initiated, developed, and funded by Bausch & Lomb' as stated in the top right hand corner of the article. No attempt was made to hide this information from the reader and was thereby in compliance with Clauses 9.10 and 12.1. Bausch & Lomb provided further detail on these types of articles published by Pulse.

2 Bausch & Lomb submitted that the article did not state 'new guidelines' anywhere in the copy but use of the term 'new approaches' was with reference to emerging data cited in the article on the need for skin to muscle depth assessment at the injection site to ensure that the prescribed adrenaline auto-injector would be able to deliver an intra-muscular injection. So in that context the word 'new' was entirely appropriate and accurate.

3 With regard to the accusation that many of the suggestions were 'unscientific', Bausch & Lomb submitted that the references were from allergy experts, published in peer reviewed journals or presented at international allergy symposia and to that end had scientific credibility.

a) Bausch & Lomb accepted, that the author could have said 'up to 68%'. However, three references were offered to support the statement - Johnstone *et al*, 2015 reported STMDs >15mm in 68% of adults. The others quoted lower percentages in children, namely 60% in Bewick *et al*, 2013 and 30% in Stetcher *et al*, 2009. Bausch & Lomb did not regard it in anyway being misleading or misrepresentative of the current situation given the references stated covering both the adult and child allergy population.

With regard to the anatomy of subcutaneous tissue and its relationship with muscle and the deep fascia, when pressure was applied to the skin, the muscle compartment was compressed and displaced by the subcutaneous tissue – not the other way round. A needle pressed into the flesh, would perhaps progress an additional 2mm towards the muscle compartment, beyond its physical length. Bewick *et al*, 2013 specifically investigated compression, to counter the common misunderstanding that pressing hard on the skin could help push the needle nearer the muscle:

'… skin surface-to-muscle depth was measured in a subgroup of 7 children ages 5 to 14 years (median, 8 years), after applying enough pressure with a trainer EpiPen and an adjacently placed ultrasound probe positioned on the outer mid-thigh to trigger the device. The EpiPen trainer is a reasonable surrogate for the medicinal device because it has previously been shown to require equivalent force for activation. The median compression was 0.5 mm (interquartile range, 0.0 -1.2 mm). In 3 children younger than 7 years old there was little or no change in skin surface-to-muscle depth after compression. In the overall cohort, the skin-to-muscle depth at the mid-thigh was 2.4 mm (0.8 - 3.2 mm) greater than the needle length, which suggests that compression of tissues when firing autoinjectors would not alter the proportion of children whose injection was subcutaneous rather than intramuscular. There was no significant correlation between BMI or age and change in depth with compression'.

b) The current edition of the BNF Section 3.4.3 Adrenaline, Intramuscular Injection for self-injection, Emerade, included 'Dose by intramuscular injection, Adult and Child over 12 years at risk of severe anaphylaxis, 500 micrograms repeated after 5 -15 minutes as necessary'. This was amended in September 2014. Bausch & Lomb provided a screen shot of the relevant on-line version, to support the statement in the article.

c) Bausch & Lomb submitted that the audience for Pulse was health professionals who would be aware that the UK Resuscitation Guidelines were not for self-administration. The fact that these guidelines supported the use of a 500mcg dose and that Emerade was currently the only auto-injector was relevant and important to convey to the audience. Bausch & Lomb submitted that it would expect health professionals to refer to the prescribing information prior to any usage and to that end the advice on which product was suitable for which patient would be clear. The statement was correct in that it stated 'some' not 'all' patients, which would be misleading.

d) Bausch & Lomb submitted that it was common practice for the pharmaceutical industry and in this case the 'distributor' to financially support NHS facilities and staff to assess the value of medicines. For the complainant to infer that it invalidated the outcome of any of such studies or questions the integrity of the investigators and authors was a concerning development. The author of the guide was a healthcare psychologist, who should have the right to respond in their own right to the allegations.

In response to a request for further information Bausch & Lomb stated that the 'cost per annum' savings were made on the basis that the AAI was not used. The bulk of all AAIs in circulation were never used in the management of anaphylaxis and a longer shelf life was a cost beneficial factor in that case as the requirement to replace the pen would be less frequent.

Bausch & Lomb confirmed that it did not take up the additional option of 'online' publication of the 'Quick Guide' and no additional laminated copies were supplied and therefore were not circulated by Bausch & Lomb sales teams.

PANEL RULING

The Panel noted Bausch & Lomb's comments about the study author. It was for Bausch & Lomb to include any comments in its submission if it so wished. It was not the role of the Panel to contact third parties for views.

The Panel noted that the Pulse Quick Guide was supplied with Pulse as an A4 laminated loose insert, a full page Emerade advertisement appeared on the reverse. The comparison of shelf life at production, cost to the NHS and cost per annum were included in a table comparing Emerade, EpiPen and Jext. The table also included doses and exposed needle length.

The Panel noted that the Pulse Guide article was tendered amongst a range of options during a meeting between Bausch & Lomb and Pulse in April 2015; the content would be collaboratively determined between them. Subsequent to the manuscript being submitted by the author, Bausch & Lomb reviewed it to ensure factual accuracy rather than having editorial control. The Panel noted Bausch & Lomb's submission that the Pulse Quick Guide was clearly identified as being 'Initiated, developed, and funded by Bausch & Lomb' as stated in the top right hand corner of the article. The Panel noted that it appeared adjacent to the heading 'Pulse Quick Guide'. However, it was in a very small font size compared to the heading and subheading, in a black type face and was not emboldened. In the Panel's view, this would be missed by many readers. The Panel did not consider that the statement was prominent enough to ensure that readers would be aware of the company's role at the outset. The Panel also noted that 'see reverse for prescribing information' appeared at the bottom of the article in black, unemboldened font and appeared, at first glance, to be part of the article itself. The Panel noted the requirements of Clause 12.1 and its supplementary information that when a company paid for, or otherwise secured or arranged the publication of promotional material in journals such material must not resemble independent editorial matter. The Panel noted that the overall impression given to readers was the most relevant factor. The Panel noted its comments above and considered that the nature of the material and role of the company was not clear. This misleading impression was compounded by the prominence of the Pulse and Nursing in Practice logos at the very bottom of the Guide. Some readers might assume that the article was independent editorial matter. The material was disguised in that regard. A breach of Clause 12.1 was ruled.

The Panel noted the complainant's allegation that the Emerade device had been available in the UK for over 2 years and the complainant was unaware that any 'New guidelines' were presented. Clause 7.11 stated that the word 'new' must not be used to describe any product or presentation which had been generally available or any therapeutic indication which had been promoted, for more than twelve months in the UK. In the Panel's view it was not necessarily unreasonable to assume that this timeframe should similarly apply when referring to guidelines and the like. The Panel noted that the Quick Guide was entitled 'New approaches in the management and treatment of anaphylaxis' as submitted by Bausch & Lomb; the Quick Guide referred to new approaches rather than new guidelines as alleged by the complainant. Whilst the Panel noted that Emerade was first authorized in January 2013 it queried whether there were in fact new approaches in the management of treatment of anaphylaxis considering the length of time Emerade had been available. However, the allegations related to 'new guidelines' and as neither this phrase nor a closely similar phrase had been used or implied, the Panel ruled no breach of Clause 7.11 on this narrow ground.

The Panel noted the complainant's allegation that the claim '…68% of the allergy population having a STMD greater than the most common AAI …' was unscientific and poorly referenced. The complainant queried if this was really the case including in children. The Panel noted that Johnstone *et al* reported STMDs >15mm in 68% of adults. The two other references quoted lower percentages in children, namely 60% and 30%. The Panel considered that the claim in question implied that 68% of the entire allergy population had an STMD greater than that of the most common AAIs. This was not so. The

Panel considered that the statement was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that the Guide stated that 'the BNF now includes a recommendation that adults at risk of anaphylaxis should receive 500mcg AAI dose by intramuscular injection for self-administration, adrenaline 1mg/l (1 in 1000) repeated after 5-15 minutes if necessary'. The screenshot of the BNF, from November 2014, provided by Bausch & Lomb stated 'Dose by intramuscular injection, ADULT and CHILD over 12 years at risk of severe anaphylaxis, 500 micrograms repeated after 5-15 minutes as necessary. The Panel noted that the BNF referred to severe anaphylaxis while the Guide did not make a distinction. The Emerade summary of product characteristics (SPC) recommended an initial dose of 300 to 500mcg for use in adolescents and adults. It also stated that in some cases one dose was not sufficient to revoke the effects of a severe allergic reaction and a second injection with Emerade might be necessary after 5-15 minutes. In the Panel's view the reference to the BNF dose in the Guide was misleading. The Guide did not refer to severe anaphylaxis as mentioned in the BNF and neither the Guide nor the BNF reflected the dose recommended in the SPC. A breach of Clause 7.2 was ruled.

The Panel noted the complainant's allegation that the dosage suggestions of the UK Resuscitation Council were for professionals, not for patients for self-administration. The complainant also queried what 'for some' patients actually meant. The Panel considered that it would be helpful if the Guide was clear that the UK Resuscitation Council guidelines were for health professionals considering that elsewhere the Guide was concerned with self administration. However, it did not consider that in the circumstances it was misleading and on this narrow ground ruled no breach of Clause 7.2. In the Panel's view, the Guide should be clearer about both the licensed dose of Emerade and the patients for whom 500mcg adrenaline was recommended. The SPC stated that 500mcg was not recommended for use in children. The UK Resuscitation Council guidelines recommended 500mcg for patients aged 12 and over except for those that were small or prepubertal. The Panel considered that the Guide was not sufficiently clear regarding the licensed doses. There was a possibility that it might lead to some patients being inappropriately prescribed a dose of 500mcg. This was clearly contraindicated in children. The Panel considered that the Guide was misleading and did not promote the rational use of the medicine. Breaches of Clauses 7.2 and 7.10 were ruled. The Panel noted its ruling that the licensed doses in the Guide were misleading. In the Panel's view such material could potentially have an impact on patient safety. The Panel ruled a breach of Clause 9.1 as high standards had not been maintained. The Panel noted that prejudicing patient safety was an activity likely to be ruled in breach of Clause 2. The Panel noted that there was no evidence to show that patient safety had been adversely affected but considered that to provide misleading information about licensed doses was a serious matter particularly given that the 500mcg dose was contraindicated in children and on balance a breach of Clause 2 was ruled.

With regard to the allegation that the cost per annum savings were on the basis that the AAI was not used, the Panel noted Bausch & Lomb's submission that as the bulk of all AAI's in circulation were never used, a longer shelf life was a beneficial factor as the requirement to replace the pen would be less frequent. The Panel noted that Emerade had a shelf life at production of 30 months compared to EpiPen and Jext with 18 months each. The Panel examined the table comparing the products. Emerade cost £26.94 for the 150 and 300mcg dose and £28.74 for the 500mcg dose. EpiPen cost £26.45 for both doses (150 and 300mcg), and Jext cost £23.99 for both doses. The final column gave the cost per annum; the cheapest being Emerade at £10.78 (150 and 300mcg). The column detailing shelf-life was headed 'Shelf life at production (months)'. In addition the bullet point in the conclusion read 'Emerade reduces cost, with the longest shelf life at production (30 months) compared to Jext /EpiPen (18 months). The Panel considered that it was clear that the longer shelf life referred to the maximum shelf life from the date of production. Whilst the supply chain was relevant the Panel considered that the Guide was sufficiently clear that it was referring to the shelf life at production. The Panel did not consider that readers would be misled in this regard and ruled no breach of Clause 7.2. The Panel considered that neither the table nor the bullet point 'Emerade reduces cost with the longest shelf-life at production …' were incapable of substantiation on this point and no breach of Clause 7.4 was ruled.

Complaint received **24 September 2015**

Case completed **11 December 2015**

ANONYMOUS HEALTH PROFESSIONAL v SANOFI

Company meeting

An anonymous, non-contactable health professional complained about a meeting held in Barcelona in July 2015 that he/she was invited to attend by Sanofi.

The complainant noted that after being invited to attend the meeting, he/she was then told that it was cancelled as it was not compliant with Sanofi UK policies and the industry code of ethics as the medicine did not have a licence. The complainant alleged that the meeting was apparently still going to be held, however only some countries could attend. The complainant discovered that another UK colleague had attended and spoken at the meeting. The complainant was told that the meeting was clearly promotional about Praluent (alirocumab) and was the reason the UK did not attend. However, as that particular doctor was an investigator Sanofi had made an exception. The complainant's concern was how often and with how many other doctors exceptions had been made.

The detailed response from Sanofi is given below.

The Panel noted Sanofi's submission that the UK affiliate had no involvement in the organisation of and arrangements for the APEX meeting held in Barcelona in July 2015 which was organised by Sanofi's European Medical Affairs group for cardiovascular disease based at Sanofi's Paris office. The audience included 60 participants from Europe and 3 from China. Sanofi UK did not invite any UK health professionals to attend nor did any Sanofi UK staff attend. The Panel did not have a delegate list but noted that according to Sanofi there were no UK delegates in the audience. The Panel noted that a single UK health professional was contracted directly by the Sanofi European office to be present for the duration of the meeting.

In this regard the Panel noted that the UK company would be responsible for any acts and omissions of its overseas affiliate in relation to the speaker. Sanofi UK reviewed and confirmed that the Sanofi contractual arrangements were satisfactory.

The Panel noted that the UK health professional's role was to oversee the delivery of the meeting which included co-chairing, acting as a moderator/ facilitator for two workshops and delivering two presentations. The health professional was selected on the basis of his expertise in the epidemiology of atherosclerosis and involvement in alirocumab studies. The health professional had attended advisory boards concerning the alirocumab clinical trial programme.

The Panel noted Sanofi's submission that the objectives of the meeting were to share knowledge and experience on the clinical management of patients at high cardiovascular risk, and to provide a forum for exchange on how to facilitate the implementation of guidelines and latest evidence into clinical practice. Contrary to Sanofi's submission two of the five presentations mentioned alirocumab including the UK health professional's presentation which was also inconsistent with Sanofi's submission that he was not speaking about any Sanofi product.

The Panel had to consider whether alirocumab had been promoted to the UK health professional, prior to receiving its marketing authorisation. The Panel noted Sanofi's submission that at the time of the meeting alirocumab was under review by the EMA and subsequently received a positive opinion from the CHMP on 23 July 2015 and a European marketing authorisation in September 2015. In these circumstances and given Sanofi's role and commercial interest, the Panel queried whether such a meeting could be considered as anything other than promotional. The Panel noted the UK health professional's role at the meeting and that the contractual responsibilities required attendance for the entire time. The Panel noted Sanofi's submission that the health professional's expertise was such that he was already very familiar with all of the material presented. In the Panel's view the UK health professional was not present at the meeting at any point as a delegate. Given the health professional's role at the meeting and his involvement with the alirocumab studies, the Panel did not consider that alirocumab had been promoted to the UK health professional and thus on the narrow grounds of the complaint it had not been promoted prior to the grant of its marketing authorization. No breach of the Code was ruled. The Panel consequently ruled no breach of the Code in relation to the allegation of disguised promotion to the UK health professional. The Panel considered that there was no evidence to show that the health professional had not been suitably qualified to provide the services contracted or that his/her engagement had been an inducement to prescribe, supply, administer, recommend, buy or sell any medicine and no breaches of the Code were ruled. The Panel noted its rulings above and did not consider that Sanofi UK had failed to maintain high standards or brought discredit upon and reduced confidence in the pharmaceutical industry and ruled no breaches of the Code were ruled including Clause 2.

An anonymous, non-contactable health professional complained about a meeting titled APEX held in Barcelona 3-4 July 2015 that he/she was invited to attend by Sanofi.

COMPLAINT

The complainant stated that he/she had been invited to attend the meeting and was then told that it

was cancelled as it was not compliant with Sanofi UK policies and the industry code of ethics as the medicine was still under development and did not have a licence. The complainant alleged that the meeting was apparently still going to be held, however only some countries could attend. The complainant found this to be very ethical from Sanofi.

The complainant stated that after bumping into a colleague at the European Society of Cardiology (ESC), he/she discovered that another UK colleague had attended and spoken at the meeting. The complainant was told that the meeting was clearly promotional about Praluent (alirocumab) even though it was meant to be educational and was the reason the UK did not attend. However, as that particular doctor was the principal investigator in Sanofi's outcomes trial the company had made an exception.

The complainant found it to be very unethical and was horrified if it were true. The complainant stated that it sounded like serious misconduct and after the recent corruption and bribery headlines in the news thought it should be investigated further. The complainant's concern was how often and with how many other doctors exceptions had been made.

The complainant stated that he/she had engaged with many companies in the past and thankfully most did not act in such a manner, however it only took one to re-inforce the negative perception that many doctors already held about the pharmaceutical industry.

The complainant suggested that it was looked into as a serious matter if it were true.

When writing to Sanofi, the Authority asked it to consider the requirements of Clauses 2, 3.1, 9.1, 12.1, 18.1 and 23.1 of the Code.

RESPONSE

Sanofi stated that the APEX meeting was a medical education event organised by Sanofi's European Medical Affairs group for Cardiovascular Disease at Sanofi's Paris office. The UK affiliate had no involvement in, nor contributed to the organisation of and the arrangements for the meeting.

The meeting was a closed event organised and delivered by a steering committee of clinical experts contracted by Sanofi to deliver this service. The objectives of the meeting were to share knowledge and experience on the clinical management of patients at high cardiovascular risk, and to provide a forum for exchange on how to facilitate the implementation of guidelines and latest evidence into clinical practice. A copy of the agenda was provided along with membership of the steering committee.

The audience was by invitation, and comprised senior physicians from across Europe and China whose clinical or epidemiological practice concerned atherosclerosis and coronary heart disease. Attendees were nominated by medical affairs personnel from Sanofi. A total of 63 participants formed the audience (60 from Europe, 3 from China). In addition, 6 members of the APEX programme steering committee were present, four of whom also delivered or moderated plenary lectures. Three additional health professionals delivered or moderated plenary lectures. There were no UK clinicians in the audience and no Sanofi UK personnel attended. The Sanofi UK affiliate had not been able to receive the meeting materials in a timeframe sufficient to allow certification at a date early enough to allow attendees to make arrangements to attend. Sanofi UK therefore did not invite UK clinicians to attend.

The overall aim of the meeting was to expose the participants to up-to-date scientific knowledge on the identification, evaluation and management of patients with dyslipidaemia and at high risk of cardiovascular disease, and through the workshops to provide them with practical experience of identifying and addressing key issues.

Over the two days of the meeting, participants experienced five lectures totalling 3.5 hours, and spent 6-7 hours in workshop sessions (both contributing to their own and receiving feedback from other work streams). A copy of the final agenda was provided.

Day one of the meeting comprised an opening plenary with three lectures on epidemiology and treatment of atherosclerosis:

1 The current landscape, advances and challenges in dyslipidaemia (40 minutes)
2 The current landscape advances and challenges in atherosclerosis and high cardiovascular risk patients (40 minutes)
3 What are the challenges of diagnosing and treating familial hypercholesterolaemia in the real world? (40 minutes).

This was followed by a series of parallel workshops for participants to address key topics. In summary, the identification, management and challenges therein of patients at high risk of cardiovascular disease. The workshop session ran for 3 hours 40 minutes.

The second day started with a three hour session to review the outputs of the five work streams from Day 1. This was followed by a closing plenary session with two lectures below, before the meeting was summarised and closed.

4 The holistic management of patients with dyslipidaemia and high cardiovascular risk: the exciting future (45 minutes)
5 Moving towards absolute risk assessment to guide clinical decision making (45 minutes).

The materials used at the meeting were prepared by the individual speakers and not by Sanofi, and were in a format chosen by the presenters (either that of their own academic institution or a standard blank template). There was no style required nor applied to any materials used by presenters.

Having reviewed the entire content of the meeting, Sanofi submitted that it was clear that presentations 1, 2, 3 and 5 focussed only on dyslipidaemia/

atherosclerosis and its management. None of these presentations discussed Sanofi products (licensed or in development) – the most frequent reference to pharmacotherapy being (as expected) statins.

Presentation 4 sought to provide an overview of the various medicines and treatments currently in development for the management of dyslipidaemia/ atherosclerosis. The content of this presentation was broad, covering four areas: therapies directed against low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and other therapies. Sanofi had a product in only one of those categories – proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors to reduce LDL – in the form of alirocumab (Praluent), a PCSK-9 inhibitor.

In this presentation, which totalled 88 slides, PCSK-9 inhibitors were covered in 37 slides (42% of the content), of which 17 slides (19%) presented facts concerning alirocumab. A copy of the slides were provided.

At the time of the meeting alirocumab was under review by the EMA and subsequently received a positive opinion from the CHMP on 23 July 2015 and a European marketing authorisation in September 2015.

A single UK clinician attended in the role of steering committee member for the programme and was selected on the basis of his/her professional expertise in atherosclerosis. In addition, the health professional had a role in Sanofi's studies of alirocumab in atherosclerosis and had attended global advisory boards concerning the alirocumab clinical trial programme. The health professional was contracted directly by the Sanofi European office to be present for the duration of the meeting as a steering committee member. The health professional's role as steering committee member was to oversee the delivery of the meeting (which included chairing Day 1), and to act as moderator/ facilitator for two workshop sessions. In addition, the health professional was contracted to prepare and deliver two presentations:

- 'What are the challenges of diagnosing and treating familial hypercholesterolaemia in the real world?'
- 'Moving to absolute risk assessment to guide clinical decision making'.

Sanofi submitted that it was clear from the content of both the UK health professional's presentations that non-promotional lectures on those topics, were delivered. Sanofi products were not referred to at any point. In particular, there was no discussion on alirocumab.

