NUMBER 89 August 2015

CODE OF PRACTICE REVIEW

PMCPA | Prescription Medicines Code of Practice Authority

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

CODE IN CONTEXT

We have now delivered two 'Train the Trainer' sessions (in March and June) to launch Module 1 of the Code in Context toolkit. The aim of this toolkit is to enable in-house compliance specialists to run interactive workshops which will increase the value that staff attach to self-regulation and encourage positive engagement with the Code. The toolkit can be tailored to include in-house procedures and processes and includes a number of scenarios for discussion.

Feedback so far has been positive and particularly popular is the use of scenarios to challenge participants to think like various stakeholders including patients, health professionals, journalists, and the Code of Practice Panel.

We are very grateful to the Compliance Network for its input, particularly in identifying elements that colleagues find challenging, and developing ways to discuss the Code to help with issues faced by the industry.

The plan is to make the Code in Context training more widely available later in the year. Additional Code in Context Modules are currently under development.

Please contact Elly Button for more details ebutton@pmcpa.org.uk.

* REMINDER *

ABPI unaccredited examination to end this year.

Clause 16.3 of the Code requires representatives to take an appropriate examination within their first year of employment and pass it within two years. The ABPI has been offering either the unaccredited examination or the more recently introduced accredited examination.

Please note that the unaccredited ABPI examination finishes on 31 December 2015. Staff currently studying for this examination need to pass it by the end of 2015. From 1 January 2016 the ABPI will only offer the accredited examination.

CONSULTATION ON CHANGES TO THE CODE

Full details of the proposed changes to the 2015 ABPI Code of Practice for the Pharmaceutical Industry and the Constitution and Procedure for the PMCPA are available on the PMCPA website for public consultation.

They were also sent to The Medicines and Healthcare Products Regulatory Agency, the Competition and Markets Authority, the Serious Fraud Office, the British Medical Association, the Royal Pharmaceutical Society and the Royal College of Nursing. The consultation ends on 11 September.

There were a number of reasons for the proposed changes including the work done by the group established by the ABPI Board to review the Code. A draft of the 2016 Code and Constitution and Procedure will be available shortly. The consultation responses will be reviewed and the final proposals agreed by the ABPI Board of Management before they are put before the ABPI membership for approval in November.

If approved, the 2016 Code will come into operation on 1 January 2016 with the usual transition period for newly introduced requirements until 30 April 2016.

BE CLEAR AND SPECIFIC AT THE OUTSET

The Constitution and Procedure for the Prescription Medicines Code of Practice Authority (Paragraph 5.3) requires inter-company dialogue in advance of any complaint from a pharmaceutical company being accepted. Complaints can only proceed if the Director of the PMCPA is satisfied that the complainant company informed the respondent company that it proposed to make a formal complaint and offered inter-company dialogue at a senior level in an attempt to resolve the matter, but that this was refused or dialogue proved unsuccessful.

Normally at the start of inter-company dialogue, a telephone call is made to alert the respondent company to a complaint and to outline the basis of that complaint. This should be followed by written details of the specific points thought to be in breach of the Code, including the relevant clauses. Companies must not make very general allegations with little detail during inter-company dialogue, subsequently allege that the dialogue was unsuccessful and then add more clarity and specificity to their concerns only when they submit a formal complaint to the Authority. Should that happen then the Authority is likely to consider that the requirements for inter-company dialogue have not been met and the complaint will not proceed.

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:

Friday 16 October
Monday 14 December

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

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

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

CASE AUTH/2747/1/15

ANONYMOUS HEALTH PROFESSIONAL v ASTELLAS PHARMA EUROPE

Arrangements for a meeting

An anonymous, non-contactable health professional complained about the arrangements for a meeting organised by Astellas Pharma Europe, in Milan, February 2014.

The complainant noted that Astellas had invited him/her and colleagues to a meeting in Milan, to obtain advice about prostate cancer. More than 100 other clinicians were at this large advisory board meeting and Astellas presented the benefits of its medicine an unlicensed indication for enzalutamide. The complainant alleged that Astellas was not truthful as to why delegates had been invited to the meeting and the company promoted something it should not have done.

The detailed response from Astellas Europe is given below.