In advance of the meeting, the UK affiliate reviewed the contractual arrangements made with the UK health professional, in accordance with its standard operating procedure (SOP) on the engagement of UK health professionals by overseas Sanofi entities. The review confirmed that:

- The UK health professional was appropriately qualified to deliver the required service.
- The nature of the meeting and hospitality/ subsistence provided were appropriate to allow a UK health professional to be contracted to deliver the service.
- The fee for service was in accordance with Sanofi's 'fair market value' policy on the determination of service fees.
- The contract between Sanofi and the UK health professional contained the specific clauses required for UK health professionals, including those concerning anti-bribery and corruption safeguards, transparency disclosure and allowable expenses for travel and subsistence.

Consideration was given as to whether the UK health professional's presentations required review and certification. Sanofi's SOP only required review of presentations by UK health professionals to a non-UK audience outside the UK when they were speaking about Sanofi products. It was clear from the details provided that the UK health professional was not speaking about any Sanofi product; the presentations were therefore neither reviewed nor certified in the UK. Responsibility to ensure the contents met the requirements where the meeting was organised/conducted (France/Spain) fell to the meeting organiser.

Copies of the UK health professional's presentations were provided; as these were not reviewed by the UK affiliate there was no certificate associated with them. A copy of the contract with the UK health professional was also provided.

Sanofi submitted that the meeting in question was organised independently of the UK company, which played no part in any arrangements, including the choice of venue, speakers, content of the meeting or selection of attendees. The UK's only action was to decline involvement through not being able to certify materials sufficiently in advance of the meeting to allow UK physicians to arrange to attend. Sanofi submitted that in that respect it applied sound principles consistent with the letter and spirit of the Code, and that no breach with respect to those points had occurred.

The UK health professional was contracted to be present at the entire meeting in his role as steering committee member and (at times) facilitator and speaker. The content of his presentations concerned disease processes only, without reference to Sanofi products. Furthermore, there was no audience member from the UK. Sanofi submitted that it was clear from the agenda that the health professional was not contracted to deliver promotion nor disguised promotion in any way. In that respect there was no evidence of any breach of Clause 18.1. The UK health professional was contracted to deliver the services described above as required by Clause 23.1, and Sanofi contended there had been no breach of that section of the Code.

The main question however was whether alirocumab was promoted to the UK health professional whilst he/she was present at the meeting. Sanofi submitted that this did not occur. The UK health professional attended the entire meeting in the contracted role of

steering committee member responsible for delivery of the meeting, rather than as a member of the audience to receive information. In that role health professional would already be familiar with the material that all speakers were to deliver.

Beyond this, the level of information provided in the plenary that covered alirocumab would be far less than that already known by the UK health professional considering his role in the alirocumab development programme. The health professional would have already been familiar with the properties of alirocumab in much greater detail than was covered in a 45 minute presentation covering the breadth of emerging therapies. The alirocumab studies presented had also been published in high-impact medical journals with which the UK health professional would have been fully familiar through his/her professional and academic standing. To suggest that the presentation promoted the use of alirocumab to this UK health professional was to imply that he/she would have limited prior knowledge of the product, which was clearly not the case.

In summary Sanofi submitted that the UK health professional's engagement as a service provider for the full meeting, at which there was presentation of data concerning a Sanofi product with which he/she was already deeply familiar could not be considered promotion to him/her. Sanofi therefore submitted that there was no breach of Clause 3.1.

Having reviewed the events preceding the APEX meeting and of the meeting itself, Sanofi submitted that it had followed the requirements of the Code. The UK affiliate had no involvement in the organisation of the meeting and did not allow UK health professionals to form part of the audience as arrangements for the meeting could not be provided sufficiently in advance.

The single UK attendee was present as an appropriately-contracted service provider for the duration of the meeting, was not required to (nor did he/she) deliver any promotion concerning Sanofi products. As a member of the organising committee, he was exposed to data on a Sanofi product in development on which he/she was already deeply familiar.

Sanofi submitted that no breach of Clauses 3.1, 18.1 or 23.1 occurred, and in consequence no breach of Clauses 9.1 or 2.

PANEL RULING

The Panel noted Sanofi's submission that the UK affiliate had no involvement in the organisation of and arrangements for the APEX meeting held in Barcelona in July 2015 which was organised by Sanofi's European Medical Affairs group for cardiovascular disease based at Sanofi's Paris office. The audience included 60 participants from Europe and 3 from China; Sanofi UK did not invite any UK health professionals to attend either as delegates or speakers. Nor did any Sanofi UK staff attend. The Panel did not have a delegate list but noted that according to Sanofi there were no UK delegates in the audience. The Panel noted that a single UK health professional was contracted directly by the Sanofi European office to be present for the duration of the meeting as a steering committee member which brought the complaint within the scope of the Code.

In this regard the Panel noted that the UK company would be responsible for any acts and omissions of its overseas affiliate in relation to the speaker. Sanofi UK reviewed and confirmed that the Sanofi contractual arrangements were satisfactory.

The Panel noted that the UK health professional's role was to oversee the delivery of the meeting which included co-chairing, acting as a moderator/facilitator for two workshops and delivering two presentations titled 'What are the challenges of diagnosing and treating familial hypercholesterolaemia in the real world' and 'Moving to absolute risk assessment to guide clinical decision making'. The health professional was selected on the basis of his expertise in atherosclerosis; he had also had a role for Sanofi's alirocumab studies and had attended advisory boards concerning the alirocumab clinical trial programme.

The Panel noted the complainant's allegation that the meeting promoted alirocumab. Alirocumab did not have a marketing authorization at the time of the meeting. The Panel noted Sanofi's submission that the objectives of the meeting were to share knowledge and experience on the clinical management of patients at high cardiovascular risk, and to provide a forum for exchange on how to facilitate the implementation of guidelines and latest evidence into clinical practice. Contrary to Sanofi's submission two of the five presentations mentioned alirocumab. 'The holistic management of patients with dyslipidaemia and high cardiovascular risk: the exciting future' provided an overview of the various medicines and treatments currently in development for the management of dyslipidaemia/atherosclerosis including alirocumab. The UK health professional's presentation 'Moving towards absolute risk assessment to guide clinical decision making' (presentation 5) included a slide on the ODYSSEY trial and alirocumab. This was also inconsistent with Sanofi's submission that the UK health professional was not speaking about any Sanofi product.

The Panel had to consider whether alirocumab had been promoted to the UK health professional, prior to receiving a marketing authorisation. The Panel noted Sanofi's submission that at the time of the meeting alirocumab was under review by the EMA and subsequently received a positive opinion from the CHMP on 23 July 2015 and a European marketing authorisation in September 2015. In these circumstances and given Sanofi's role and commercial interest, the Panel queried whether such a meeting could be considered as anything other than promotional. The Panel noted the UK health professional's role at the meeting and that the contractual responsibilities required attendance for the entire time. The Panel noted Sanofi's submission that the health professional's expertise was such that he was already very familiar with all of the

material presented. In the Panel's view the UK health professional was not present at the meeting at any point as a delegate. Given the health professional's role at the APEX meeting and his involvement with the alirocumab studies, the Panel did not consider that alirocumab had been promoted to the UK health professional and thus on the narrow grounds of the complaint it had not been promoted prior to the grant of its marketing authorization. The Panel ruled no breach of Clause 3.1. The Panel consequently ruled no breach of Clause 12.1 in relation to the allegation of disguised promotion to the UK health professional. The Panel considered that there was no evidence to show that the health professional had not been suitably qualified to provide the services contracted or that his/her engagement had been an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. The Panel therefore ruled no breach of Clause 23.1 and consequently no breach of Clause 18.1. The Panel noted its rulings above and did not consider that Sanofi UK had failed to maintain high standards or brought discredit upon and reduced confidence in the pharmaceutical industry. No breach of Clause 9.1 and consequently Clause 2 was ruled.

Complaint received **29 September 2015**

Case completed **28 October 2015**

DIRECTOR OF PHARMACY v GRÜNENTHAL

Conduct of a representative

A director of pharmacy complained about the conduct of a representative from Grünenthal. The representative had promoted Palexia (tapentadol) and Versatis (lidocaine). Palexia was indicated for the relief of moderate to severe acute pain in adults, which could be adequately managed only with opioid analgesics. Versatis was indicated in adults for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection.

The complainant alleged a significant amount of promotional material for Palexia and Versatis had been left on one of the care of the elderly wards in his hospital with the intention of promoting to staff, patients and carers. The complainant provided some of the material retrieved by one of the pharmacists from the ward.

The complainant further alleged that the representative had stated that the pharmacy department actively sought to curtail consultants' freedom to prescribe Grünenthal products; this despite the presence of both Palexia and Versatis on the local formulary.

The complainant alleged that in his view the behaviours exhibited breached the Code.

The detailed response from Grünenthal is given below.

The Panel noted that the Grünenthal representative conducted a promotional meeting with ward staff, the meeting being held in a room at the closed end of a short corridor which was remote from, and to one side of, the bed area. Grünenthal stated that the room was for the use of clinical staff only. In the Panel's view, given the ward layout, it was unlikely that carers or patients would have used the corridor or entered the staff room. The Panel noted that the representative took material to the meeting for 12 attendees; only 8 turned up and one took some of the leftover material for a colleague. The representative left the remaining material in the staff room.

The Panel noted that the complainant had alleged that the material had been found 'on the ward' by a colleague; he had not described where on the ward the material had been found. The Panel noted that even if some of the material had been found in an area accessible by patients or carers the complainant had provided no information to prove that, on the balance of probabilities, it had been left there by the representative – it could have inadvertently been put down by one of the attendees. Once leavepieces and the like were given to staff, representatives had no control of what happened to them.

The Panel considered that the complainant had not established, on the balance of probabilities, that the representative had left promotional material on a part of the ward accessible to patients and carers. The material had been distributed to those categories of persons whose need for or interest in it could be reasonably assumed. No breach of the Code was ruled.

With regard to the spare material which was left by the representative, the Panel considered that although it might be good practice to have removed the material at the end of a meeting, whether it was acceptable to do otherwise would depend on a number of factors such as the location and general use of the area in which the material was left and the amount which was left. In the Panel's view, it was not unreasonable, in the context of a pre-planned meeting, to leave promotional material for those who had been expected to attend but were absent on the day. The material had been left in a room used by clinical staff following a promotional meeting with health professionals. In any event, the Panel noted its comments above about a representative having no way of controlling what health professionals did with material after a meeting was finished. On balance, the Panel ruled no breach of the Code.

The Panel noted that the briefing material for the Versatis and the Palexia leavepieces clearly informed representatives that the materials were promotional items for health professionals which should not be left with receptionists or secretaries unless specifically requested to do so, in writing, by a health professional. The Palexia briefing stated that the item 'should only be left with [health professionals] following a promotional call'. The Versatis leavepiece briefing clearly stated that the leavepiece was not to be left with or shown to patients. In the Panel's view none of the briefing material advocated either directly or indirectly that the leavepieces should be used with patients or carers in a way which would be likely to breach the Code. No breach of the Code was ruled.

The Panel noted the complainant's allegation that the representative had stated that the pharmacy department was actively trying to curtail prescribing of Grünenthal's medicines despite the fact that both Palexia and Versatis were on the formulary. The Panel noted Grünenthal's submission regarding what appeared to be confusion about the prescribing of Palexia to in-patients and that it could only be prescribed if a form, ordinarily used for the assessment and approval of high cost medicines, was completed and submitted. In the Panel's view, given Grünenthal's account of the apparent confusion about how Palexia could be prescribed, it was not unreasonable for the representative to try to find out what the situation was. Grünenthal had submitted that some health professionals in the hospital had expressed frustration about the matter. Overall, the Panel did not consider that

it had any information before it to show that in trying to establish the facts, the representative had disparaged the opinions of any health professional. No breach of the Code was ruled.

The Panel noted its rulings above and did not consider that the representative had failed to maintain a high standard of ethical conduct. No breaches of the Code were ruled.

A director of pharmacy complained about the conduct of a representative from Grünenthal Ltd. The representative had promoted Palexia (tapentadol) and Versatis (lidocaine).

Palexia was indicated for the relief of moderate to severe acute pain in adults, which could be adequately managed only with opioid analgesics. Versatis medicated plaster was indicated for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia, PHN) in adults.

COMPLAINT

The complainant stated that it had been brought to his attention that during September 2015, a significant amount of promotional material for Palexia and Versatis had been left on one of the care of the elderly wards in his hospital with the intention of promoting to staff, patients and carers. The complainant provided some of the material retrieved by one of the pharmacists from the ward. The complainant alleged breaches of Clauses 11.1 and 11.2.

The complainant stated that he was later informed that the Grünenthal representative had stated that in his/her view the pharmacy department in the trust actively sought to curtail consultants' freedom to prescribe Grünenthal products; this despite the presence of both Palexia and Versatis on the local health economy formulary as part of the pain management guidelines. The formulary was overseen by the health economy formulary management group which consisted of GPs, consultants, pharmacists and patients. The complainant alleged that this displayed a poor knowledge of the organisation, in breach of Clauses 8.2, 9.1 and 15.2.

The complainant stated that he had written to Grünenthal with his concerns.

The complainant stated that in his view the behaviours exhibited were in breach of the Code, unwelcome and detrimental to an active professional relationship which was desired with the pharmaceutical industry.

When writing to Grünenthal, the Authority asked it to respond in relation to Clauses 8.2, 9.1, 11.1, 11.2 and 15.2 of the Code as cited by the complainant. In addition Grünenthal was asked to respond in relation to Clause 15.9.

RESPONSE

Grünenthal confirmed that the complainant had contacted the company in advance of his complaint to the PMCPA. Grünenthal submitted that it had asked the complainant for more specific details associated with the allegations but they had not been forthcoming (copies of the correspondence was provided). Grünenthal noted that the details and sequence of events contained within the letter sent to the company differed from that sent to the PMCPA.

With regard to the allegation that significant amounts of promotional materials were left on a care of the elderly ward, with the intention of promoting to staff, patients and carers, Grünenthal noted that all healthcare interactions were logged within the company's customer record management (CRM) system. The data indicated that there was only one meeting in the care of the elderly department in September 2015. Grünenthal confirmed that the representative in question had passed the ABPI Examination for Representatives and a copy of the certificate was provided.

At an investigatory interview to discuss the details of the meeting, the representative in question confirmed that pharmaceutical companies were invited to hold meetings with the care of the elderly team in a private staff room adjacent to the ward. Grünenthal noted that a hand drawn schematic of the room in relation to the patient areas of the ward (copy provided) showed that the room was separated from patient areas of the ward and located at the end of a corridor beside the staff kitchen so no through traffic passed the room. Bins for confidential waste and a stack of chairs hindered easy access along the far end of the corridor to the staff room and the staff kitchen; this would be inappropriate and a health and safety issue if the area was accessed by patients and carers, especially as patients admitted onto a care of the elderly ward might use walking or mobility aids. The small staff room was available for clinical staff only.

The representative confirmed that he/she met eight health professionals and asked each of them to sign an attendance register (copy provided). The representative confirmed that he/she promoted Versatis and Palexia to those who attended. Promotional material for each product was displayed along with food and beverages for the participants.

The representative had expected twelve people to attend the meeting but on the day only eight members of the team were able to attend. In readiness for the meeting, the representative had prepared and displayed twelve copies of three promotional leavepieces. Each attendee took a copy of each item, and one attendee took additional copies to share with a colleague(s) unable to attend. The representative could not recall if this individual took one or more additional copies of each item. At the end of the meeting, the representative left the remaining leavepieces in the room and strongly refuted that this constituted a 'significant' amount of promotional material as there might have been a maximum of three copies of each. The representative was very clear in that no promotional material was left in any area within the vicinity of the ward that patients or carers could access.

Three promotional leavepieces were provided at the meeting, two for Versatis and one for Palexia.

Grünenthal briefly described the content and purpose of each leavepiece and submitted that each was appropriate to provide health professionals from a care of the elderly department.

Copies of each item along with the associated approval certificate and briefing material (Clause 15.9) on how to use each item were provided. Copies of the summary of product characteristics (SPC) for each product and details of the qualifications of the signatories who certified the promotional items and the briefing material were also provided.

Grünenthal submitted that the volume of promotional material provided at the pre-planned meeting was appropriate with reference to the number of health professionals expected to attend it, and the number of people who were able to attend on the day. In addition Grünenthal confirmed that no promotional material was provided to, nor left in areas used by, patients or carers. Grünenthal therefore denied breaches of Clauses 11.1 and 11.2.

Grünenthal stated that with regard to the complainant's allegation that the representative was of the view that the pharmacy department in the trust actively sought to curtail consultants' freedom to prescribe Grünenthal products, Grünenthal stated that in interviewing the representative, it became clear that a genuine level of confusion existed within the hospital with regard to the prescribing of Palexia to in-patients (this was not the case for referrals). The representative stated that during numerous interactions with health professionals at the hospital, he/she had been told that there had been difficulties prescribing Palexia. The complainant was correct that the published joint local formulary and associated guidelines for both primary and secondary care positioned Palexia after co-codamol, tramadol, morphine, buprenorphine, and oxycodone /Fentanyl patch, and the representative confirmed that he/she promoted Palexia in line with these guidelines. In practice, however, he/she had been told that there were difficulties prescribing Palexia to in-patients, even when in line with the agreed published guidelines of use.

A care of the elderly nurse recently told the representative that patients were 'waiting to go on Palexia which is a shame'. Three named care of the elderly consultants stated that they had been 'stopped from prescribing Palexia', and 'we want to prescribe Palexia but we can't'. The representative stated that he/she had been consistent in his/her response, asking why these issues existed, to which each individual had stated they did not know or could not understand it. The representative had noted that Palexia was included within the formulary to which everyone had said they were aware but they still had problems prescribing it for in-patients. The representative had asked that the individuals themselves request further clarification as he/she had no additional information.

As the representative had been told of the issues from the individuals referred to above, he/she sought clarification and asked a named pain consultant from the hospital if this was actually correct. As a result of this dialogue, the pain consultant requested a meeting with the complainant in August 2015 to clarify the situation. The complainant declined and so the consultant met with two other representatives of the pharmacy department instead. At this meeting which took place in either late August or early September, the consultant was informed that the use of Palexia with in-patients was only possible after a form was completed and submitted; the form was ordinarily used for the assessment and approval of high cost medicines and the consultant had not heard of it being used for other purposes. The use of the form for Palexia was not described within the guidelines published by the trust, and its use for Palexia could not be understood when the most commonly prescribed form, Palexia SR 50mg, cost £24.91 for a 56 tablet pack and £12.46 for a 28 tablet pack. This was in comparison to very expensive medicines used in oncology and orphan diseases which had very high associated costs for which the use of the form would be appropriate. The volume of prescribing by the hospital was low so it could not be claimed that this decision had been influenced by the amount of money the hospital spent on Palexia. A strategic consultant to the pain department within the hospital who also attended the meeting reportedly advised the named pain consultant that he needed to push back on the use of the form based on its feasibility, stating that it was not the best use of resources nor was it reasonable to be expected to use it. The pain consultant additionally contacted a member of the hospital's drugs and therapeutics committee to see if he could help understand why such issues existed when prescribing Palexia in the hospital. Grünenthal was unaware of any clarification arising from this discussion.

Grünenthal noted that a named consultant from the care of the elderly team was on the trust's medicines management committee. The representative had asked this individual whether he might be able to find out what the overall issue was with regards the use of Palexia in the hospital. The representative asked whether information could be obtained to understand how Palexia could be prescribed according to the published formulary and guidelines and offered to provide appropriate support of whatever kind might be necessary or helpful to the individual. Grünenthal submitted that this conversation might relate to the verbal conversation referred to by the complainant. Given the situation, Grünenthal considered that it was a reasonable question to ask, and it was raised with an appropriate individual; clarification was being sought from many individuals and questions were often directed to the representative by hospital clinicians. The representative refuted the allegation that in asking this question he/she disparaged the clinical or scientific opinions of health professionals. On the contrary, Grünenthal submitted that offering help to health professionals who had approached the representative with these questions supported the clarification and adherence to the formulary position for the product.

Grünenthal understood that in addition to the complications described above, that there were ongoing issues between the pharmacy department

and individuals in the pain department including allegations against individuals, subsequent counter allegations, and internal procedures that had involved the hospital human resources department. Grünenthal submitted that through no fault of its own, it appeared to have been caught up in those disputes and was why this complaint had been submitted.

Grünenthal denied the complainant's allegations with regard to Clauses 9.1 and 15.2. All the representative's materials were certified for use with health professionals, and briefing documents were provided to support their appropriate and compliant use by promotional teams. All material used by the representative was appropriate for care of the elderly staff and he/she provided an appropriate amount of material for the September meeting. The representative was experienced and was clear that he/she had never left promotional material in an area accessible to patients or carers.

The representative refuted the allegation that he/she had disparaged the clinical or scientific opinions of health professionals and maintained that he/she had always maintained a high standard of ethical conduct when working at this and any other hospital.

Grünenthal reiterated its complete commitment to adhering to the Code in all its business activities.

PANEL RULING

The Panel noted that, as stated in the introduction to the Constitution and Procedure, complainants had the burden of proving their complaints on the balance of probabilities. The Panel further noted Grünenthal's submission that it had unsuccessfully requested further details from the complainant. Copies of the correspondence provided showed that the company had sought clarification with regard to, *inter alia*, the location and quantity of promotional material found on the ward and what the representative specifically stated about the use of Grünenthal's medicines in the hospital. Further, in response to the PMCPA's acknowledgement of his complaint, the complainant had stated to the case preparation manager that he had more information should it be required. The case preparation manager asked for the information to be sent as soon as possible but received no reply.

The Panel noted the complainant's allegation that a representative had left a significant amount of promotional material for Palexia and Versatis on a hospital ward, clearly with the intention of promoting to staff, patients and carers. The Panel noted that Grünenthal acknowledged that its representative had conducted a promotional meeting with ward staff, the meeting being held in a room at the closed end of a short corridor which was remote from, and to one side of, the bed area. Grünenthal stated that the room was for the use of clinical staff only. In the Panel's view, given the sketch provided of the ward layout, it was unlikely that carers or patients would have cause to use the corridor or enter the staff room. The Panel noted that the representative took enough material to the meeting for 12 attendees; only 8 turned up on the day one of whom took some of the leftover material to share with an absent colleague. The representative left the remaining material in the staff room. The Panel noted that the representative planned to give three pieces of material to each attendee. Given the number of attendees on the day and the fact that one took at least one piece of material to share with a colleague, the number of pieces left by the representative was unlikely to be more than 11.

The Panel noted that the complainant had alleged that the material had been found 'on the ward' by a colleague. The complainant had not described where on the ward the material had been found. The Panel noted that even if some of the material had been found in an area accessible by patients or carers rather than the meeting room, the complainant had provided no information to prove that, on the balance of probabilities, it had been left there by the representative – it could have inadvertently been put down by one of the attendees. Once leavepieces and the like were given to staff, representatives had no control of what happened to them.

The Panel considered that the complainant had not established, on the balance of probabilities, that the representative had left promotional material on that part of the ward accessible to patients and carers. The material had been distributed to those categories of persons whose need for or interest in it could be reasonably assumed. No breach of Clause 11.1 was ruled.

The Panel noted that Clause 11.2 stated that restraint should be exercised over the frequency of distribution and the volume of promotional material distributed. With regard to the spare material which was left by the representative, the Panel considered that although it might be good practice to have removed the material at the end of a meeting, whether it was acceptable to do otherwise would depend on a number of factors such as the location and general use of the area in which the material was left and the amount which was left. In the Panel's view, in this case it was not unreasonable, in the context of a pre-planned meeting, to leave copies for those who had been expected to attend but were absent on the day. The material had been left in a room used by clinical staff following a promotional meeting with health professionals. In any event, the Panel noted its comments above about a representative having no way of controlling what health professionals did with material after a meeting was finished. On balance, the Panel ruled no breach of Clause 11.2.

The Panel noted that the briefing material for the Versatis leavepiece (ref UK/V15 0012) and the Palexia leavepiece (ref UK/P14 0021b) clearly informed representatives that the materials were promotional items for health professionals which should not be left with receptionists or secretaries unless specifically requested to do so, in writing, by a health professional. The Palexia briefing stated that the item 'should only be left with [health professionals] following a promotional call'. The briefing material for the Versatis leavepiece (ref V12 0051(1)) clearly stated that the item was not to be left with or shown

to patients. In the Panel's view none of the briefing material advocated either directly or indirectly that any of the leavepieces should be used with patients or carers in a way which would be likely to breach the Code. No breach of Clause 15.9 was ruled.

The Panel noted the complainant's allegation that the representative had stated that the pharmacy department was actively trying to curtail prescribing of Grünenthal's medicines despite the fact that both Palexia and Versatis were on the formulary. The Panel noted Grünenthal's submission regarding what appeared to be confusion about the prescribing of Palexia to in-patients and that it could only be prescribed if a form, ordinarily used for the assessment and approval of high cost medicines, was completed and submitted. In the Panel's view, given Grünenthal's account of the apparent confusion about how Palexia could be prescribed, it was not unreasonable for the representative to try to find out what the situation was. Grünenthal had submitted that some health professionals in the hospital had expressed frustration about the matter. Overall, the Panel did not consider that it had any information before it to show that in trying to establish the facts, the representative had disparaged the opinions of any health professional. No breach of Clause 8.2 was ruled.

The Panel noted its rulings above and did not consider that the representative had failed to maintain a high standard of ethical conduct. No breach of Clauses 15.2 and 9.1 were ruled.

Complaint received **6 October 2015**

Case completed **16 November 2015**

CASE AUTH/2799/10/15

ANONYMOUS ONCOLOGIST v PIERRE FABRE

Promotion of Vinorelbine

An anonymous, non-contactable complainant complained about promotional material for Navelbine (vinorelbine), available on the Pierre Fabre stand at the European Society for Medical Oncology (ESMO) Congress held in Vienna in September 2015.

The complainant noted the phrase 'Rare Cumulative Toxicity' which appeared on the stand panels and similar phraseology which appeared in materials available on the stand. The complainant had used vinorelbine for many years and had not found its side-effects to be a rarity; most of his/her patients had had some adverse reaction, particularly gastrointestinal side-effects.

The complainant queried claims in an efficacy brochure including the majority of patients (79%) were able to dose escalate to 80mg/m^2 and 'Easily Manageable Adverse Events'. In the complainant's practice, most patients were only able to bear 60mg/m^2. The complainant further submitted that adverse events were certainly not easy for clinicians or patients to manage, let alone endure.

The complainant stated that when he/she questioned the Pierre Fabre representative on the stand regarding the above, he/she was told that vinorelbine had a rare cumulative toxicity because patients only took the medicine for three weeks out of four (toxicities reduced during the rest week) after which, the cycle continued. The complainant submitted that this explanation was nonsensical because as long as the patient took the medicine, there were toxicities, and therefore the statement 'rare cumulative toxicities' was misleading.

The complainant queried whether patient safety might be at risk.

The detailed response from Pierre Fabre is given below.

The Panel first considered whether the promotion of Navelbine at the ESMO Congress in Vienna, from an exhibition stand organised and funded by the French global team, came within the scope of the Code. UK employees provided substantial support to the global team by manning the stand together with representatives from other affiliates. The welcome pack provided to 20 UK based oncologists invited by the UK company to attend the congress included details of where to find the Pierre Fabre stand. In that regard, the Panel considered that Pierre Fabre in the UK had invited the UK health professionals to view the promotional material on the stand. Further, in the Panel's view, it was more than likely that when UK delegates, and particularly the 20 invited by the UK affiliate, Pierre Fabre Limited, visited the Pierre Fabre stand, they would talk to UK representatives. The Panel noted its comments above about the UK company directing UK delegates to the stand and therefore considered that the promotion of vinorelbine to UK health professionals on the stand at the ESMO Congress fell within the scope of the UK Code.

The Panel noted that the claim 'Rare Cumulative Toxicity' on the front page of an efficacy brochure detailing the use of Navelbine in metastatic breast cancer and advanced non small cell lung cancer (NSCLC) was referenced to Petrelli *et al* (2011) and Aapro and Finek (2012). Aapro and Finek reviewed 31 studies which included more than 1,000 patients with metastatic breast cancer. Petrelli *et al* referred specifically to the lack of risk of major cumulative toxicity when vinorelbine was administered in combination with labatinib in metastatic breast cancer. Aapro and Finek stated that 'As shown in different studies, oral vinorelbine based-regimens allowed a longer duration of treatment, as a result of their activity and the absence of cumulative toxicities'. In the Panel's view, there was a difference between cumulative toxicity and acute toxicity and the claim was not misleading as alleged; it did not imply that acute toxicity was rare but rather that cumulative toxicity was rare. Pierre Fabre had provided relevant data regarding cumulative toxicity. Given all the circumstances, the Panel ruled no breaches of the Code.

The claim that the majority of patients (79%) were able to dose escalate to 80mg/m^2 appeared on a page detailing the use of Navelbine in metastatic breast cancer. The Panel noted that the claim actually read '79% of patients were able to escalate to the standard dose of 80mg/m^2' and was referenced to Steger *et al*, a poster presented at ESMO in 2014 which included the results of a phase II study to evaluate the efficacy and safety of single agent oral vinorelbine as first line chemotherapy in 70 breast cancer patients presenting with bone metastases without visceral involvement. The Panel further noted that the summary of product characteristics (SPC) stated that the first three administrations of Navelbine should be 60mg/m^2 of body surface area, once weekly. It was recommended that beyond the third administration, the dose should be increased to 80mg/m^2 once weekly except in those patients whose neutrophil count dropped below certain parameters. The Panel considered that whilst the claim was based on the poster, it unequivocally implied that around 4 in 5 of all patients could tolerate a dose escalation to 80mg/m^2. The study, however, was only conducted in a small specific population and the claim did not make it clear that there were certain patients in whom dose escalation would not be appropriate. In that regard the Panel did not consider that a statement on two other pages of the brochure which provided a means of calculating doses and which read 'Continue with standard dose of 80mg/m^2/week depending on blood count' was sufficient

to clarify the claim at issue. The claim should be able to standalone. The Panel did not consider that Steger *et al* was sufficiently robust to support the strong claim. In that regard the Panel considered that the claim was misleading and could not be substantiated and breaches of the Code were ruled.

The Panel noted that the claim 'Easily Manageable Adverse Events' was referenced to Bennouna *et al* (2014), a study involving 153 patients (premetrexed/ cisplatin (n=51) or oral vinorelbine/cisplatin (n=102)) with non small cell lung cancer. The discussion section of the paper stated that the safety profile differed across the 2 doublets, but the incidence and severity of adverse events was acceptable and easily manageable in both arms. The study did not provide further detail regarding how the manageability of adverse events was assessed. The Panel noted that it was particularly important not to mislead with regard to side-effects. The Panel, however, noted the highly specialised therapy area and that the material was for use at a European oncology congress. In the Panel's view the audience would be familiar with the side effect profile of cytotoxic medicines generally. The Navelbine SPC listed a number of adverse reactions some of which were reversible or could be managed with supportive treatment. In the Panel's view, given the therapy area and the target audience, the claim 'Easily Manageable Adverse Events' was not unreasonable. In that regard the Panel did not consider that the claim was misleading. The Panel considered that the claim could be substantiated. No breaches of the Code were ruled.

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

With regard to Clause 2, the Panel noted that prejudicing patient safety was an activity likely to be ruled in breach of Clause 2. The Panel noted that there was no evidence to show that patient safety had been adversely affected. The Panel was, however, concerned about the misleading claim about dose escalation to 80mg/m^2 but noted that it did not suggest that all patients could dose escalate. Other information in the leavepiece referred to administering 80mg/m^2 depending on blood count. On balance no breach of Clause 2 was ruled.

The Panel noted the complainant's allegation regarding the misleading response received when questioning the Pierre Fabre representative on the stand. The Panel noted that Pierre Fabre was not able to identify the oncologist or the representative in question. As the complainant was non-contactable it was not possible to ask him/her for further information. The Panel noted Pierre Fabre's submission that all of the UK employees who had manned the stand denied that such a conversation took place. The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. It was impossible to know what had transpired between the parties. Although noting that extreme dissatisfaction was usually required before an individual was moved to complain, on the basis of the information before it the Panel ruled no breaches of the Code.

An anonymous, non-contactable complainant who described him/herself as an oncologist, complained about promotional material for Navelbine (vinorelbine), available on the Pierre Fabre stand at the European Society for Medical Oncology (ESMO) Congress held in Vienna, 25-29 September 2015. The complainant drew particular attention to an efficacy brochure (ref July 2015 – 798979).

Vinorelbine was indicated as a single agent or in combination for the first line treatment of stage 3 or 4 non small cell lung cancer and the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

COMPLAINT

The complainant noted the phrase 'Rare Cumulative Toxicity' which appeared on most of the Pierre Fabre panels. The complainant stated that he/she had used vinorelbine for many years and had not found its side-effects to be a rarity. Most of his/her patients had had some adverse reaction to vinorelbine, particularly gastrointestinal side-effects.

The complainant stated that Pierre Fabre also provided materials on the stand with similar phraseology. The complainant queried some of the statements in a brochure, including the majority of patients (79%) were able to dose escalate to 80mg/m^2, and 'Easily Manageable Adverse Events'. In the complainant's practice, most patients were not able to tolerate the high dose, and were only able to bear 60mg/m^2. Moreover, when making such a decision, there were a majority of factors that needed to be taken into consideration including underlying comorbidities, previous treatments, etc. The complainant submitted that adverse events were certainly not easy for clinicians or patients to manage, let alone endure.

The complainant stated that when he/she questioned the Pierre Fabre representative on the stand regarding the above mentioned observations, he/she was met with bemusement and was told that vinorelbine had a rare cumulative toxicity because patients only took the medicine weekly for three weeks, and then broke for a week (toxicities reduced during this rest week). After which, the cycle continued. The complainant submitted that this explanation was nonsensical because as long as the patient took the medicine, there were toxicities, and therefore the statement 'rare cumulative toxicities' was misleading.

The complainant stated that having worked with Pierre Fabre in the past, he/she was extremely disappointed with the quality of its current materials as patient safety might be at risk.

When writing to Pierre Fabre, the Authority asked it to consider the requirements of Clauses 7.2, 7.4, 7.9, 9.1 and 2 of the Code.

RESPONSE

Pierre Fabre submitted that the 2015 ESMO Congress was an international meeting attended by medical oncology experts from around the world including,

as it was held in Europe rather than the US, a large number from the UK. The Pierre Fabre stand was organised and funded by Pierre Fabre SA, the French global team, which had full responsibility for preparation of the panels and all materials on the stand. The UK affiliate (Pierre Fabre Limited) was not involved in the organisation of the stand or any materials on it but representatives employed by the UK supported Pierre Fabre SA by manning the stand, together with representatives from other affiliates. In addition Pierre Fabre Limited invited 20 UK oncologists to attend the congress.

Pierre Fabre submitted that after considering the Code and the complaint, it did not consider that materials distributed from the Pierre Fabre stand at ESMO fell within the scope of the Code.

The supplementary information to Clause 1.11 stated 'Activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European country as well as the national code of the country in which the activities take place or the material are used'.

Furthermore, the supplementary information to Clause 1.1, which defined the scope of the Code stated 'It also applies to promotion to UK health professionals and other relevant decision makers at international meetings held outside the UK, except that the promotional material distributed at such meetings will need to comply with local requirements'.

Pierre Fabre submitted that the Pierre Fabre SA stand at ESMO and the materials on it had to comply with the requirements of the Austrian and French Codes; as the meeting was held outside the UK and the UK affiliate was not involved in the organisation of the stand or preparation of the materials, they did not fall within the scope of the UK Code.

Pierre Fabre noted that the complainant did not state the location of the ESMO Congress or the Pierre Fabre entity that organised the stand. According to Pierre Fabre, in these circumstances, the PMCPA could not know whether the subject of the complaint fell within the scope of the Code and therefore within its jurisdiction. Based on the above and the clear wording of the Code, Pierre Fabre did not believe that the stand or associated materials fell within the jurisdiction of the PMCPA and, therefore it did not provide a detailed response to the complaint with respect to those matters.

Pierre Fabre submitted that it was concerned to cooperate fully in relation to any genuine complaint made to the PMCPA within the scope of the Code and if the Panel disagreed with Pierre Fabre's analysis of the issue it would provide further information.

A number of UK employees were present on the stand organised by Pierre Fabre SA during the course of the congress. The complainant did not identify the representative with whom he/she had a discussion and Pierre Fabre accepted that this could have been a UK employee.

Pierre Fabre submitted that it had spoken with every UK employee who was at the ESMO Congress and none recalled having any discussion with any oncologist or other person consistent with the description provided in the complaint. All employees stated that they would not have responded to an enquiry in the manner alleged due to a full verbal briefing provided by the UK prior to the meeting.

In response to a request from the case preparation manager for a complete response to the complaint and additional information, Pierre Fabre provided a list of the global signatories and their job titles and noted that in addition to the stand, Pierre Fabre SA organised a scientific symposium that took place on 26 September.

The Pierre Fabre stand was manned by some of the affiliates that attended the congress. The UK promotional team manned the stand for the majority of the timeslots available. A full rota was included in the internal briefing document which was provided. The global briefing in relation to stand duty was done on the morning of 25 September.

The UK affiliate did not see the stand panels or any of the material that was available on the stand prior to the meeting. That being the case, on the afternoon of 25 September, the UK team was given guidance on how to man the promotional stand. Given that the promotional items had not been through the UK approval process, the representatives were directed not to use any material or allude to any materials/panels on the stand. If a UK health professional came to the stand, the representatives were instructed to take their details and follow up if appropriate upon their return to the UK.

Pierre Fabre submitted that there was no opportunity nor was it feasible to prepare a formal brief for the UK representatives and certify it before the start of the congress; the UK team was due to man the stand the following day.

'Rare Cumulative Toxicity'

Pierre Fabre disagreed with the complainant's view that the above claim was misleading, and could not be substantiated. The company believed that the oncologist was confused with the terminology used; cumulative toxicity vs acute toxicity. It was clear that the complainant was concerned about acute side-effects. Chronic or cumulative toxicity manifested as a result of continuous exposure to a chemical, in this case vinorelbine. However, Pierre Fabre believed that the complainant meant adverse reactions based in the acute setting, hence his/her description of gastrointestinal side-effects.

Petrelli *et al* (2011) stated '…combination of lapatinib with oral vinorelbine as first line chemotherapy in patients with HER2-neu-positive metastatic breast cancer …is characterised by good tolerability and activity, and can be applied for a prolonged period without the risk of major cumulative toxicity in either first or subsequent lines of treatment..'.

Aapro and Finek (2012) stated '…in different clinical trial settings, oral vinorelbine-based regimens allowed a longer duration of treatment, as a result of their activity and the absence of cumulative toxicities.'

Pierre Fabre submitted that the claim 'Rare Cumulative Toxicity' was not misleading, was capable of substantiation and reflected available evidence on adverse reactions and it denied breaches of Clauses 7.2, 7.4 and 7.9.

Majority of patients (79%) were able to dose escalate to 80mg/m²

The claim in the leavepiece read '79% of patients were able to escalate to the standard dose of 80mg/m²'. The claim referred to a first line phase II study, Steger *et al* (2014) that reported out of the 70 patients enrolled, 79% managed to dose escalate to 80mg/m² from the initial dose of 60mg/m². Moreover, the oral vinorelbine SPC had the following guidance on dosing:

> 'As a single agent, the recommended regimen is:
> first three administrations
> 60mg/m²
>
> Subsequent administrations
> Beyond the third administration it is recommended to increase the dose of Navelbine to 80mg/m² once weekly except in those patients for whom the neutrophil count dropped once below 500/mm³ or more than once between 500 and 1000/mm³ during the first three administrations at 60mg/m².
>
> For combination regimens, the dose and schedule will be adapted to the treatment protocol.'

Pierre Fabre stated that it was important to note that oral vinorelbine's licence was different across Europe and it had clearly indicated the aforementioned with the following statement '… NAVELBINE Oral is registered on a national basis …. Please refer to the Summary of Product Characteristics (SmPC) of your specific country …' on the front page of the leavepiece. Oral Vinorelbine was indicated in the UK as a single agent or in combination for the first line treatment of stage 3 or 4 non small cell lung cancer and the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline regimen.

Pierre Fabre was unable to comment on the particular practice of the complainant but submitted that the information provided was fair, balanced and unambiguous. The reference that supported 79% of patients escalating up to 80mg/m² was capable of substantiation and hence, Pierre Fabre denied breaches of Clauses 7.2 and 7.4.

'Easily Manageable Adverse Events'

The claim 'Easily Manageable Adverse Events' was taken directly from an international randomized phase II study in non small cell lung cancer (Bennouna *et al*, 2014). Bennouna *et al* compared 153 patients on pemetrexed/cisplatin and vinorelbine/cisplatin, and found 'the safety profile differed across the 2 doublets, but the incidence and severity of adverse events was acceptable and easily manageable in the 2 arms …'

Pierre Fabre summarised the safety section of the study and considered that the claim 'Easily Manageable Adverse Events' was not misleading; it was balanced, fair, capable of substantiation and reflected current evidence on adverse reactions for the product and therefore was not in breach of Clauses 7.2, 7.4 and 7.9.

Inappropriate response from a representative

Pierre Fabre was unable to comment on what was discussed with the complainant as it could not identify the oncologist or the representative in question. The UK affiliate checked with all of its employees who manned the stand for the duration of the congress and confirmed that no such conversation took place. Moreover, all of the UK employees were briefed on Friday 25 September, not to use any of the materials on the stand or the stand panels as none of the materials were certified/approved by the UK team.

Pierre Fabre provided the briefing that was shared with all internal personnel before the congress started. The briefing included the following:

- You are invited to address questions or share scientific information about our products within their labelling in a fair, balanced, and scientific manner, in full compliance with the applicable regulations
  - The aids mentioned in the previous slide and available on the booth will support you in this task
- Beware that [Navelbine] is approved at national and not centralised level and there can be differences in its labelling from one country to another
- If asked questions not related to the products' approved labelling kindly refer the health professional to Medical Affairs staff on the scientific corner
- If confronted with a question you do not know how or cannot answer and there is no appropriate functions on site to address it, ask your physician to fill in a request card available on the booth and reassure him/her that the appropriate function will follow up locally after the congress
- Please do not venture in answers you do not fully master: regulations and products' labelling do vary from one country to another
- Whenever in doubt, refrain from taking initiative and rather refer the [health professional] to any of the [Pierre Fabre] Global MKTG (marketing) or Medical team
  - If no global staff is available, kindly ask the [health professional] to leave his/her contact details on the request card or to come back at a later time
- An [adverse event] form is available on site and should be used according to the pharmacovigilance regulations in the same way you would use it in your daily field activity.'

Pierre Fabre submitted that not only had it briefed its employees adequately, the UK affiliate additionally had a second briefing session for the UK employees that would man the stand. Thus, Pierre Fabre submitted that it had maintained high standards at all times and it denied a breach of Clause 9.1.

Pierre Fabre strongly refuted the suggestion that it had brought the pharmaceutical industry into disrepute. It could justify the claims used in its promotional material and had taken the necessary steps to ensure the representatives behaved in a professional manner while manning the stand at ESMO.

Additionally, the UK affiliate did not know beforehand what material would be used for the congress. The UK team was briefed not to use any material on the stand when it became apparent that the material and claims differed to the UK version and that any discussion which required the use of material would have to be done once the individuals concerned were back in the UK, using UK approved material.

Clause 2 was used as a sign of particular censure, and Pierre Fabre submitted that it had not warranted such a reprimand and was thus not in breach of that clause.

In response to a request for further information, Pierre Fabre submitted that eight UK employees attended the congress. Pierre Fabre also provided copies of the meeting application form, the delegate invitation letter, the invitation letters to Pierre Fabre UK delegates, the Pierre Fabre welcome and logistics pack including the itinerary for Pierre Fabre UK delegates, the Pierre Fabre Symposium invitation and details of the Pierre Fabre stand as well as email confirmation of hospitality review under the Austrian Code. The relevant certificates were also provided for all of the items listed. Pierre Fabre submitted that one of the final signatories did not certify the itinerary as he only received that job bag on the penultimate day of the congress.

PANEL RULING

The Panel noted that, as a preliminary issue, it had to consider whether promotion of Navelbine, at the ESMO Congress, by Pierre Fabre came within the scope of the Code. Clause 1.1 stated that the Code applied to the promotion of medicines to members of the UK health professions and to other relevant decision makers. Furthermore, the supplementary information to Clause 1.1, Scope of the Code, stated that it also included 'promotion to UK health professionals and other relevant decision makers at international meetings held outside the UK, except that the promotional material distributed at such meetings will need to comply with local requirements'.

The Panel noted Pierre Fabre's reference to the supplementary information to Clause 1.11, Applicability of Codes, which stated that activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European country as well as the national Code of the country in which the activities took place or the material was used. Pierre Fabre submitted that the stand at ESMO and the materials on it had to comply with the requirements of the Austrian and French Codes but that, in circumstances where the meeting was held outside the UK and Pierre Fabre Limited had no involvement in the organisation of the stand or preparation of the materials, that these did not fall within the scope of the Code.

The Panel noted the supplementary information to Clause 22.1 stated that in relation to meetings organised by affiliates outside the UK 'Companies should remind their affiliates outside the UK that the ABPI Code of Practice must be complied with if UK health professionals attend meetings which they organise regardless of whether such meetings occur in the UK or abroad'.

The Panel noted that the stand at the ESMO Congress was organised and funded by Pierre Fabre SA, the French global team, which had full responsibility for preparation of the exhibition panels and all materials on the stand or distributed from it.

The Panel noted Pierre Fabre's submission that ESMO was an international meeting attended by medical oncology experts from around the world including a large number from the UK due to the meeting being held in Europe. Employees of the UK affiliate, Pierre Fabre Limited, who were at the meeting supported Pierre Fabre SA by manning the stand together with representatives from other affiliates. The Panel noted, however, that UK representatives provided just over half the man hours needed for the stand (36.5/66.5). Although there were four time slots where no UK representatives were present they were, for all but one of the remaining eight slots, always in the majority of those on the stand; for two of those time slots, only UK representatives manned the stand. In addition Pierre Fabre Limited invited 20 UK based oncologists to attend the congress. The welcome pack provided to these delegates included details of where to find the Pierre Fabre stand. In that regard, the Panel considered that Pierre Fabre in the UK had invited the UK health professionals to view the promotional material on the stand, Further, in the Panel's view, it was more than likely that when UK delegates, and particularly the 20 invited by Pierre Fabre Limited, visited the Pierre Fabre stand, they would talk to UK representatives. The Panel could not understand how the UK representatives could be expected to man the stand without referring to or being seen to use the promotional materials on it as submitted by Pierre Fabre. This submission contradicted the global briefing material which stated that material available on the stand, including the efficacy brochure at issue, would support those manning the stand.

The Panel noted its comments above about the UK company directing UK delegates to the stand and therefore considered that the promotion of vinorelbine to UK health professionals on the stand at the ESMO Congress fell within the scope of the UK Code.

The Panel noted the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedure anonymous complaints were accepted and like all complaints,

judged on the evidence provided by the parties. Complainants had the burden of proving their complaint on the balance of probabilities.

The Panel noted that the claim 'Rare Cumulative Toxicity' appeared on the front page of an efficacy brochure detailing the use of Navelbine in metastatic breast cancer and advanced non small cell lung cancer. The brochure also referred to 'manageable safety profile' and 'easily manageable adverse events'. The claim was referenced to Petrelli *et al* (2011) and Aapro and Finek (2012). Aapro and Finek reviewed 31 studies which included more than 1,000 patients with metastatic breast cancer. The Panel noted Pierre Fabre's submission that cumulative toxicity manifested as a result of continuous exposure to a chemical. The Panel noted the complainant's view that he/she had used vinorelbine for many years and had not found its side-effects to be a rarity; most of his/her patients had had some reaction to vinorelbine, especially gastrointestinal side-effects. With regard to these side-effects, the Panel noted Pierre Fabre's submission that in its view the complainant was concerned with adverse reactions in the acute setting. The Panel noted that the Navelbine summary of product characteristics (SPC) stated that the most common system organ classes involved during post-marketing experience included, *inter alia*, gastrointestinal disorders. A number of adverse reactions reported were listed by system organ and frequency. The Panel noted that Petrelli *et al* referred specifically to the lack of risk of major cumulative toxicity when vinorelbine was administered in combination with labatinib in metastatic breast cancer. Aapro and Finek stated that 'As shown in different studies, oral vinorelbine based-regimens allowed a longer duration of treatment, as a result of their activity and the absence of cumulative toxicities'. In the Panel's view, there was a difference between cumulative toxicity and acute toxicity. In the Panel's view, the claim was not misleading as alleged as it did not imply that acute toxicity was rare but rather that cumulative toxicity was rare. Pierre Fabre had provided relevant data regarding cumulative toxicity. Given all the circumstances, the Panel ruled no breaches of Clauses 7.2, 7.4 and 7.9.

The claim that the majority of patients (79%) were able to dose escalate to 80mg/m^2 appeared on a page detailing the use of Navelbine in metastatic breast cancer. The Panel noted that the claim actually read '79% of patients were able to escalate to the standard dose of 80mg/m^2' and was referenced to Steger *et al*, a poster presented at ESMO in Madrid in September 2014 which included the results of a phase II study to evaluate the efficacy and safety of single agent oral vinorelbine as first line chemotherapy in 70 breast cancer patients presenting with bone metastases without visceral involvement, enrolled between April 2010 and April 2012. The Panel further noted that the SPC stated that the first three administrations of Navelbine should be 60mg/m^2 of body surface area, once weekly. It was recommended that beyond the third administration, the dose of Navelbine should be increased to 80mg/m^2 once weekly except in those patients for whom the neutrophil count dropped once below 500/mm^3 or was more than once between 500 and 1000/mm^3 during the first three administrations. The Panel considered that whilst the claim was based on the poster, it unequivocally implied that around 4 in 5 of all patients could tolerate a dose escalation to 80mg/m^2. The study, however, was only conducted in a small specific population and it was not clear from the claim in the efficacy brochure that there were certain patients in whom dose escalation would not be appropriate based on their neutrophil count. In that regard the Panel did not consider that a statement on two other pages of the brochure which provided a means of calculating doses and which read 'Continue with standard dose of 80mg/m^2/week depending on blood count' was sufficient to clarify the claim at issue. The claim should be able to standalone. The Panel did not consider that Steger *et al* was sufficiently robust to support the strong claim. In that regard the Panel considered that, on the basis of the material before it, the claim was misleading and could not be substantiated and ruled breaches of Clauses 7.2 and 7.4.

The Panel noted that the claim 'Easily Manageable Adverse Events', was on a page of the brochure detailing the use of Navelbine in non squamous non small cell lung cancer (NSCLC). The claim was referenced to Bennouna *et al* (2014), a randomized phase II study involving 153 patients (premetrexed/cisplatin (n=51) or oral vinorelbine/cisplatin (n=102)) with NSCLC. The discussion section of the paper stated that the safety profile differed across the 2 doublets, but the incidence and severity of adverse events was acceptable and easily manageable in both arms. The study did not provide further detailing regarding how the manageability of adverse events was assessed. The Panel noted that it was particularly important not to mislead with regard to side-effects. The Panel noted, however, that this was a highly specialised therapy area and that the material was for use at a European oncology congress. In the Panel's view the audience would be familiar with the side effect profile of cytotoxic medicines generally. The Navelbine SPC listed a number of adverse reactions most of which were common (≥ 1/100 < 1/10) or very common (≥ 1/10). However some of those reactions were reversible with or without appropriate additional therapy or could be reduced in severity with supportive treatment. In the Panel's view, given the therapy area and the target audience, the claim 'Easily Manageable Adverse Events' was not unreasonable. In that regard the Panel did not consider that the claim was misleading about the adverse events associated with Navelbine. The Panel considered that the claim could be substantiated. No breaches of Clauses 7.2, 7.4 and 7.9 were ruled.

The Panel noted its rulings above of breaches of the Code and considered that high standards had not been maintained and ruled a breach of Clause 9.1.

With regard to Clause 2, the Panel noted that prejudicing patient safety was an activity likely to be ruled in breach of Clause 2. The Panel noted that there was no evidence to show that patient safety had been adversely affected. The Panel was, however, concerned about the misleading claim about dose escalation to 80mg/m^2 but noted that it did not suggest that all patients could dose escalate. Other information in the leavepiece referred to

administering 80mg/m^2 depending on blood count. On balance no breach of Clause 2 was ruled.

The Panel noted the complainant's allegation regarding the misleading response received when questioning the Pierre Fabre representative on the stand. The Panel noted Pierre Fabre's submission that it was not able to identify the oncologist or the representative in question. As the complainant was non-contactable it was not possible to ask him/her for further information. The Panel noted Pierre Fabre's submission that the UK affiliate had checked with all of its employees that had manned the stand for the duration of the congress and all denied that such a conversation took place. The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. It was impossible to know what had transpired between the parties. Although noting that extreme dissatisfaction was usually required before an individual was moved to complain, on the basis of the information before it the Panel ruled no breach of Clauses 7.2, 7.4, 7.9 and 9.1 of the Code.

Complaint received **7 October 2015**

Case completed **26 January 2016**

CASE AUTH/2800/10/15

SANOFI v AMGEN

Promotion of Repatha

Sanofi complained about a Repatha (evolocumab) leavepiece distributed by Amgen at the European Society of Cardiology (ESC) Congress, London, 29 August – 2 September 2015. Repatha was a lipid lowering medicine for, *inter alia*, adults with primary hypercholesterolaemia or mixed dyslipidaemia.

Sanofi alleged that the claim '75% additional LDL-C reduction vs placebo', which appeared on the front cover of the leavepiece, was misleading and had been 'cherry-picked' from the supporting reference (Robinson *et al* 2014). Robinson *et al* made it clear that the 75% efficacy claim vs double-placebo was not a primary endpoint nor was it likely to be a secondary endpoint. The primary endpoint was stated to be percentage change from baseline in LDL-C level; secondary endpoints included change from baseline in LDL-C level, percent change from baseline in additional lipid parameters and the proportion of patients achieving LDL-C levels < 70mg/dL. The leavepiece should, at the very least, state the results of the primary endpoint in addition to the 75% claim. A breach of the Code was alleged.

Sanofi noted the complex study design; the 75% efficacy claim was derived from only one of the 24 treatment groups so that although 1,896 patients were involved in the study as a whole, the claim was derived from a group of only 109; this was not stated. The only place any patient number was stated was in a footer which mentioned that 1,896 patients were involved in the entire study. Sanofi alleged that readers would think that the 75% efficacy claim was derived from the entire study rather than just 109 patients; they would give the efficacy claim less credibility if they realised that it was based on fewer patients than the 1,896 cited.

Sanofi stated that the group from which the 75% claim was derived was one of two in the 'high-intensity statin' category; the corresponding result for the other group in this category was 66% vs double-placebo (59% vs baseline). Sanofi submitted that in order not to mislead Amgen should have given a range of results, ie 66%-75% under the 'high-intensity statin' category. By not doing so Amgen had 'cherry-picked' the results thus misleading readers into thinking that Repatha had a higher efficacy figure than the range demonstrated in the study. As such, prescribers would be misled into prescribing Repatha for a wider group of patients than would be done otherwise. Sanofi alleged breaches of the Code.

Sanofi stated that when using the 75% efficacy claim, Amgen should also have added that the double-placebo arm (who were not on any form of lipid-lowering therapy) had an increase of LDL-C of 13%. Hence, the actual efficacy result vs baseline was much lower at 62%. Readers should be told about the 13% increase so that an informed assessment could be made about the true efficacy of Repatha from baseline. Sanofi noted that Robinson *et al* stated that the primary endpoint was percentage change from baseline in LDL-C. Therefore, headlining a result of Repatha plus a high intensity statin vs double-placebo implied a larger efficacy effect and was clinically misleading. Sanofi alleged breaches of the Code.

Sanofi further stated that positioning the 75% efficacy claim above an outline of Repatha's indications implied that the claim applied to all adult patient types with primary hypercholesterolaemia and mixed dyslipidaemia, which was not so. Sanofi alleged that such positioning the 75% efficacy claim was misleading and inconsistent with the Repatha summary of product characteristics (SPC), in breach of the Code.

Sanofi noted that the 75% efficacy claim was made at one of the world's largest cardiology scientific congresses with about 30,000 delegates in attendance. In that regard Sanofi alleged that Amgen had not upheld high standards by misleading so many health professionals and scientists.

The detailed response from Amgen is given below.

The Panel noted that Robinson *et al* was a randomized, double-blind, placebo- and ezetimibe-controlled trial to evaluate the efficacy of evolocumab (dosed once every two weeks or once a month) in patients with hypercholesterolaemia on background statin therapy. In that regard Sanofi was incorrect to state that patients in the double-placebo arm were not on any form of lipid-lowering therapy; they were on background statin therapy. The study consisted of 24 different treatment arms and so although 1,896 patients received at least one dose of the study medicines, the number of patients in each treatment arm ranged from 55 to 115. The co-primary endpoints were the percentage change from *baseline* in LDL-C level at the mean of weeks 10 and 12 and at week 12. The Panel noted that although a footnote on the front page of the leavepiece gave a brief description of the study at issue, it stated that 1,896 patients were involved without explaining that the numbers of patients in the treatment groups were considerably fewer.

The results section of Robinson *et al* stated that at the mean of weeks 10 and 12, percent reduction from baseline in LDL-C (one of the co-primary endpoints) was 59-66% with every two week dosing of evolocumab and 62-65% with monthly dosing. It was stated that these reductions corresponded to changes vs *placebo* of 66-75% and 63-75% respectively; it was from these higher figures that the claim in question was derived. The

study result highlighted in the leavepiece ('75% additional LDL-C reduction vs placebo') was that obtained from patients on atorvastatin 80mg plus evolocumab given every two weeks (n=109) vs patients on atorvastatin 80mg and double-placebo. In that regard the Panel noted Amgen's submission that the atorvastatin 80mg cohort was the most clinically relevant cohort for UK clinical practice. For patients on other background statins the treatment differences vs placebo for evolocumab dosed every two weeks ranged from 66% to 70%. In that regard the Panel noted that 75% applied only to patients on atorvastatin 80mg and the treatment differences were otherwise no more than 70%. The Panel noted that although a footnote gave brief details of the design and outcome of Robinson *et al* (including the range (66-75%) of additional LDL-cholesterol lowering vs placebo), it was an established principle under the Code that footnotes should not be used to qualify otherwise misleading headlines. The Panel further noted that the discussion section of Robinson *et al* it stated that the limitations of the study included, *inter alia*, the small sample sizes in some of the groups. In conclusion the authors stated that further studies were needed to evaluate the longer-term clinical outcomes of adding evolocumab to background statin therapy.

The Panel noted that the claim '75% additional LDL-C reduction vs placebo' appeared prominently on the front cover of the leavepiece. The claim was qualified below, in smaller print, with 'In patients with primary hypercholesterolaemia or mixed dyslipidaemia receiving atorvastatin 80mg, Repatha 140mg [every two weeks] delivered an additional 75% LDL-C reduction vs placebo'. The Panel noted, however, that the headline claim was that Repatha delivered consistent LDL-C reductions and in that regard it noted its comments above about the range of percentage reductions vs placebo. The Panel further noted that the 75% additional reductions in LDL-C levels were vs placebo. Although this figure was *based* on the co-primary endpoint it was not the co-primary endpoint *per se* which, according to the study, was vs baseline and which was a lower percentage.

The Panel further noted that detailed below the claim in question were the therapeutic indications for Repatha. In that regard the Panel considered that some readers might assume that the clinical results referred to ('75% additional LDL-C reduction vs placebo') could be achieved in all patients eligible for therapy. This was not so; that result was achieved only in a very specific treatment group. However, the Panel did not consider that the relative position of the claim to the therapeutic indications meant that the claim was inconsistent with the particulars listed in the Repatha SPC. No breach of the Code was ruled.

The Panel did not consider that the claim at issue, by emphasising the results from just one study arm, represented the balance of the evidence from Robinson *et al* even though, according to Amgen that was the most clinically relevant cohort for UK clinical practice. In that regard, however, the Panel noted that Repatha could be used in combination with other statins or alone or in combination with other lipid lowering therapies in patients who were statin intolerant, or for whom a statin was contraindicated. Section 5.1 of the Repatha SPC referred to LDL-C reductions of approximately 55% to 75%. In addition, the Panel noted that the more favourable result vs placebo had been used in the leavepiece not the results vs baseline. Overall the Panel did not consider that the information in the leavepiece was sufficiently complete, or set out in such a way as to ensure that readers could form their own opinion of the clinical significance of Robinson *et al* and the impact that it might have on their use of Repatha. A breach of the Code was ruled. The Panel considered that the prominence given to the 75% additional LDL-C reduction vs placebo in a small patient cohort, exaggerated the general efficacy of Repatha. The result would not apply to all patients eligible for Repatha therapy. A breach of the Code was ruled.

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

Sanofi complained about a Repatha (evolocumab) leavepiece (ref UKIE-P-145-0715-110865 and EUHQ-P-145-0715-110847, August 2015) distributed by Amgen at the European Society of Cardiology (ESC) Congress, London, 29 August – 2 September 2015.

Repatha was indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C (low density lipoprotein cholesterol) goals with the maximum tolerated dose of a statin; or alone or in combination with other lipid-lowering therapies in patients who were statin-intolerant, or for whom a statin was contraindicated. It was also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

Claim '75% additional LDL-C reduction vs placebo'.

The claim '75% additional LDL-C reduction vs placebo' appeared on the front cover of the six page, gate-folded leavepiece beneath the heading 'Repatha (evolocumab). The first licensed PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibitor in the EU, delivering consistent, intensive LDL-C reductions'. The claim was followed by 'In patients with primary hypercholesterolaemia or mixed dyslipidaemia receiving atorvastatin 80mg. Repatha 140mg Q2W [every two weeks] delivered an additional 75% LDL-C reduction vs placebo' which was referenced to Robinson *et al* (2014).

COMPLAINT

Sanofi alleged that the claim was misleading and had been 'cherry-picked' from Robinson *et al*. It was clear from reading Robinson *et al* that the 75% efficacy claim vs double-placebo was not a primary endpoint nor was it likely to be a secondary

endpoint. The authors stated that the primary endpoint was percentage change from baseline in LDL-C level while the secondary endpoints included change from baseline in LDL-C level, percent change from baseline in additional lipid parameters and the proportion of patients achieving LDL-C levels < 70mg/dL. The leavepiece should, at the very least, state the results of the primary endpoint in addition to the 75% claim. A breach of Clause 7.2 was alleged.

Sanofi further noted the complex study design of Robinson *et al*. The 75% efficacy claim was derived from only one of the 24 treatment groups, ie the group (n=109) of Repatha 140mg every two weeks and atorvastatin 80mg every two weeks [sic, atorvastatin was taken each day]. Sanofi noted that 1,896 patients were involved in the study but the 75% efficacy claim was derived from only 109. Nowhere in the leavepiece was the 109 patient number mentioned. The only place any patient number was stated was in a footer which mentioned that 1,896 patients were involved in the entire study. Sanofi alleged that readers would be misled into thinking that the 75% efficacy claim was derived from the entire study rather than just one of the 24 groups comprised of only 109 patients. Clinicians would naturally give the 75% efficacy claim less credibility if they realised that it was based on fewer patients than the 1,896 patient number quoted.

Sanofi stated that the group (n=109) taking Repatha 140mg every two weeks and atorvastatin 80mg was one of two groups stratified under the 'high-intensity statin' category; the other group (n=111) in this category were on Repatha 140mg every two weeks and rosuvastatin 40mg. The corresponding result for the latter group was lower at 66% vs double-placebo (59% vs baseline). Sanofi submitted that in order not to mislead, the lower result from the Repatha and rosuvastatin group should also be stated in the leavepiece. Therefore, instead of stating the 75% efficacy claim in isolation, Amgen should have given a range of results, ie 66%-75% under the 'high-intensity statin' category. By not doing so Amgen had 'cherry-picked' the higher efficacy result while ignoring the lower associated figure, thereby misleading readers into thinking that Repatha had a higher efficacy figure than the range demonstrated in the study. As such, prescribers would be misled into prescribing Repatha for a wider group of patients than would be done otherwise. Sanofi alleged breaches of Clauses 7.2 and 7.10.

Sanofi stated that when using the 75% efficacy claim, Amgen should also have added that the double-placebo arm (who were not on any form of lipid-lowering therapy) had an increase of LDL-C of 13%. Hence, the actual efficacy result vs baseline was much lower at 62%. Readers should be told about the 13% increase so that an informed assessment could be made about the true efficacy of Repatha from baseline. Sanofi noted that Robinson *et al* stated that the primary endpoint was percentage change from baseline in LDL-C. Therefore, headlining a result of Repatha plus a high intensity statin vs double-placebo implied a larger efficacy effect and was clinically misleading. Sanofi alleged breaches of Clauses 7.2 and 7.10.

Sanofi further stated that the 75% efficacy claim was positioned above text in the lower half of the first page which outlined Repatha's therapeutic indications thereby implying that the claim applied to all adult patient types with primary hypercholesterolaemia and mixed dyslipidaemia, which was clearly not so. Sanofi alleged that positioning the 75% efficacy claim above the therapeutic indications was both misleading and inconsistent with the Repatha summary of product characteristics (SPC), in breach of Clauses 3.2 and 7.10.

Sanofi noted that the 75% efficacy claim was made at one of the world's largest cardiology scientific congresses with about 30,000 delegates in attendance. In that regard Sanofi alleged a breach of Clause 9.1 as Amgen had not upheld high standards by misleading so many health professionals and scientists.

RESPONSE

Amgen confirmed that the co-primary endpoint of the pivotal Robinson *et al* study was percentage change in LDL-C from baseline vs placebo. Robinson *et al* was a phase 3, multicenter, double-blind, randomized, double-dummy, placebo- and ezetimibe-controlled study to evaluate the efficacy and safety of 12 weeks of subcutaneous (SC) evolocumab compared with placebo when administered in combination with statin therapy in hyperlipidaemic subjects. After the screening period, eligible subjects were randomized to 1 of 5 statin cohorts (atorvastatin 10mg or 80mg, rosuvastatin 5mg or 40mg, or simvastatin 40mg) for a 4 week lipid stabilization period. Following the lipid stabilization period, eligible subjects were randomized within each statin dose cohort to blinded investigation product (evolocumab, placebo or ezetimibe). The study had two co-primary endpoints, percent change from baseline in LDL-C at week 12 and mean percent change from baseline in LDL-C at weeks 10 and 12 (averaging of weeks 10 and 12, ie the LDL reduction at week 12 and the LDL reduction at 10/12 weeks). Amgen submitted that in order to calculate the treatment difference between the two arms, the following was performed to determine the outcome:

1 Determine the LDL reduction for each subject in the study vs baseline (at 12 weeks and weeks 10/12)
2 Derive a mean for the LDL reduction on each group (ie evolocumab plus statin and placebo plus statin)
3 Compare the mean LDL-C reduction in the evolocumab plus statin treatment group with that in the placebo plus statin treatment group.

Amgen submitted it was standard statistical practice that the endpoint was written at the subject level ie what was assessed in the patient. The main outcomes measure (LDL percent change from baseline) referred to the patient level data from which efficacy claims might be made depending on the objective of the study which, in this case, was the effect of evolocumab on LDL-C lowering compared with the control groups (placebo or ezetimibe). In addition to being standard statistical

practice, this was one of the key reasons why control arms were used in studies in order to obtain robust efficacy data. For the avoidance of doubt, this was specifically mentioned in the rationale and design of the study (Robinson *et al* 2014b) as follows:

> 'The aim of this phase 3 study is to evaluate the efficacy of 12 weeks of subcutaneous evolocumab (vs placebo) administered every 2 weeks or every month in combination with a statin in patients with hypercholesterolemia and mixed dyslipidemia' (emphasis added).
>
> '[Robinson *et al*] is a phase 3 trial designed to assess LDL-C response to evolocumab compared with placebo in subjects randomized to 1 of 3 commonly prescribed statins while providing comparative data against ezetimibe' (emphasis added).
>
> 'The expected number of subjects randomized to IP [investigational product] for this study was 1700, which will provide ≥98% power for testing the superiority of each evolocumab dosing regimen over placebo on the co primary endpoints within each background statin therapy group and SC dose-frequency group' (emphasis added).

The treatments difference results (vs placebo), including those for the atorvastatin 80mg arm, were shown in table 4 of Robinson *et al*. Amgen explained this in detail to Sanofi both in its written response and during the teleconference and provided it with the study design paper (Robinson *et al* 2014b). Therefore, Amgen submitted that Sanofi was wrong to infer that the claim was not based on the primary endpoint and Amgen refuted a breach of Clause 7.2.

Amgen submitted that each statin cohort could be considered as its own stand-alone study (ie 5 studies in one). Each cohort was the same, as if different studies had been run among subjects with a particular fixed stable background statin under different protocol numbers. The same held for the dose frequencies of evolocumab. The sample size and power of the study was designed such that each cohort could be evaluated on its own. The co-primary endpoints were evaluated within the statin dose groups and evolocumab dose frequency groups separately (Robinson *et al* 2014b). Multiplicity adjustments within each dose-frequency group and against each control arm were made to correct for multiple endpoints.

Thus, the 75% LDL-C reduction vs placebo was based on a statistically robust study design where each statin cohort was compared with the corresponding placebo group and considered a statistically significant primary efficacy endpoint result in its own right. The results for the atorvastatin 80mg cohort were highly significant for both of the co-primary endpoints and the 75% claim represented a pre-specified co-primary endpoint. Amgen denied a breach of Clause 7.2.

Amgen submitted that the design of the study was rigorous to ensure robust results could be achieved with regards to the efficacy of evolocumab when added to 5 different statin regimens and compared with both placebo and, in the case of the atorvastatin arms, with ezetimibe as well, at two different evolocumab doses. The 75% efficacy claim came from the evolocumab once every two weeks arm, when added to atorvastatin 80mg, vs placebo (109+55, n=164). The results for the atorvastatin 80mg cohort were highly significant for both of the co-primary endpoints. As detailed above, the 75% efficacy result represented a primary endpoint and it was therefore reasonable to use it as a headline claim. It was clearly stated in the leavepiece, below the 75%, that the claim referred to patients taking atorvastatin 80mg. Amgen submitted that the footnote clearly stated that the data had been taken from Robinson *et al*, which involved 1,896 patients with primary hypercholesterolaemia or mixed dyslipidaemia. It was clear that the numbers related to the total study; '… international trial [(Robinson *et al*)] involving 1,896 patients …'. The footnote outlined all the different statin baseline regimens used and the range of LDL-C reductions achieved, within the overall 1,896 patient study. It was wrong to argue that readers would be confused and believe that the claim '75% additional LDL-C reduction vs placebo' was based on 1,896 patients with primary hypercholesterolaemia or mixed dyslipidaemia. The indication, as per the Repatha SPC, was in combination with a maximum tolerated dose of a statin. Atorvastatin 80mg was the maximum licensed dose of atorvastatin. Furthermore, the atorvastatin 80mg cohort was the most clinically relevant cohort for UK clinical practice as it was specifically recommended in the National Institute for Health and Care Excellence (NICE) guideline on lipid modification (CG181) in secondary prevention. Rosuvastatin was not included in the NICE guidelines. It would not be appropriate to base a claim on the results of alternative statins and/or lower doses as these did not reflect the clinical guidelines which clinicians would follow. Importantly Amgen noted that, as part of the pre-vetting process for new medicines, the claim had been pre-vetted by the Medicines and Healthcare products Agency (MHRA) and no objections were raised and the claim was consistent with the Repatha SPC.

In summary, Amgen strongly refuted that the claim was misleading, it was therefore not in breach of Clause 7.2 as it was based on the following points as detailed above:

- This was a pre-specified primary end-point of the study
- Each statin cohort was analysed separately with sufficient sample size and power
- It reflected NICE guidelines on lipid modification (CG181) as well as UK clinical practice
- The claim had been pre-vetted by the MHRA
- It was consistent with the Repatha SPC.

Amgen submitted that as explained previously, the design and scale of the study were such that each arm could be considered a statistically significant result in its own right and therefore the 75% referred to a valid primary efficacy result. The 75% result was selected as it reflected the group on atorvastatin

80mg at baseline. Of the individual primary efficacy results, it was chosen as it was deemed most relevant to UK clinicians, given 80mg atorvastatin was recommended as the high intensity statin of choice in the relevant NICE clinical guideline (CG181). Rosuvastatin was not mentioned in the NICE guidelines. The range 66-75% was included in the footnotes. In discussion with Sanofi, Amgen offered to make the range more prominent underneath the claim although it continued to believe that it was unnecessary and that offer was rejected by Sanofi. Amgen was extremely disappointed to find that what it had proposed was now the subject of a complaint. Amgen had now added the range to the 75% claim, a copy of the updated leavepiece (ref UKIE-P-145-0715-110865(1)) was provided. Amgen voluntarily offered to make the 66-75% range more prominent underneath the 75% claim, and Sanofi had agreed to this compromise in other countries.

Amgen submitted that as described earlier, the primary efficacy results of the study were vs placebo or ezetimibe thus the resultant efficacy claims reflected this. Again, this was a key reason as to why trials were conducted with control arms. With regard to the comment 'who were not on any form of lipid lowering therapy', Amgen did not understand the point at issue and confirmed that all patients were randomized to one of 5 statin regimens, before being randomized to evolocumab, ezetimibe or placebo. As mentioned in the design paper (Robinson *et al* 2014b)), 'To obtain stable baseline lipid values and ensure subjects were able to tolerate statins, all subjects (irrespective of prior statin usage) entered a 4-week lipid-stabilization period on their assigned statin'. Amgen submitted that such matters indicated that Sanofi did not understand the conduct of the trial and had therefore made an unfounded complaint. The claim was based directly on the primary endpoint of the trial and Amgen therefore refuted breaches of Clauses 7.2 and 7.10.

The context of the claim and nature of the study from which it was derived were made clear in the wording around the claim and in the footer. Amgen considered that it was good practice to make the licensed therapeutic indication of the product clear on the first page of the leavepiece (which was taken verbatim from the SPC). This was explicitly stated on the leavepiece under the heading 'Therapeutic indications'. Such detail was what one would expect when a new medicine came to the market and also one of the MHRA's requirements. In Amgen's view, Sanofi appeared to have asserted that the therapeutic indications should always be placed in isolation on a page. This was incorrect and not required by the Code. Amgen submitted that that complaint was unfounded and it denied a breach of Clauses 3.2 and 7.10.

For the detailed reasons outlined above, Amgen did not consider that ESC delegates had been misled and it therefore denied a breach of Clause 9.1. Amgen had applied its usual high standards throughout the process and noted that all promotional materials used at the ESC had been pre-vetted and approved by the MHRA and no claims had been made that were inconsistent with the Repatha SPC.

PANEL RULING

The Panel noted that Robinson *et al* was a randomized, double-blind, placebo- and ezetimibe-controlled trial to evaluate the efficacy of evolocumab (dosed either once every two weeks or once a month) in patients with hypercholesterolaemia on background statin therapy. In that regard Sanofi was incorrect to state that patients in the double-placebo arm were not on any form of lipid-lowering therapy; they were on background statin therapy. The study consisted of 24 different treatment arms and so although 1,896 patients received at least one dose of the study medicines, the number of patients in each treatment arm ranged from 55 to 115. The co-primary endpoints were the percentage change from *baseline* in LDL-C level at the mean of weeks 10 and 12 and at week 12. The Panel noted that although a footnote on the front page of the leavepiece gave a brief description of the study at issue, it stated that 1,896 patients were involved without explaining that the numbers of patients in the treatment groups were considerably fewer.

The results section of Robinson *et al* stated that at the mean of weeks 10 and 12, percent reduction from baseline in LDL-C (one of the co-primary endpoints) was 59-66% with every two week dosing of evolocumab and 62-65% with monthly dosing. It was stated that these reductions corresponded to changes vs *placebo* of 66-75% and 63-75% respectively; it was from these higher figures that the claim in question was derived. The study result highlighted in the leavepiece ('75% additional LDL-C reduction vs placebo') was that obtained from patients on atorvastatin 80mg plus evolocumab given every two weeks (n=109) vs patients on atorvastatin 80mg and double-placebo. In that regard the Panel noted Amgen's submission that the atorvastatin 80mg cohort was the most clinically relevant cohort for UK clinical practice. For patients on other background statins the treatment differences vs placebo for evolocumab dosed every two weeks were 66% (rosuvastatin 40mg, n=111), 70% (atorvastatin 10mg, n=110), 69% (simvastatin 40mg, n=112) and 67% (rosuvastatin 5mg, n=113). In that regard the Panel noted that the headline figure of 75% applied only to patients on atorvastatin 80mg and the treatment differences were otherwise no more than 70%. In the study arms which included evolocumab dosed monthly then the treatment differences vs placebo were similar ie 75% (atorvastatin 80mg, n=110), 63% (rosuvastatin 40mg, n=112), 63% (atorvastatin 10mg, n=110), 68% (simvastatin 40mg, n=115) and 67% (rosuvastatin 5mg, n= 115). The Panel noted that although a footnote gave brief details of the design and outcome of Robinson *et al* (including the range (66-75%) of additional LDL-cholesterol lowering vs placebo), it was an established principle under the Code that footnotes should not be used to qualify otherwise misleading headlines. The Panel further noted that the discussion section of Robinson *et al* it stated that the limitations of the study included, *inter alia*, the small sample sizes in some of the groups. In conclusion the authors stated that further studies were needed to evaluate the longer-term clinical outcomes of adding evolocumab to background statin therapy.

The Panel noted that the claim '75% additional LDL-C reduction vs placebo' appeared prominently on the front cover of the leavepiece. The claim was qualified below, in smaller print, with 'In patients with primary hypercholesterolaemia or mixed dyslipidaemia receiving atorvastatin 80mg, Repatha 140mg [every two weeks] delivered an additional 75% LDL-C reduction vs placebo'. The Panel noted, however, that the headline claim was that Repatha delivered consistent LDL-C reductions and in that regard it noted its comments above about the range of percentage reductions vs placebo. The Panel further noted that the 75% additional reductions in LDL-C levels were vs placebo. Although this figure was *based* on the co-primary endpoint it was not the co-primary endpoint *per se* which, according to the study, was vs baseline and which was a lower percentage.

The Panel further noted that below the claim in question, the leavepiece detailed the therapeutic indications for Repatha. In that regard the Panel considered that some readers might assume that the clinical results referred to ('75% additional LDL-C reduction vs placebo') could be achieved in all patients eligible for Repatha therapy. This was not so; that result was achieved in a very specific treatment group ie those taking atorvastatin 80mg. The Panel noted the alleged breach of Clause 3.2 with regard to the positioning of the 75% efficacy claim above the therapeutic indications. The Panel did not consider that the relative position of the claim to the therapeutic indications meant that the claim was inconsistent with the particulars listed in the Repatha SPC. No breach of Clause 3.2 was ruled.

The Panel did not consider that the claim at issue, by emphasising the results from just one study arm, represented the balance of the evidence from Robinson *et al* even though, according to Amgen that was the most clinically relevant cohort for UK clinical practice. In that regard, however, the Panel noted that Repatha could be used in combination with other statins or alone or in combination with other lipid lowering therapies in patients who were statin intolerant, or for whom a statin was contraindicated. Section 5.1 of the Repatha SPC referred to LDL-C reductions of approximately 55% to 75%. In addition, the Panel noted that the more favourable result vs placebo had been used in the leavepiece not the results vs baseline. Overall the Panel did not consider that the information in the leavepiece was sufficiently complete, or set out in such a way as to ensure that readers could form their own opinion of the clinical significance of Robinson *et al* and the impact that it might have on their use of Repatha. A breach of Clause 7.2 was ruled. The Panel considered that the prominence given to the 75% additional LDL-C reduction vs placebo in a small patient cohort, exaggerated the general efficacy of Repatha. The result would not apply to all patients eligible for Repatha therapy. A breach of Clause 7.10 was ruled.

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

Complaint received **20 October 2015**

Case completed **11 January 2016**

CASE AUTH/2801/11/15

VOLUNTARY ADMISSION BY JANSSEN

Outdated prescribing information

Janssen-Cilag voluntarily admitted that its Stelara (ustekinumab) advertisement published in the Annals of Rheumatic Disease (ARD), October 2015, contained outdated prescribing information.

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

Janssen stated that its media booking agency notified it on 5 October that the publishing group wished to apologize for its error in placing the Stelara advertisement at issue. The publishing group had over printed the Stelara bound insert advertisement commissioned for the June 2015 issue of the ARD and had, without Janssen's knowledge, inserted them into the October 2015 edition.

The Stelara advertisement in the October 2015 edition of the ARD had been prepared, approved and certified in April 2015 and contained November 2014 prescribing information. The Stelara prescribing information was updated in June 2015 with the addition of wording for the plaque psoriasis paediatric indication; dosing information in paediatrics and the availability of a 45mg vial. This information would not be relevant to the ARD rheumatology audience. Janssen confirmed that the June 2015 prescribing information contained no additional/different safety information compared with the November 2014 prescribing information, and therefore the outdated prescribing information in the advertisement at issue had not risked patient safety. Janssen asked the publishing group to confirm that future advertisement placements would be confirmed with the relevant product manager at least 5 days prior to the journal closing.

Janssen acknowledged a breach because the expired prescribing information included in the advertisement was not consistent with the summary of product characteristics (SPC) at the time of publication.

Further details from Janssen are given below.

The Panel noted Janssen's submission that the publishing group had, without Janssen's prior knowledge, inserted the Stelara bound insert commissioned for the June 2015 issue of the ARD into the October 2015 edition. This advertisement had been prepared, approved and certified in April 2015 and contained the November 2014 prescribing information. The current prescribing information was dated June 2015. The Panel noted that after submitting its voluntary admission and receiving the PMCPA's letter, Janssen found out that the publishing group had placed another insert which was prepared in March 2015, and which also contained the November 2014 prescribing information, in BMJ Clinical Research, 5 September, again without the consent or prior knowledge of Janssen or its media booking agency. The Panel noted that the April 2015 advertisement was the subject of the voluntary admission.

The Panel noted that the first side of the advertisement related to use of Stelara in the treatment of moderate-to-severe plaque psoriasis. The reverse side referred to active psoriatic arthritis and contained the November 2014 prescribing information. The Panel noted Janssen's submission that the addition of the plaque psoriasis paediatric indication would not be relevant to the ARD rheumatology audience.

The Panel noted that the Stelara prescribing information was updated in June 2015 to reflect the addition of the paediatric (12 years and over) plaque psoriasis indication and included dosing information in the paediatric population and the availability of a 45mg vial. The November 2014 prescribing information stated that Stelara was not recommended in children under 18, whereas the June 2015 prescribing information stated that it was not recommended in children under 12 years. The Panel noted Janssen's submission that the June 2015 prescribing information contained no additional/different safety information. The Panel noted that the June 2015 prescribing information side effects, stated 'studies show adverse events reported in ≥ 12 year olds with plaque psoriasis were similar to those seen in previous studies in adults with plaque psoriasis'.

The Panel noted that although Janssen had been let down by the publishing group which had admitted full responsibility for the error, it was an established principle under the Code that pharmaceutical companies were responsible for third parties even if that third party acted outside the instructions from the pharmaceutical company.

The Panel noted that whilst the first side of the advertisement promoted Stelara for use in moderate-to-severe plaque psoriasis, it was not clear whether the advertisement was restricted to the adult population or not. In the Panel's view some readers might assume that the advertisement related to all patients with moderate-to-severe plaque psoriasis who could be treated with Stelara ie anyone from the age of 12. In the Panel's view, the prescribing information should thus have also included the paediatric indication and dosage information in line with the SPC. The advertisement contained out of date prescribing information which was not in line with the SPC. The Panel ruled a breach of the Code as acknowledged by Janssen.

The Panel noted Janssen's submission that following the update of the Stelara prescribing information in June 2015, all affected materials were withdrawn within the agreed timelines. However, the telephone

briefing of the media booking agency was not followed up in writing so the briefing had not been formally documented as required by the relevant standard operating procedure. The Panel further noted that Janssen had asked the publishing group to confirm that all future advertisement placements would be confirmed with the relevant product manager 5-14 days prior to the journal closing. The Panel noted that in addition to the advertisement at issue a further advertisement also containing outdated prescribing information had been published in a different BMJ publication. The Panel considered that high standards had not been maintained and a breach of the Code was ruled as acknowledged by Janssen.

Janssen-Cilag Ltd voluntarily admitted that the October 2015 edition of the Annals of Rheumatic Disease (ARD) published a two page bound insert advertisement for Stelara (ustekinumab) (ref PHGB/STE/0415/0010) that contained outdated prescribing information.

Stelara was indicated for the treatment of moderate-to-severe plaque psoriasis in adults who failed to respond to, or who had a contraindication to, or were intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A). Stelara was also indicated for the treatment of moderate-to-severe plaque psoriasis in adolescents from the age of 12 years who were inadequately controlled by, or were intolerant to, other systemic therapies or phototherapies. Stelara was also indicated alone or in combination with MTX for the treatment of active psoriatic arthritis in adults when the response to previous non-biological disease-modifying anti-rheumatic medicine therapy had been inadequate.

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

VOLUNTARY ADMISSION

Janssen stated that it received notification from its media booking agency, on 5 October that the publishing group wished to apologize for its error in placing a Stelara advertisement in the October 2015 edition of ARD. The publishing group had over printed the Stelara bound insert advertisement commissioned for the June 2015 issue of the ARD and had, without Janssen's prior knowledge, inserted them into the October 2015 edition.

The Stelara marketing team regularly communicated with the media booking agency to ensure that all published advertisements were fully copy approved, certified and complied with the Code. However, the decision by the publishing group to run the advertisement of its own volition, and without prior permission from Janssen or the booking agency, meant that there was no opportunity to discuss the particular advertisement placement.

The October 2015 edition of the ARD was distributed on 21 September 2015 including the Stelara advertisement at issue which was originally prepared, approved and certified in April 2015 and contained the November 2014 prescribing information. The Stelara prescribing information was updated in June 2015 to reflect the addition of the paediatric plaque psoriasis indication, which would not be relevant to the ARD rheumatology audience. The changes to the prescribing information included wording for the paediatric plaque psoriasis indication; dosing information in the paediatric population and the availability of a 45mg vial formulation. Janssen confirmed that the June 2015 prescribing information contained no additional/different safety information compared with the November 2014 prescribing information, and therefore the outdated prescribing information in the advertisement at issue had not risked patient safety. Janssen provided a copy of the November 2014 Stelara prescribing information and an annotated version of the June 2015 prescribing information indicating the changes. Janssen requested confirmation from the publishing group that all future advertisement placements would be confirmed with the relevant Janssen product manager 5-14 days prior to the journal closing. The Stelara marketing team and the media booking agency would also continue to communicate regularly to ensure it met the Code standards.

Janssen admitted a breach of Clause 4.1 because the expired prescribing information included in the advertisement was not consistent with the summary of product characteristics (SPC) at the time of publication. Janssen submitted that it had voluntarily contacted the PMCPA about the incident; it had not received any complaint from the ARD readership or companies. Janssen submitted that it took responsibilities under the Code very seriously and sincerely regretted the actions taken by the publishing group. Janssen registered its dissatisfaction with the publishing group which confirmed that any future advertisements would only be placed with prior agreement from Janssen.

When writing to confirm that the matter would be taken up under the Code, the Authority asked Janssen to provide any further comments it might have in relation to Clauses 4.1 and 9.1.

RESPONSE

Janssen submitted that following the June 2015 prescribing information update, the changes were confirmed with the media booking agency and Janssen provided direction to ensure that all subsequent planned advertisement placements included the updated text. In addition, following notification of the unauthorised placement of the Stelara advertisement at issue, Janssen received written confirmation from the publishing group that all future advertisement placements would be confirmed with Janssen prior to the journal closing date. Janssen provided a copy of its standard operating procedure (SOP) for the Withdrawal of Materials. The procedure was followed in principle, after the Stelara prescribing information was updated in June 2015 ie all affected materials were withdrawn within the agreed timelines. However, the briefing of

the media booking agency by teleconference was not followed up in writing, therefore there was no formal documentation of the briefing as required by the SOP. The relevant Janssen employees had since been reminded of their responsibility in ensuring that they appropriately document all evidence of withdrawal following a prescribing information update. The Stelara prescribing information was updated in June 2015 to reflect the addition of the paediatric plaque psoriasis indication. The changes to the prescribing information included:

- Wording for the paediatric plaque psoriasis indication
- Dosing information in the paediatric population and the availability of a 45mg vial.

The June 2015 prescribing information contained no additional/different safety information compared with the November 2014 prescribing information. Janssen therefore submitted that the inclusion of the outdated prescribing information in the Stelara advertisement at issue, had not risked patient safety. Janssen submitted that after receiving the PMCPA's letter, its media booking agency informed it that a double-page insert containing the November 2014 prescribing information was also placed by the publishing group in the 5 September 2015 edition of the BMJ Clinical Research (CR) journal. This was again without the consent or prior knowledge of Janssen.

Janssen submitted that it took its responsibilities under the Code very seriously and sincerely regretted its oversight in not appropriately documenting the briefing of the media booking agency and also the actions taken by the publishing group in publishing Stelara advertisements in both the ARD and the BMJ CR containing outdated prescribing information. Janssen stressed that it would not have allowed either of the advertisements to go to press had it been aware of them in advance. While Janssen maintained that the events had not risked patient safety, the failure of the relevant employees to fully document its SOP regarding the withdrawal of advertisements and its recent finding that a second advertisement was placed with outdated Stelara prescribing information, that a breach of Clause 9.1 be considered for failing to maintain its usual high standards.

Janssen submitted that it had taken further steps to look at how it could further optimise its process and training of employees to ensure that it fully document the process related to the briefing of agencies.

PANEL RULING

The Panel noted Janssen's submission that the publishing group had, without Janssen's prior knowledge, inserted the Stelara bound insert commissioned for the June 2015 issue of the ARD into the October 2015 edition. This advertisement at issue was originally prepared, approved and certified in April 2015 and contained the November 2014 prescribing information. The current prescribing information was dated June 2015. The Panel noted that after submitting its voluntary admission and receiving the PMCPA's letter, Janssen was informed by its media booking agency that another insert (ref PHGB/STE/0515/0011) which was prepared in March 2015 and also contained the November 2014 prescribing information had been published by the publishing group in BMJ Clinical Research on 5 September, again without the consent or prior knowledge of Janssen or its media booking agency. The Panel noted that the April 2015 advertisement was the subject of the voluntary admission.

The Panel noted that the first side of the advertisement related to use of Stelara in the treatment of moderate-to-severe plaque psoriasis. The reverse side referred to active psoriatic arthritis and contained the November 2014 prescribing information. The Panel noted Janssen's submission that the addition of the paediatric plaque psoriasis indication would not be relevant to the ARD rheumatology audience.

The Panel noted that the Stelara prescribing information was updated in June 2015 to reflect the addition of the paediatric (12 years and over) plaque psoriasis indication to include dosing information in paediatrics and the availability of a 45mg vial. The November 2014 prescribing information stated that Stelara was not recommended in children under 18, whereas the June 2015 prescribing information was updated to state that it was not recommended in children under 12 years. The Panel noted Janssen's submission that the June 2015 prescribing information contained no additional/different safety information. The Panel noted that the June 2015 prescribing information side effects, stated 'studies show adverse events reported in ≥ 12 year olds with plaque psoriasis were similar to those seen in previous studies in adults with plaque psoriasis'.

The Panel noted Janssen's submission that the publishing group had admitted full responsibility for the error. Whilst Janssen had been let down by the publisher, it was an established principle under the Code that pharmaceutical companies were responsible for third parties even if that third party acted outside the instructions from the pharmaceutical company.

The Panel noted that Clause 4.2 required the prescribing information to include a succinct statement of the information in the SPC relating to the dosage and method of use relevant to the indications quoted in the advertisement and, where not otherwise obvious, the route of administration. The supplementary information to Clause 4.1 required that the prescribing information be consistent with the SPC for the medicine.

The Panel noted that whilst the first side of the advertisement promoted Stelara for moderate-to-severe plaque psoriasis, it was not clear whether the advertisement was restricted to the adult population or not. In the Panel's view some readers might assume that the advertisement related to the entire patient population for whom the product was indicated for the treatment of moderate-to-severe plaque psoriasis ie both adults and adolescents from the age of 12. In the Panel's view, the prescribing information should thus have also included the

paediatric indication and dosage information in line with the SPC. The advertisement contained out of date prescribing information which was not in line with the SPC. The Panel ruled a breach of Clause 4.1 as acknowledged by Janssen.

The Panel noted Janssen's submission that following the update of the Stelara prescribing information in June 2015, all affected materials were withdrawn within the agreed timelines. However, the briefing of the media booking agency by teleconference was not followed up in writing so there was no formal documentation of the briefing, as required by the relevant SOP. The Panel further noted that Janssen had requested confirmation from the publishing group that all future advertisement placements would be confirmed with the relevant Janssen product manager 5-14 days prior to the journal closing. The Panel noted that in addition to the advertisement at issue a further advertisement also containing outdated prescribing information had been published in a different BMJ publication. The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled as acknowledged by Janssen.

Complaint received **3 November 2015**

Case completed **21 December 2016**

CASE AUTH/2802/11/15

ALK-ABELLÓ v BAUSCH & LOMB

Use of the word 'new'

ALK-Abelló UK complained about a promotional article published in Pulse as a Pulse Quick Guide. The article was entitled 'New approaches in management and treatment of anaphylaxis' and discussed various features of adrenaline auto injectors including Emerade marketed by Bausch & Lomb. Page 1 of the Pulse Quick Guide stated that the material had been initiated, developed, and funded by Bausch & Lomb; an advertisement for Emerade appeared on the reverse.

Emerade was indicated for the emergency treatment of severe acute allergic reactions (anaphylaxis) triggered by allergens in foods, medicines, insect stings or bites, and other allergens as well as for exercise-induced or idiopathic anaphylaxis.

ALK-Abelló alleged that the claim 'Emerade offers a new higher dose…' implied that a new higher dose of Emerade had been launched within the last 12 months. This was not so. The Emerade summary of product characteristics (SPC) stated that the first date of marketing authorization was 3 January 2013. ALK-Abelló alleged a breach of the Code.

The detailed response from Bausch & Lomb is given below.

The Panel noted that the Emerade 500mcg SPC stated that the date of first marketing authorization/ renewal of authorization was 3 January 2013. The Panel further noted Bausch & Lomb's submission that the 500mcg dose referred to in the claim at issue had been available for over 12 months. The Panel ruled a breach of the Code as acknowledged by Bausch & Lomb.

ALK-Abelló UK complained about an article (ref EME-UK-1507-04, prepared July 2015) published in Pulse as a Pulse Quick Guide. The article was entitled 'New approaches in management and treatment of anaphylaxis' and discussed various features of adrenaline auto injectors including Emerade marketed by Bausch & Lomb UK Ltd.

Emerade was indicated for the emergency treatment of severe acute allergic reactions (anaphylaxis) triggered by allergens in foods, medicines, insect stings or bites, and other allergens as well as for exercise-induced or idiopathic anaphylaxis.

COMPLAINT

Page 1 of the Pulse Quick Guide stated that the material had been initiated, developed, and funded by Bausch & Lomb; an advertisement for Emerade appeared on the reverse. In ALK-Abelló's view, the Pulse Quick Guide was promotional and needed to comply with the Code.

ALK-Abelló alleged that a claim in the conclusion section, 'Emerade offers a new higher dose…' implied that a new higher dose of Emerade had been launched within the last 12 months which was not so. The Emerade summary of product characteristics (SPC) stated that the first date of marketing authorization was 3 January 2013. ALK-Abelló alleged a breach of Clause 7.11.

RESPONSE

Bausch & Lomb stated that unfortunately the claim 'Emerade offers a new higher dose...' was not compliant with the requirements of Clause 7.11 as the higher dose had been available for over 12 months. Bausch & Lomb sincerely apologised for the oversight and gave assurance that going forward it would ensure vigilance in checking materials and that particular clause.

Bausch & Lomb submitted that the Pulse Quick Guide was a one-off publication which did not have any on-line coverage, nor were any additional laminated copies made and it had not been circulated by Bausch & Lomb sales teams. The company had written to Pulse to advise that the article must not be reprinted or circulated in any form as it was not in compliance with Clause 7.11. There should not be any further situations where a health professional would be exposed to the material.

PANEL RULING

The Panel noted that Clause 7.11 required that the word 'new' must not be used to describe any product or presentation which had been generally available, or any therapeutic indication which had been generally promoted, for more than twelve months in the UK. The Panel noted that the Emerade 500mcg SPC stated that the date of first marketing authorization/renewal of authorization was 3 January 2013. The Panel further noted Bausch & Lomb's submission that the 500mcg dose referred to in the claim 'Emerade offers a new higher dose…' had been available for over 12 months. The Panel ruled a breach of Clause 7.11 as acknowledged by Bausch & Lomb.

Complaint received **5 November 2015**

Case completed **11 December 2015**

COMPLAINANT v ALEXION

Conference programme booklet

A contactable complainant alleged that Alexion Pharma UK's entry in the programme booklet for a UK medical society meeting, held in Sheffield in November 2015, promoted an unlicensed medicine.

The detailed response from Alexion is given below.

The Panel noted that the programme booklet included a list of the pharmaceutical companies and other organisations which had exhibited at or sponsored the event together with a paragraph about each. The paragraph about Alexion referred to the establishment of a premier global metabolic rare disease franchise with the development of two late-stage therapies, Strensiq for hypophosphatasia and Kanuma for lysosomal acid lipase deficiency. In the Panel's view some readers might consider that the wording implied that Strensiq and Kanuma were still in the late stages of development and that was not so. The Panel, however, noted Alexion's submission that the wording referred to the global development stage of the medicines and that both Strensiq and Kanuma had received a UK marketing authorization in August 2015 and therefore no pre-licence promotion had taken place at the meeting in November 2015. The Panel thus ruled no breaches of the Code including no breach of Clause 2.

A contactable complainant, who wished to remain anonymous, complained about Alexion Pharma UK's entry in the programme booklet for the British Society for Paediatric Endocrinology and Diabetes (BSPED) meeting, held in Sheffield from 25-27 November 2015. Alexion was one of a number of pharmaceutical companies that had sponsored the meeting.

COMPLAINT

The complainant alleged that Alexion had promoted an unlicensed medicine and he provided pictures of the programme and text that was of concern. The complainant did not state which unlicensed medicine was at issue but text from the programme provided by him stated, *inter alia*, that 'Alexion is also establishing a premier global metabolic rare disease franchise with the development of two late-stage therapies, Strensiq (asfotase alfa) for hypophosphatasia (HPP) and Kanuma (sebelipase alfa) for Lysosomal Acid Lipase Deficiency (LAL-d)'.

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

RESPONSE

Alexion submitted that its exhibition stand at the BSPED meeting had contained educational material designed to improve disease awareness of hypophosphatasia. Alexion submitted that it also had a corporate statement in the programme booklet which described the company and included a statement on the global development status of Strensiq and Kanuma. Alexion submitted that both medicines had received marketing authorizations on 28 August 2015 so there was no pre-licence promotion at the meeting in November 2015; a link to the electronic Medicines Compendium (eMC) website was provided.

Alexion submitted that it had taken into account Clauses 2, 3.1, 3.2 and 9.1 and considered that the documents provided proved that there was no promotion of any unlicensed medicines at the meeting and therefore no breaches of the Code. Alexion provided copies of the approved materials used at the meeting.

In response to a request from the case preparation manager for further information, Alexion provided copies of the Kanuma and Strensiq summaries of product characteristics (SPCs) and an original copy of the programme booklet. Alexion submitted that the programme booklet was given to each delegate upon arrival as part of an information pack distributed by BSPED at the registration desk.

PANEL RULING

The Panel noted the complainant's allegation that Alexion had promoted an unlicensed medicine. The Panel noted that the programme booklet included a list of the pharmaceutical companies and other organisations which had exhibited at or sponsored the event together with a paragraph about each. The paragraph about Alexion referred to the establishment of a premier global metabolic rare disease franchise with the development of two late-stage therapies, Strensiq for hypophosphatasia and Kanuma for lysosomal acid lipase deficiency. In the Panel's view some readers might consider that the wording implied that Strensiq and Kanuma were still in the late stages of development and that was not so. The Panel, however, noted Alexion's submission that the wording referred to the global development stage of the medicines and that both Strensiq and Kanuma had received a UK marketing authorization in August 2015 and therefore no pre-licence promotion had taken place at the meeting in November 2015. The Panel thus ruled no breach of Clause 3.1. The Panel noted that Alexion had been asked to respond in relation to the requirements of Clause 3.2 which required that the promotion of a medicine be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics. In the Panel's view the complainant has not alleged a breach of that clause and the Panel ruled no breach

accordingly. The Panel subsequently ruled no breach of Clauses 9.1 and 2.

During the consideration of this case, the Panel noted that Alexion's entry into the programme booklet referred to Soliris (eculizumab), Strensiq and Kanuma and the indications for each. It was also stated that the company was evaluating potential indications for Soliris in additional severe and rare disorders. The Panel queried whether the entry went beyond being a corporate piece, as submitted by Alexion, and instead promoted the three medicines cited. The Panel was concerned that as promotional copy the paragraph did not comply with the requirements of the Code such as the need to include prescribing information and avoid exaggerated claims etc; it requested that Alexion be advised of its concerns.

Complaint received **26 November 2015**

Case completed **28 January 2016**

CASE AUTH/2804/11/15

ANONYMOUS HEALTH PROFESSIONAL/DIRECTOR v MERCK SERONO

Call rates and uncertified material

An anonymous, non-contactable complainant, who described themselves as a senior neurologist, alleged that for the last year Merck Serono's conduct was destructive for health professionals and threatened the correct therapy pathway for patients. In particular the complainant stated that he/she did not want constant pressure from local representatives to attend meetings with no information. The representatives had also persistently requested appointments with multiple sclerosis nurses and their attendance at meetings. The complainant referred to representatives being expected to meet targets that would breach call rates and what the Code permitted.

The complainant also alleged that promotional material such as exhibition panels and material on iPads had not been certified before use.

Call rates had been at issue in Case AUTH/2756/5/15. As the complaint thus included an implied allegation of a breach of undertaking, that part of the complaint was taken up in the name of the Director as the Authority was responsible for ensuring compliance with undertakings.

The detailed response from Merck Serono is given below.

The Panel noted that the complaint was dated 20 November 2015 ie 5 months after the completion of Case AUTH/2756/5/15 and referred to the activities in question taking place 'over the last year'.

The Panel noted the complainant's allegation that Merck Serono representatives had persistently requested appointments with MS nurses and made *ad hoc* calls to his/her centres.

Call rates had similarly been at issue in Case AUTH/2756/5/15 in which particular regard was paid to an incentive scheme which the Panel considered was, in reality, a requirement and achieving the stated call rate would mean that, in the absence of adequate briefing, the frequency of representatives' calls would cause inconvenience. Breaches of the Code were ruled and Merck Serono provided the requisite undertaking and assurance. The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

Turning to the present case, Case AUTH/2804/11/15, the Panel noted that it was impossible to determine with any precision when the representatives' persistent activity described by the complainant occurred. The Panel noted that the undertaking in Case AUTH/2756/5/15 was dated 24 July 2015. The Panel now noted, however, that the representatives were no longer incentivised on calls or contact rates. Nonetheless, the Panel noted that the complainant had referred to the conduct of Merck Serono representatives and of them being expected to meet targets that would breach call rates and what the Code permitted of them. The Panel noted the difficulty in dealing with complaints when specific details were not provided and the complainant was non contactable; it was often impossible in such circumstances to determine precisely when and what had happened. The complainant bore the burden of proof and based on the evidence provided, it was not possible to determine whether the matters raised by the complainant occurred before or after the provision of the undertaking in Case AUTH/2756/5/15.

The Panel considered that between the date of the signed undertaking in Case AUTH/2756/5/15 and the date of the current complaint, it had not been demonstrated that in contacting the complainant and other health professionals at his/her centres the representatives had caused inconvenience or had failed to maintain high standards of ethical conduct although clearly the complainant was dissatisfied. Further, briefing material trained out to the representatives in September 2015 clearly distinguished between 'calls' and 'contacts' and stated that a representative should call on a doctor or other prescriber no more than three times in a year. The complainant had not established that over calling had occurred. No breaches of the Code were ruled. The activities in question prior to 24 July 2015 were covered by the ruling in Case AUTH/2756/5/15.

The Panel noted that the complainant was further concerned that representatives had been given uncertified promotional material including a pull-up exhibition banner for Rebif and an iPad app for use by the neurology representatives. The Panel noted Merck Serono's submission that the exhibition pull-up banner was never fully reviewed or certified as it was never used. The complainant had provided no evidence to the contrary. The Panel thus ruled no breach of the Code.

The Panel noted Merck Serono's submission that the iPad app had been uploaded to the representatives' iPads before it was certified. The Panel ruled a breach of the Code as acknowledged by Merck Serono. The Panel was concerned to note that the lack of certification had only come to light when Merck Serono had finalised a new app to replace the previous version; the uncertified app was,

according to the email sent on the 1 September 2015 to withdraw it, launched to the representatives in March 2015. In the Panel's view by failing to certify the first app, Merck Serono had failed to maintain high standards and a breach of the Code was ruled.

The Panel noted its rulings above regarding the use of uncertified promotional material. This was particularly disappointing given that in Case AUTH/2756/5/15 a breach of the Code was ruled with regard to uncertified representative's briefing material. The Panel noted that certification was the process by which companies ensured compliance and it considered that Merck Serono's poor record in this regard was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted that the complainant also generally alleged that Merck Serono had used promotional stands at two major meetings that had not been certified; no details were provided. Conversely, Merck Serono had provided a list of the materials used at the two meetings and submitted that they had all been certified. As the complainant bore the burden of proof, and bearing in mind all the evidence, the Panel considered that the complainant had not established that any materials used at the meetings had not been certified. No breach of the Code was ruled.

An anonymous, non-contactable complainant who described themselves as a senior neurologist complained about the conduct of management and promotional practices within Merck Serono.

The matters raised included the persistence of representatives calling upon health professionals trying to persuade them to attend promotional meetings. Call rates had been at issue in Case AUTH/2756/5/15. As the complaint thus included an implied allegation of a breach of undertaking, that part of the complaint was taken up in the name of the Director as the Authority was responsible for ensuring compliance with undertakings.

COMPLAINT

The complainant alleged that for the last year Merck Serono had conducted itself in a manner that was destructive for health professionals and threatened the correct therapy pathway for patients. The complainant highlighted various issues that he/she became aware of after speaking to his/her local Merck Serono representative and chose to remain anonymous so as not to compromise the identity of that representative.

The complainant explained that Merck Serono representatives had persistently requested appointments with multiple sclerosis (MS) nurses and made ad hoc calls to his/her centres which was a nuisance. After a long working relationship with the local Merck Serono representative and after not hearing from him/her for a while, the complainant believed it was courteous to meet with him/her when some time became available.

At a meeting during one of the complainant's clinic shifts, the representative informed the complainant that he/she was 'no longer working at Merck Serono due to his/her growing concerns over the new management that had taken over from the beginning of the year'. The representative proceeded to retract the statement and state that he/she 'Believed the time had come for him/her to seek new opportunities'.

The complainant asked the representative to elaborate on his/her concerns as it affected the centres indirectly. The representative explained that there had been a worrying amount of internal change within Merck Serono and more than half the team had left the company due to the misconduct of management. The team was expected to meet targets that would breach call rates and what the Code permitted; a colleague who had addressed this issue in the past was pushed out of the company. The representative explained that knowing these discussions, the director had face-to-face interactions and telephone conferences where these discussions could not be recorded. The representative mentioned that the sales manager had left the company along with various other team members due to the misconduct of the director and did not want such misconduct to affect his/her future employment.

The complainant stated that he/she had been persistently contacted by the local Merck Serono representative requesting his/her attendance at promotional meetings and wanting to secure dates against his/her availability. When the complainant asked for information about the content of the meeting, the representative informed him/her that the representatives had yet to receive the information themselves. The complainant advised the representative that he/she was busy and did not wish to attend the meeting but was then approached by another Merck Serono representative from a nearby area querying if the complainant had changed his/her mind about attending. The complainant explained that as a consultant his/her time was precious and he/she did not want constant pressure from local representatives to attend meetings with no information. The complainant had also received feedback from the nurses at different centres that they had been aggressively receiving communications from Merck Serono to attend uninformative meetings.

The complainant asked why the issues had not been addressed internally by the representatives; given the amount of time they had been with the company, their concerns should have been addressed. The representative mentioned that the new management were personal acquaintances of the director which made it difficult for the representatives to turn to anyone for support. The complainant also noted that the representative felt suppressed in the situation and obliged to terminate his/her employment with the company in order to maintain his/her professional integrity and ethical standards.

Furthermore, the representative later found out that they had been given promotional material that had not been certified by the correct copy approval process. The materials at issue were commercial

stands (REB14-0067) still being used at promotional meetings and materials used on iPads (REB15-0004) which the director was aware of and continued to promote. When another representative challenged internal management about the matter, it was stated that they were overpaid to do what they were currently doing and that it would be very simple to get contractors to do their jobs. The complainant stated that rules should not be ignored in order to sell products and a company with so much history should be very aware of the certification requirements of Clause 14.1. The complainant stated that his/her centres were upset to have lost such a highly regarded representative and to be told about the loss of ethics of a formerly well-established pharmaceutical company.

The representative went on to elaborate that this was not the only item he/she had been asked to use which was invalid; he/she had also used bigger promotional stands at major meetings such as the Multiple Sclerosis (MS) Trust, and the Association of British Neurologists (ABN) congress that had not been certified.

When writing to Merck Serono, the Authority asked it to consider Clause 14.1 as cited by the complainant and also Clauses 2, 9.1, 15.2, 15.4, 15.9 and 29. Clause 29 was referred to in relation to a potential breach of the undertaking in Case AUTH/2756/5/15 with regard to representatives' targets.

RESPONSE

Merck Serono submitted that it promoted Rebif (interferon beta-1a), for use in the treatment of relapsing multiple sclerosis. Merck Serono noted that it had accepted the rulings of breaches of the Code in relation to the recent cases about call rates and call frequency (Cases AUTH/2756/5/15 and AUTH/2754/5/15). The company had signed the forms of undertaking and immediately implemented a number of corrective and preventative actions to ensure that it fully complied with its undertakings, and that the quality of the representative briefings and the conduct of its representatives would not be called into question again. In that regard, Merck Serono strongly refuted a breach of Clause 29, and therefore also strongly refuted breaches of Clauses 2, 9.1, 15.2, 15.4, and 15.9. The reasons were detailed below.

According to the introduction to the PMCPA Constitution and Procedure, the complainant had the burden of proving his/her complaint on the balance of probabilities. As the complainant and any specific call or meeting had not been identified, investigation into this matter had been very difficult. Nevertheless, Merck Serono took any allegation of inappropriate conduct of its staff very seriously and immediately launched a full investigation based on the aspects that had been referred to by the complainant.

1 Conduct of management

Since the rulings in the cases referred to above, Merck Serono had formulated and implemented a number of corrective and preventative actions (CAPA), a copy of the CAPA plan was provided, the full details of which were discussed below. Cross-functional monthly compliance committee meetings and monthly governance meetings were established which, *inter alia*, monitored those corrective and preventative actions. The meetings were chaired by the general manager since June 2015. The actions and outcome of those meetings were communicated and discussed at leadership team meetings.

Merck Serono noted that the complainant had not mentioned any specific timeframe. Because these changes and actions were promptly implemented following the previous complaints, Merck Serono submitted that it would relate to a period prior to the corrective actions being fully implemented.

2 Call/contact frequency and targets given to representatives

a) Implementation of CAPA plan

Merck Serono submitted that the following corrective and preventive actions as set out in the CAPA plan were all completed prior to receiving this complaint:

- The customer-relationship-management (CRM) system was changed in order to better capture contact and call data, and to enable the representatives to differentiate between contact and call more easily when capturing such data. Screenshots of the amended CRM system were provided;

- A new representative briefing document on face-to-face calls and contacts with prescribers was created and certified (GEN15-0085 August 2015). The briefing introduced the changes to the CRM system and clearly set out the requirements of the Code in relation to 'contacts' and 'calls';

- The briefing document was emailed to all sales managers on 2 September 2015 with a covering note and instructions to them to cascade the information and appropriately brief their teams;

- At the national sales conference on 16 September 2015, all the representatives were trained on Merck Serono's compliance policies and on the Code requirements in relation to calls and contacts using the new briefing material. Signed training records were provided;

- All sales managers were asked to review all briefing materials which might have been sent out to the respective sales teams in the past 12 months and confirm that all such briefings complied with the company's guidance on calls/contacts and were appropriately certified.

b) Targets given to representatives

The basis on which the neurology representatives were incentivised was changed to ensure compliance with the Code and the undertakings given in Cases AUTH/2756/5/15 and AUTH/2754/5/15.

The 2015 sales incentive letter issued to the neurology representatives was sent out in January 2015. The incentive described in this letter comprised two elements:

- 75% of the bonus was based on achieving a certain number of active patients under treatment with Rebif; and

- 25% of the bonus was based on achieving a quarterly key performance indicator (KPI) to be set out and communicated separately.

The KPI set out in the first quarter of 2015 - which applied only in March 2015 - was the subject of Case AUTH/2756/5/15. That temporary incentive which was aimed at increasing the call frequency was found not to comply with the Code and was therefore not repeated.

In the second and third quarters of 2015 no additional KPIs were defined. Instead, in those quarters, the bonus paid to representatives was entirely based on the number of new or active patients starting Rebif treatment.

Neurology representatives were no longer incentivised on number of calls or contacts with health professionals. Merck Serono provided an anonymised excel spreadsheet to show the payments of quarterly bonuses to the neurology representatives for the first three quarters of 2015. Merck Serono stated that this clearly demonstrated that the incentive scheme for representatives was changed in accordance with the undertakings given in Cases AUTH/2756/5/15 and AUTH/2754/5/15

c) Meetings

Merck Serono noted the complainant's allegation that he/she was persistently contacted by Merck Serono representatives and asked to attend promotional meetings without receiving any information about the content of those meetings. Allegedly the representatives themselves did not know about the content of the planned meetings.

Before a promotional meeting or event from Merck Serono could be actively pursued, it needed to undergo a thorough internal review and approval process. The review process focused on the content of such planned meetings, the meeting requirements, hospitality and a potential disclosure of any transfers of value.

Merck Serono explained that it used CLEAR (Merck Serono Compliance Electronic Approval System) to review and approve interactions with health professionals. For each event there had to be a workflow in CLEAR to document the interaction.

Before an interaction could take place, it had to be approved by reviewers from various functions. In particular, a needs assessment had to be completed in CLEAR to evaluate why an interaction with a health professional should take place and follow a global compliance standard. The needs assessment set out specific justifications for a promotional or educational meeting/program, and for inviting a particular health professional, as well as details of accommodation, transport and meals as appropriate. The reviewers/approvers in the CLEAR workflow checked the data entered in the system by the proponent and either confirmed or rejected the interaction. The final approval came from the compliance manager. This process ensured that no meetings/events for health professionals could be set up without a clearly defined and pre-approved promotional or medical/ scientific educational content.

Representative's discussions about pre-approved meetings/events with a health professional, had to be done in a way which did not inconvenience the health professional, in accordance with the Code and in line with the health professional's wishes. This was clearly laid out in the latest certified 'Guide for all Merck Serono UK and Ireland customer-facing employees' on face-to-face calls and contacts with prescribers.

Merck Serono submitted that in summary, no evidence had been provided that any alleged breach of the Code occurred after the undertakings in the previous cases had been signed. Merck Serono was confident that the urgency of the actions taken by managers conveyed the seriousness of the matter to members of staff and it had nothing to suggest that all members of staff had not fully adhered to company guidelines and policies.

Merck Serono strongly refuted that it had breached its undertakings, and submitted that since the previous complaints it had complied with the requirements of Causes 15.2, 15.4, and 15.9 and had complied with Clause 2 and 9.1.

3 Use of uncertified promotional material

a) Promotional material ref REB14-0067

Merck Serono noted that this was a pull-up exhibition banner for Rebif developed by a marketing agency under the motto 'rain or shine' and was originally intended to be used from April 2014 onwards. It was uploaded into Zinc on 26 March 2014 but was never fully reviewed or certified, nor was it ever used or made public as the campaign was cancelled in January 2015. The job was withdrawn from Zinc on 15 January 2015.

Merck Serono thus denied a breach of Clause 14.1; the material was never used and there was no evidence to show that it was ever made public.

b) Promotional material ref REB15-004

Merck Serono submitted that this was an iPad app for use by the neurology representatives. Unfortunately the app was uploaded to the representatives' iPads before it was fully reviewed and certified. When this came to light, the app was immediately recalled on 1 September 2015. Merck submitted that unfortunately on this occasion, it could not deny a breach of Clause 14.1.

Merck Serono noted, however, that this was stopped as soon as it became apparent and an internal investigation was started to find the cause of the problem. It seemed to have been a miscommunication between the then medical director and an interim marketer about the certification status of the material under review.

This breach came to light when Merck Serono was finalising a new iPad app to replace the version referred to above. It was certified and trained out to representatives at the national sales conference on 16 September 2015.

Corrective actions were taken as soon as the breach became apparent and the material was immediately withdrawn. In addition, face-to-face refresher training on Merck Serono's compliance policies was delivered at the national sales conference on 16 September 2015.

c) Promotional material for the MS Trust meeting

As the complainant did not focus on a specific timeframe, Merck concentrated on the most recent 2015 MS Trust meeting. Merck submitted that all material used at the event was fully reviewed, approved and certified before use and thus there was no breach of Clause 14.1.

d) Promotional material for the ABN Congress

As the complainant did not focus on a specific timeframe, Merck Serono again concentrated on the most recent 2015 ABN Congress. In 2015 the main material used on the stand was a video loop which was fully reviewed, approved and certified before use thus there was no breach of Clause 14.1.

e) Other promotional materials used by neurology representatives

Merck Serono listed all promotional materials currently used by its representatives and submitted that they had all been certified on the dates given and were available upon request for inspection.

f) Final signatories

Merck Serono enclosed a copy of a letter sent to the PMCPA on 22 September 2015 listing the company's current final medical and non-medical signatories, a copy of which was also sent to the Medicines and Healthcare products Regulatory Agency (MHRA). All certified materials referred to above had been certified by the people referred to in the signatories' letter sent to the PMCPA.

Merck Serono submitted that compliance with the Code was taken very seriously across the organisation. Clear reasons had been given as to why the Code had not been breached with regard to the allegations relating to Clauses 15.2, 15.4, 15.9. Therefore as those allegations appeared currently unfounded, there was no breach of Clauses 29, 2 or 9.1 either.

Merck Serono submitted that it was extremely regrettable that Clause 14.1 had been breached. Nevertheless Merck Serono had managed this issue to ensure it would not happen again. It therefore followed that high standards had been maintained and there was no breach of Clauses 9.1 or 2.

PANEL RULING

The Panel noted that the complainant, who stated that he/she was a senior MS consultant, was anonymous. As stated in the introduction to the Constitution and Procedure, anonymous complaints were accepted and like all complaints, judged on the evidence provided by both parties. Although the Panel accepted that a high degree of dissatisfaction was usually required before a complainant was moved to submit a complaint, complainants nonetheless had the burden of proving their complaint on the balance of probabilities. The complainant had not provided any evidence to substantiate his/her allegations and as he/she was non-contactable it was not possible to ask for further information. The complainant referred to the activities in question taking place 'over the last year' but had not provided further details about when the activities took place. The Panel noted that the complaint was dated 20 November 2015 ie five months after the completion of Case AUTH/2756/5/15.

The Panel noted the complainant's allegation that Merck Serono representatives had persistently requested appointments with MS nurses and made ad hoc calls to his/her centres.

Call rates had similarly been at issue in Case AUTH/2756/5/15 in which particular regard was paid to an incentive scheme which required six calls per day which Merck Serono had submitted ran during March 2015. In that case the Panel considered that the incentive scheme was, in reality, a requirement and achieving it would mean that, on the balance of probabilities, representatives would breach the Code in that, in the absence of consistent terminology and briefing on how to achieve 6 contacts/day and remain compliant with the Code, the frequency of representatives' calls would cause inconvenience. Breaches of the Code were ruled and Merck Serono provided the requisite undertaking and assurance. The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

Turning to the present case, Case AUTH/2804/11/15, the Panel noted that it was impossible to determine with any precision when the representatives' persistent activity described by the complainant occurred. The Panel noted its comments above in this regard. The undertaking in Case AUTH/2756/5/15 was dated 24 July 2015. The Panel noted Merck Serono's submission that the incentive scheme in question in the previous case applied only in March 2015 was incorrect. In the previous case the Panel had noted that representatives had been briefed in May 2015 to achieve six calls per day. The Panel now noted, however, that the representatives were no longer incentivised on calls or contact rates.

Nonetheless, the Panel noted that the complainant had referred to the conduct of Merck Serono representatives and of them being expected to meet targets that would breach call rates and what the Code permitted of them. The Panel noted the difficulty in dealing with complaints when specific details were not provided and the complainant was non contactable; it was often impossible in such circumstances to determine precisely when and what had happened. The complainant bore the burden of proof and based on the evidence provided, it was not possible to determine whether the matters raised by the complainant occurred before or after the provision of the undertaking in Case AUTH/2756/5/15.

The Panel noted its comments above in relation to the timeframe of the activities in question. The Panel considered that between the date of the signed undertaking in Case AUTH/2756/5/15 and the date of the current complaint, it had not been demonstrated that in contacting the complainant and other health professionals at his/her centres the representatives had caused inconvenience or had failed to maintain high standards of ethical conduct although clearly the complainant was dissatisfied. Further, briefing material trained out to the representatives in September 2015 clearly distinguished between 'calls' and 'contacts' and stated that a representative should call on a doctor or other prescriber no more than three times in a year. The complainant had not established that over calling had occurred. No breach of Clauses 15.2, 15.4 and 15.9 were ruled. Consequently, no breaches of Clauses 29, 9.1 and 2 were also ruled. The activities in question prior to 24 July 2015 were covered by the ruling in Case AUTH/2756/5/15.

The Panel noted that the complainant was further concerned that representatives had been given uncertified promotional material including a pull-up exhibition banner for Rebif and an iPad app for use by the neurology representatives. The Panel noted Merck Serono's submission that the exhibition pull-up banner was never fully reviewed or certified as it was actually never used and the campaign was cancelled in January 2015 and the job was withdrawn from the Zinc system on 15 January 2015. The complainant had provided no evidence to the contrary. The Panel thus ruled no breach of Clause 14.1 in relation to this piece of material.

The Panel noted Merck Serono's submission that the iPad app had been uploaded to the representatives' iPads before it was fully reviewed and certified. The Panel ruled a breach of Clause 14.1 as acknowledged by Merck Serono. The Panel was concerned to note that the lack of certification had only come to light when Merck Serono had finalised a new iPad app to replace the previous version; the uncertified app which, according to the email sent on the 1 September 2015 to withdraw it, was launched to the representatives in March 2015. In the Panel's view by failing to certify the first app, Merck Serono had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted its rulings above regarding the use of uncertified promotional material. This was particularly disappointing given that in Case AUTH/2756/5/15 a breach of Clause 15.9 was ruled with regard to uncertified representative's briefing material. The Panel noted that certification was the process by which companies ensured compliance and it considered that Merck Serono's poor record in this regard was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted that the complainant was further concerned that Merck Serono had also used promotional stands at major meetings such as the MS Trust, and the ABN congress that had not been certified. The complainant had neither referred to any specific material nor provided any material to substantiate his/her allegations. Conversely, Merck Serono had provided a list of the materials used at the two meetings and submitted that they had all been certified. As the complainant bore the burden of proof, and bearing in mind all the evidence, the Panel considered that the complainant had not established that any materials used at the MS Trust, and the ABN congress had not been certified. No breach of Clause 14.1 was ruled.

During the consideration of this case the Panel was concerned to note that although Merck Serono had implemented a number of corrective and preventive actions following Case AUTH/2756/5/15, the undertaking was signed on 24 July 2015 but the representatives were not re-briefed about calls until 16 September 2015. Whilst the Panel appreciated the time required to prepare a briefing, it was important to ensure that staff were briefed forthwith following a breach of the Code to avoid a possible breach of undertaking. The Panel requested that Merck Serono be advised of its concerns in this regard.

Complaint received **30 November 2015**

Case completed **5 February 2016**

CASE AUTH/2810/12/15

ANONYMOUS v TEVA

Promotion of DuoResp Spiromax

An anonymous, non-contactable complainant, who described him/herself as a general practitioner, complained about an advertisement for DuoResp Spiromax (budesonide/formoterol fumarate dehydrate) placed in the Primary Care Respiratory Update by Teva UK.

The advertisement featured the claim 'The moment I picked it up I knew how to use it*' next to the photograph of a patient. The claim 'Intuitive design' appeared under the photograph and both claims were referenced to Rychlik *et al* (2014) and Plusa *et al* (2015). 'Intuitive to use' was also so referenced. The asterisk referred to a statement in small, grey font at the very bottom of the advertisement (below the prescribing information) 'Instructions for use should be followed as per the patient information leaflet'.

The complainant stated that he/she often used budenoside/formoterol inhalers and noticed from the advertisement that DuoResp Spiromax was easy for patients to use. If retraining was not required it would save a considerable amount of time. The patient information leaflet told a different story. Although it looked like a metered dose inhaler it should not be shaken and an air vent in front of the patient's lip could easily be blocked so it was likely that many patients might incorrectly use this inhaler without training. The complainant considered that the inhaler did have a place, but was disappointed that the reality of clinical usage did not match the initial impression.

The detailed response from Teva is given below.

The Panel noted that the headline claim 'The moment I picked it up I knew how to use it' and the strapline 'Intuitive design' were both referenced to Plusa *et al* and Rychlik *et al*. The Panel noted, however, that Rychlik *et al* was a presentation on incremental innovation and consisted largely of a preview of Plusa *et al* which was a qualitative market research study in which asthma/chronic obstructive pulmonary disease (COPD) patients and health professionals were interviewed to obtain opinions on DuoResp Spiromax and compare it with a currently used Turbohaler or Accuhaler. The main goal of the study was to answer two questions: How likely health professionals and patients were to use and even switch to the Spiromax and which benefits/features of Spiromax should be communicated to maximize its potential in the market?

One part of the study involved interviews with 181 health professionals experienced in the treatment of asthma and COPD across 9 European countries. The other part of the study involved 261 interviews with 80 asthma/COPD patients from mostly these countries. The patients must not have used Easi-Breathe before and must use a Turbohaler or an Accuhaler. It was not explained in the study when or why the patients were interviewed on more than one occasion. The Panel queried whether 261 was the sum total of interviews with 80 patients and 181 health professionals. The study stated that respondents (health professionals and patients) evaluated the DuoResp Spiromax after they had seen a demonstration video, tried an empty device and in the case of health professionals had additionally read the product profile. In that regard the Panel disagreed with Teva's submission that the study clearly supported the intuitive nature of the Spiromax device and the ability to handle it without any instruction. Further the Panel noted that the study concluded that training could not be completely eliminated '…but the easy training use of the inhaler is a step in the right direction …'.

The Panel noted the authors' findings and queried statements such as '76% of patients handled [Spiromax] correctly without receiving any instruction' given that they had all seen a demonstration video. The Panel considered that some important detail was missing from the published report as in its absence readers could not fully understand the study methodology nor the importance of its outcomes. Nonetheless, the Panel noted that whilst the majority of patients and health professionals were positive about Spiromax, there were still 25% of patients and 13% of health professionals who did not find it intuitive or very intuitive.

The Panel noted that the advertisement portrayed a patient's perspective of Spiromax and that Plusa *et al* had interviewed only 80 patients vs 181 health professionals. The Panel considered that readers would assume from the advertisement that all patients would immediately know how to use DuoResp Spiromax from the moment it was dispensed and would not need to be counselled in the correct use of the device. This was not so and in that regard the Panel was very concerned about the possible risk that some asthma or COPD patients would lose control of their symptoms for want of adequate training. The advertisement stated in small, grey font, below the prescribing information, that instructions for use should be followed as per the patient information leaflet. In the Panel's view this statement was easily missed. The Panel noted that Teva acknowledged that some patients had difficulty in using inhalers and it recommended that health professionals refer patients to the patient information leaflet. The Panel considered that the reference to the patient information leaflet for instructions on how to use the Spiromax device contradicted the headline claim 'The moment I picked it up I knew how to use it'. Further, that patients were required to follow instructions as per the patient information leaflet meant that the

device was not unequivocally intuitive as implied. The Panel considered that in the circumstances, the claims 'The moment I picked it up I knew how to use it' and 'Intuitive design' in the advertisement were misleading as to the ease of use of Spiromax and ruled a breach of the Code. The Panel considered that high standards had not been maintained and ruled a further breach of the Code.

An anonymous, non-contactable complainant, who described him/herself as a general practitioner, complained about an advertisement for DuoResp Spiromax (budesonide/formoterol fumarate dehydrate) placed in the Primary Care Respiratory Update by Teva UK Limited.

DuoResp Spiromax was indicated in adults 18 years of age and older in the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β_2 adrenoceptor agonist) was appropriate; in patients not adequately controlled with inhaled corticosteroids and as needed inhaled short-acting β_2 adrenoceptor agonists or controlled on both inhaled corticosteroids and long-acting β_2 adrenoceptor agonists. The medicine was also indicated in the symptomatic treatment of patients with severe chronic obstructive pulmonary disease (COPD) (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who had significant symptoms despite regular therapy with long-acting bronchodilators.

The advertisement featured the claim 'The moment I picked it up I knew how to use it*' next to the photograph of a patient. The claim 'Inuitive design' appeared under the photograph and both were referenced to Rychlik *et al* (2014) and Plusa *et al* (2015). Another claim 'Intuitive to use' was also so referenced. The asterisk referred to a statement at the very bottom of the advertisement (below the prescribing information) 'Instructions for use should be followed as per the patient information leaflet'. The statement appeared in small, grey font.

COMPLAINT

The complainant stated that he/she often used budenoside/formoterol inhalers and noticed the advertisement for DuoResp Spiromax. Apparently it was easy for patients to use; the advertisement included the claim 'The moment I picked it up I knew how to use it' and referred to an intuitive design. The complainant noted that getting patients to use inhalers was increasingly difficult given the number of new options and he/she was pleased that this would save him/her a considerable amount of time if retraining was not required. The complainant alleged that the patient information leaflet told a very different story. Although it looked like a metered dose inhaler such as the often used Ventolin, it should not be shaken and an air vent which would be in front of the patient's lip could easily be blocked so it was highly likely that there would be a large number of patients who would incorrectly use this inhaler without training. The complainant considered that the inhaler did have a place, but was disappointed that the reality of clinical usage did not match the initial impression.

When writing to Teva, the Authority asked it to respond in relation to Clauses 9.1 and 7.2 of the Code.

RESPONSE

Teva queried what the substantive proposed complaint was. Teva noted that the complainant compared the 'reality of clinical usage' to the advertised claims but Teva's impression was that the complainant had not actually handled or prescribed the product.

Teva submitted that the advertisement in question referred to the intuitive nature of the Spiromax device, as substantiated by the references and also referred the reader to the need to read the patient information leaflet for instructions of use. The summary of product characteristics (SPC) stated that use of DuoResp Spiromax followed three simple steps: open, breathe and close.

Teva submitted that the advertisement headline 'The moment I picked it up I knew how to use it' and the strapline 'Intuitive design' were referenced to Plusa *et al* and Rychlik *et al* which clearly supported the intuitive nature of the Spiromax device and the ability to handle the device without any instruction.

Teva recognised that some patients had difficulty in using inhaled medication and therefore, albeit having supporting data on the intuitive nature of the Spiromax device, it still recommended that health professionals referred patients to the patient information leaflet.

Teva submitted that although it could not comment on the complainant's perception, it had been fair and balanced in the promotion of DuoResp Spiromax; it had recommended health professionals refer patients to the patient information leaflet and accurately referred to published data. Teva therefore, refuted the allegation that the advertisement in question was inconsistent with the reality of clinical usage and such data referred to.

PANEL RULING

The Panel noted that the headline claim 'The moment I picked it up I knew how to use it' and the strapline 'Intuitive design' were both referenced to Plusa *et al* and Rychlik *et al*. The Panel noted, however, that Rychlik *et al* was a presentation on incremental innovation delivered at a world respiratory conference in May 2014. The presentation consisted largely of a preview of Plusa *et al*. Thus, although two references had been cited in support of the claims, they both only referred to one set of data ie that from Plusa *et al*. The Panel noted that Plusa *et al* was a qualitative market research study in which asthma/COPD patients and health professionals were interviewed to obtain opinions on DuoResp Spiromax and compare it with a currently used Turbohaler or Accuhaler. The main goal of the study was to answer two questions: How likely health professionals and patients were to use and even switch to the Spiromax and which benefits/features of Spiromax should be communicated to maximize its potential in the market?

The study was in two parts which appeared to be wholly separate. One part of the study involved interviews with 181 health professionals experienced in the treatment of asthma and COPD across 9 European countries (France, Germany, Italy, Spain, UK, Netherlands, Belgium, Denmark and Sweden). The other part of the study involved 261 interviews with 80 asthma/COPD patients from the same countries except for Denmark where there were no patients. The patients must not have used Easi-Breathe before and must use a Turbohaler or an Accuhaler. It was not explained in the study when or why the patients were interviewed on more than one occasion. The Panel queried whether 261 was the sum total of interviews with 80 patients and 181 health professionals. The study stated that respondents (health professionals and patients) evaluated the DuoResp Spiromax after they had seen a demonstration video, tried an empty device and in the case of health professionals had additionally read the product profile. In that regard the Panel disagreed with Teva's submission that the study clearly supported the intuitive nature of the Spiromax device and the ability to handle the device without any instruction. Further the Panel noted that the study concluded that training could not be completely eliminated '…but the easy training use of the inhaler is a step in the right direction in the treatment of patients with asthma and COPD'.

The study reported that the new device was considered to be user friendly by 80% of patients; 75% considered the device to be intuitive or very intuitive mainly due to ease of use. The study also reported that 76% of patients handled the new device correctly without receiving any instruction. 80% of patients found Spiromax to be more intuitive than their currently used device. Plusa *et al* stated that the majority of health professionals (78%) regarded the new device as user friendly and that it was considered to be intuitive or very intuitive by 87%; 87% also handled it correctly without receiving any instruction. Comparison with the currently used device showed that 89% of health professionals found the new device to be more intuitive than the currently used device and 78% considered it to be easier to teach to their patients than the currently used device.

The Panel noted the authors' findings above and queried statements such as '76% of patients handled [Spiromax] correctly without receiving any instruction' given that they had all seen a demonstration video. The Panel considered that some important detail was missing from the published report as in its absence readers could not fully understand the study methodology nor the importance of its outcomes. Nonetheless, the Panel noted that whilst the majority of patients and health professionals were positive about Spiromax, there were still 25% of patients and 13% of health professionals who did not find it intuitive or very intuitive.

The Panel noted that the advertisement portrayed a patient's perspective of Spiromax and that Plusa *et al* had interviewed only 80 patients vs 181 health professionals. The Panel considered that readers would assume from the advertisement that all patients would immediately know how to use DuoResp Spiromax from the moment it was dispensed to them and that patients would not need to be counselled in the correct use of the device. This was not so and in that regard the Panel was very concerned about the possible risk that some asthma or COPD patients would lose control of their symptoms for want of adequate training. The advertisement stated in small, grey font, below the prescribing information, that instructions for use should be followed as per the patient information leaflet. In the Panel's view this statement was easily missed. The Panel noted that Teva acknowledged that some patients had difficulty in using inhalers and it recommended that health professionals refer patients to the patient information leaflet. The Panel considered that a statement referring readers to the patient information leaflet for instructions on how to use the Spiromax device contradicted the headline claim 'The moment I picked it up I knew how to use it'. Further, that patients were required to follow instructions as per the patient information leaflet meant that the device was not unequivocally intuitive as implied. The Panel considered that in the circumstances, the claims 'The moment I picked it up I knew how to use it' and 'Intuitive design' in the advertisement were misleading as to the ease of use of Spiromax and ruled a breach of Clause 7.2. The Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1.

Complaint received **17 December 2015**

Case completed **3 February 2016**

ANONYMOUS v ALLERGAN

Alleged inappropriate payments to health professionals

An anonymous, non-contactable complainant alleged that Allergan had made large payments to doctors to endorse Botox and other products.

The detailed response from Allergan is given below.

The Panel noted that the complainant could not be contacted for any more information; he/she had provided no detail as to when or to whom the allegedly large payments had been made. The Panel noted Allergan's reference to policies and procedures which it submitted provided a framework which ensured that its relationships with health professionals were appropriate and transparent. On the basis of the information before it, the Panel considered that there was no evidence to support the complainant's allegation. No breach of the Code was ruled.

COMPLAINT

An anonymous complainant, who was initially contactable but later could not be contacted at the email address provided, contacted the Authority and simply stated 'large payments made by Allergan to top doctors to endorse Botox and other products'.

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

RESPONSE

Allergan submitted that it operated within a framework of policies and procedures which set out to ensure that such activities did not occur. Allergan stated that its code of conduct outlined its commitment to integrity and ethical conduct and stated that any interaction with a health professional: served an appropriate and ethical business purpose; did not interfere with the health professional's independent medical judgment and did not violate local law, regulation or company policy or procedure. The code identified that there were risks inherent in Allergan's interactions with health professionals and that Allergan must ensure that such interactions were ethical and complied with company policies and procedures.

Allergan's global Anti-Bribery and Anti-Corruption policy aimed to ensure that all business activities carried out by, or on behalf of, Allergan were in line with all applicable legal and ethical requirements regarding anti-bribery and anti-corruption. The policy prohibited the offer or payment of any money or item of value with the intention of inappropriately influencing the recipient or obtaining an improper advantage. It required that all payments or transfers of value were for a legitimate reason and appropriately documented including relevant contracts and should not be excessive.

Allergan stated that its regional Commercial Compliance Principles Policy applied across the Europe, Middle East & Africa (EAME) region and was designed to ensure continued compliance with all applicable laws, rules and regulations and the Allergan Code of Conduct, by laying down key principles and minimum compliance standards applicable to Allergan commercial activities within the region. It provided general standards with regards to consultancy services with health professionals, including:

- There must be a clear business need for the engagement of the health professional
- Health professionals must be selected based on their qualifications, experience and expertise, as well as their ability to provide a service of value and not on their status as a user of Allergan products
- The business need would dictate the duration and the intensity of the engagement
- Services should not be conditional upon a requirement of the consultant to prescribe, supply, sell or administer any Allergan pharmaceutical or medical device product
- Compensation payable should be based on the nature of, and commensurate to, the services provided, and should be paid based on services actually provided
- All engagements with health professionals should be recorded in the form of an approved written agreement.

Allergan's regional Healthcare Professional Consultancy Procedure set the standards for establishing written consultancy agreements with health professionals acting as consultants for, or on behalf of, Allergan. In particular, the document set out fair market value rates for consultancy agreements which were used by the UK company to ensure that payments were appropriate. The regional procedures determined the specific fair market values and UK specific standard operating procedures (SOPs) and policies linked into these regional procedures.

Allergan further explained that UK/Ireland specific SOPs and policy documents covering meetings, hospitality and copy approval were in place to cover the basic principles to follow in relation to meetings organised by Allergan which took place in the UK or Ireland, or meetings organised by Allergan which involved attendance by UK/Irish health professionals at venues outside of the UK/Ireland.

The SOPs and policies provided guidance on logistical arrangements, hospitality (subsistence), and consultant payments. The same principles applied to meetings that Allergan supported but had not necessarily organised eg payment of speaker fee or for exhibition space.

Moreover all interactions with health professionals requiring engagement for speaking, training or advisory boards were subject to internal review and approval procedures covered by the SOPs noted above.

In addition to the internal policies and procedures, since 2013 Allergan disclosed transfers of value as required by the Code and intended to report in 2016 any transfer of value made in 2015 on an individual named basis, dependent on obtaining the relevant consent.

Allergan submitted that in 2012 it paid £264,775.32 to 206 consultants, averaging £1,285.32 per consultant. In 2013 it paid £558,439.75 to 384 consultants, averaging £1,454.27 per consultant and in 2014 it paid £837,300.45 to 514 consultants, averaging £1,628.99 per consultant.

Allergan submitted that an increase in payments was in line with Allergan operating in new therapy areas and the approval of new indications for existing products.

The complaint referred to payments being made in order to gain endorsement of Allergan products. As discussed above, Allergan policies and procedures precluded this kind of activity. Allergan submitted that it conducted training workshops on certain products, either because of the highly technical nature of their use (eg the VYCROSS range of dermal fillers) and/or because its product was the only one with a specific indication (eg Botox indications for chronic migraine and overactive bladder). In these cases Allergan entered into a consultancy agreement with a health professional, who would be an experienced prescriber/user of its products and would typically be a key opinion leader. The training concentrated on Allergan products. It was possible that the complainant was confusing those events, which were run in order to educate on the safe and effective use of Allergan products, with the endorsement of Allergan products by health professionals. All materials associated with those training events clearly identified the nature of the event so as not to leave any doubt for attendees.

Allergan was asked to consider whether payments to doctors had been the subject of internal concerns or complaints such as whistleblowing. As evidenced by the policies and procedures that it had in place, Allergan submitted that hopefully it was clear that payments to health professionals had been the subject of review and oversight by the company. Allergan's records indicated that there had been no whistleblowing complaints related to payments made to UK health professionals.

Allergan noted that the anonymous complaint was vague and contained no specific examples which Allergan could attempt to defend. There appeared to be two points to consider; that payments to UK health professionals were large and that they were made to encourage the endorsement of its products. On both counts, on the basis of the detailed and adequate procedural documents outlined above, robust internal review and approval procedures being in place, and the fact that Allergan openly declared transfers of value as required by the relevant Code, the company strongly refuted the allegations and denied breaches of Clauses 18.1, 9.1 and 2.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure for the Prescription Medicines Code of Practice Authority, stated that anonymous complaints would be accepted but that like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant could not be contacted for any more information.

The Panel noted that in this case the complaint consisted of a single allegation with no detail as to when or to whom the allegedly large payments had been made. The Panel noted Allergan's submission including its reference to policies and procedures which provided a framework which ensured that its relationships with health professionals were appropriate and transparent. On the basis of the information before it, the Panel considered that there was no evidence to support the complainant's allegation that Allergan had paid doctors large amounts of money to endorse Botox and other products. No breach of Clauses 2, 9.1 and 18.1 were ruled.

Complaint received **16 December 2015**

Case completed **21 January 2016**

CASE AUTH/2817/12/15

ALK-ABELLÓ/DIRECTOR v BAUSCH & LOMB

Breach of undertaking

ALK-Abelló alleged that Bausch & Lomb UK had failed to comply with the undertaking given in Case AUTH/2802/11/15 regarding use of the word 'new' in relation to the promotion of Emerade (adrenaline auto-injector). The claim now at issue appeared on a website.

As the complaint concerned an alleged breach of undertaking it was taken up by the Authority in the name of the Director as the Authority was responsible for ensuring compliance with undertakings.

The detailed response from Bausch & Lomb is given below.

The Panel noted that Bausch & Lomb had accepted the ruling of a breach in Case AUTH/2802/11/15 in relation to the claim 'new higher dose' for Emerade which appeared in a Pulse Quick Guide. The company's undertaking was signed on 10 December and stated that the last date the material was used or appeared was September 2015.

The Panel noted that a form of undertaking and assurance was an important document. Companies had to give an undertaking that the material in question and any similar material, if not already discontinued or no longer in use would cease forthwith and give an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted Bausch & Lomb's submission that following its provision of the undertaking it ensured that all references to the word new had been removed from printed material. The Panel further noted that in March 2015, and unconnected to the previous complaint, Bausch & Lomb had instructed the website administrator to remove all reference to the word new from the Emerade website. Bausch & Lomb submitted that it understood that that had been actioned and its checks confirmed this to be so. The webpage now at issue was on the section of the Emerade website for health professionals and was the second page that they were likely to click on. In that regard the Panel queried the robustness of the checks carried out by Bausch & Lomb. Regardless of why, the Panel considered that as the Emerade website continued to describe Emerade as 'new', after Bausch & Lomb had given its undertaking in Case AUTH/2802/11/15, it had failed to comply with that undertaking. Thus the Panel ruled a breach of the Code. High standards had not been maintained and a breach of Code was ruled. The Panel considered that Bausch & Lomb's failure to comply with its undertaking brought discredit upon and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

ALK-Abelló Ltd alleged that Bausch & Lomb UK Ltd had failed to comply with the undertaking given in Case AUTH/2802/11/15 regarding use of the word 'new' in relation to the promotion of Emerade (adrenaline auto-injector). A breach of Clause 7.11 was ruled in that case.

As the complaint concerned an alleged breach of undertaking it was taken up by the Authority in the name of the Director as the Authority was responsible for ensuring compliance with undertakings.

COMPLAINT

ALK-Abelló alleged that the claim 'The new adrenaline auto-injector for emergency treatment of anaphylaxis' which appeared on an Emerade website breached the undertaking given in Case AUTH/2802/11/15.

ALK-Abelló noted that the top of the webpage clearly stated 'Information for healthcare professionals only in the UK'. The website was promotional and should comply with the Code. ALK-Abelló was concerned that the webpage referred to Emerade as new. It noted the title of the page 'The new adrenaline auto-injector for emergency treatment of anaphylaxis', and further down the page 'New Emerade'. The references to 'new' were despite the ruling in Case AUTH/2802/11/15; a breach of Clause 29 was alleged.

When writing to Bausch & Lomb, the Authority asked it to respond in relation to Clauses 9.1 and 2 of the 2015 Code in addition to Clause 29 cited by ALK-Abelló.

RESPONSE

Bausch & Lomb submitted that as per its undertaking in Case AUTH/2802/11/15 to remove all references to the word 'new' in its promotional materials, it had taken great care with all printed materials to ensure that that was so and submitted that it was fully compliant.

Case AUTH/2802/11/15 referred to an article published in Pulse, Bausch & Lomb notified the publishers that no further distribution or copies of the inserts should be made which the publishers agreed. Bausch & Lomb's sales teams did not have any copies of the insert to distribute so no withdrawal was required.

At the end of February 2015, Bausch & Lomb assumed the sales and marketing of Emerade from the previous distributor. One of its first actions on 2 March 2015 was to request the removal of all references to the word 'new' from the Emerade.com website by the website administrator. Bausch & Lomb understood that this had been done and its checks confirmed this to be so. Turning to

Case AUTH/2817/12/15 Bausch & Lomb was very concerned that one of the webpages had been overlooked and still included the word 'new'. In mitigation Bausch & Lomb submitted that it was not a deliberate action to deviate from its undertaking and it would implement better processes to avoid similar issues going forward.

PANEL RULING

The Panel noted that in the previous case, Case AUTH/2802/11/15, ALK-Abelló had complained in November 2015 about the claim 'Emerade offers a new higher dose …' which appeared in a Pulse Quick Guide and implied that a new higher dose of Emerade had been launched within the last 12 months. The Panel noted that the Emerade 500mcg summary of product characteristics (SPC) stated that the date of first marketing authorization/renewal of authorization was 3 January 2013. The Panel further noted Bausch & Lomb's submission that the 500mcg dose referred to in the claim had been available for over 12 months. A breach of Clause 7.11 was ruled which was accepted by Bausch & Lomb; the company's undertaking signed on 10 December 2015 stated that September 2015 was the last date the material was used or appeared.

The Panel noted that a form of undertaking and assurance was an important document. Companies had to give an undertaking that the material in question and any similar material, if not already discontinued or no longer in use would cease forthwith and give an assurance that all possible steps would be taken to avoid similar breaches of the Code in future (Paragraph 7.1 of the Constitution and Procedure). It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted Bausch & Lomb's submission that following its provision of the undertaking it had taken great care with all printed materials to ensure that all references to the word new had been removed. The Panel further noted that in March 2015, and unconnected to the previous complaint, Bausch & Lomb had instructed the website administrator to remove all reference to the word new from the Emerade website. Bausch & Lomb submitted that it understood that that had been actioned and its checks confirmed this to be so. No copies of the correspondence between the parties etc were provided. The webpage now at issue was on the section of the Emerade website for health professionals and was the second page that they were likely to click on. In that regard the Panel queried the robustness of the checks carried out by Bausch & Lomb. Regardless of why, the Panel considered that as the Emerade website continued to refer to 'New Emerade' and 'The new adrenaline auto-injector for emergency treatment of anaphylaxis' after Bausch & Lomb had given its undertaking in Case AUTH/2802/11/15, it had failed to comply with that undertaking. Thus the Panel ruled a breach of Clause 29. High standards had not been maintained and a breach of Clause 9.1 was also ruled. The Panel noted the importance of complying with undertakings and considered that Bausch & Lomb's failure to comply with its undertaking brought discredit upon and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

During its consideration of this case the Panel was concerned that Bausch & Lomb had only stated that it reviewed printed materials after providing its undertaking in Case AUTH/2802/11/15 in December 2015. The undertaking covered all closely similar materials and so, regardless of their format, all materials should have been examined. The Panel requested that its concerns be drawn to Bausch & Lomb's attention.

Complaint received **23 December 2015**

Case completed **2 February 2016**

CODE OF PRACTICE REVIEW – February 2016

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

AUTH/2789/8/15	Roche/Director v Merck Serono	Alleged breach of undertaking	No Breach	No appeal	Page 3
AUTH/2793/9/15	**Clinical pharmacist v AstraZeneca**	**Identifying patients suitable for Forxiga treatment**	**Breaches Clauses 3.2,7.2,9.1**	**No appeal**	**Page 11**
AUTH/2796/9/15	**General practitioner v Bausch & Lomb**	**Pulse Quick Guide**	**Breaches Clauses 2, 7.2, 7.4, 7.10, 9.1 and 12.1**	**No appeal**	**Page 16**
AUTH/2797/9/15	Anonymous, non contactable health professional v Sanofi	Company meeting	No Breach	No appeal	Page 21
AUTH/2798/10/15	Director of Pharmacy v Grünenthal	Conduct of a representative	No Breach	No appeal	Page 26
AUTH/2799/10/15	**Anonymous Oncologist v Pierre Fabre**	**Promotion of Vinorelbine**	**Breaches Clauses 7.2, 7.4, and 9.1**	**No appeal**	**Page 31**
AUTH/2800/10/15	**Sanofi v Amgen**	**Promotion of Repatha**	**Breaches Clauses 7.2, 7.10 and 9.1**	**No appeal**	**Page 38**
AUTH/2801/11/15	**Voluntary admission by Janssen**	**Outdated Prescribing Information**	**Breaches Clauses 4.1 and 9.1**	**No appeal**	**Page 44**
AUTH/2802/11/15	**ALK-Abelló v Bausch & Lomb**	**Use of the word new**	**Breach Clause 7.11**	**No appeal**	**Page 48**
AUTH/2803/11/15	Complainant v Alexion	Conference programme booklet	No breach	No appeal	Page 49
AUTH/2804/11/15	**Anonymous health professional/ Director v Merck Serono**	**Call rates and uncertified material**	**Breaches Clauses 2, 9.1 and 14.1**	**No appeal**	**Page 51**
AUTH/2810/12/15	**Anonymous v Teva**	**Promotion of DuoResp Spiromax**	**Breaches Clauses 7.2 and 9.1**	**No appeal**	**Page 57**
AUTH/2816/12/15	Anonymous v Allergan	Alleged inappropriate payments to health professionals	No breach	No appeal	Page 60
AUTH/2817/12/15	**Alk-Abello/Director v Bausch & Lomb**	**Breach of undertaking**	**Breaches Clauses 2, 9.1 and 29**	**No appeal**	**Page 62**

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.