The Panel noted that Astellas Europe's submission that the most practical, effective and expedient way to quickly gather a group of advising urologists, oncologists and uro-oncologists from a number of countries with the two expert speakers was to hold the advisory board meetings in one European location, rather than to organise separate advisory boards in individual countries. The Panel considered that holding multiple simultaneous local advisory board meetings overseas, in one central location would not necessarily be unacceptable providing all the aspects complied with the Code. There had to be valid and cogent reasons for holding meetings at venues outside the UK. In this regard, the Panel noted that the UK health professionals were not otherwise attending an international meeting or other event in Milan. The Panel queried whether the availability of the two speakers was an adequate justification given the nature of the meeting and that local experts on the data were available for each advisory board.

The Panel noted this was the third such meeting held by Astellas. The previous two meetings had taken place before and immediately after the initial marketing authorization of Xtandi in the treatment of adult men with metastatic castration-resistant prostate cancer whose disease had progressed on or after docetaxel therapy. The meeting at issue was held prior to the grant of the marketing authorization for a new indication for the treatment of men with metastatic castration-resistant prostate cancer who were asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy was not yet clinically indicated.

The Panel queried whether the contents of the two previous meetings held in 2012 and 2013 were as distinct as submitted by Astellas. Whilst one advisory board was in the post-chemotherapy indication, the objectives were, nonetheless, similar to the advisory board at issue. Given the advice previously received, the Panel queried whether there remained a *bona fide* need for advice such as to justify the meeting in question.

The Panel noted the criteria and process for the selection of experts. The Panel noted that participants at advisory board meetings would reasonably be expected to have sufficient expertise and experience in the relevant disease area that their contribution would be beyond that of simply having experience of treating patients for that particular disease and certainly be relevant to the advice sought by the company. The Panel considered that the number of local experts identified seemed quite large and queried whether participation was driven by who could attend as opposed to who should attend to provide Astellas with appropriate advice.

Participants were not required to do any pre-reading or other preparation. The meeting had two distinct sections; the first section lasted just over 2 hours and included presentations from the two speakers on 'The role of the androgen receptor signalling pathway in mCRPC [metastatic castration-resistant prostate cancer]' and 'Enzalutamide in mCRPC'. Astellas submitted these ensured a common understanding of new treatment options and the Phase 3 data. Both presentations were followed by 25 minute Q&A sessions. The second section of the meeting lasted for 2 hours and 25 minutes. Attendees were split into their respective country/regional advisory board meetings where over 2 hours, 10 minutes they completed two exercises. Firstly, to differentiate enzalutamide from competitors in the proposed target patient population and secondly, to look at current prescribing practice across the patient pathway in mCRPC including where enzalutamide might fit into that pathway now and in the future.

The Panel noted Astellas' submission that two thirds of the total time was dedicated to seeking advice. This included the two Q&A sessions, which the Panel considered were for the attendees to ask questions such that they were equipped to participate in the advisory boards rather than a means of providing advice to the company. The time allocated for the provision of advice was therefore less than fifty percent of the total meeting time.

The Panel considered that it would have been helpful if the data could have been sent in advance as pre-reading so that participants could have come prepared to provide advice at the outset. The Panel

further noted that Astellas' company attendees included, a data expert for each national advisory board meeting and noted its comments above in this regard about the availability of the speakers. The Panel accepted that it was important that participants understood the data and this might be particularly relevant given the different approaches to treating prostate cancer be that by urologists or oncologists. It was concerned that this was listed as one of the three objectives for the meeting. The Panel noted, however, that the sole purpose of advisory board meetings should be to gain advice from the participants; the presentation of current data should not be the primary reason to attend.

The Panel examined the meeting report and was concerned to note that 75 questions were raised following the presentations and many of these did not appear to be related to Astellas' submission of the need for a common understanding of the data. Further, the plenary session was rated as the most useful/valuable aspect of the meeting by 38.8% of health professional respondents with the panel discussion scoring 27.1% and the discussion with colleagues from the same country scoring 34.1%. The audience was asked to suggest interesting topics that could be the focus of future meetings. Company feedback included 'ideal opportunity to be with KOLs', '… the advisers provided useful insights', 'they … want to know more relevant information about enzalutamide and research with it' and 'working groups are not always well accepted'. The feedback from both groups included a comment about sending material for pre-reading and further time for discussion.

The Panel noted that the provision of advice related to the completion of the two exercises. The information provided to each group for the first exercise consisted of a document entitled 'Differentiating enzalutamide in mCRPC' below the heading was the sentence 'Please see below statements, based on the PREVAIL data, to be used as reference during the ranking exercise'. The Panel was concerned about the universally positive nature of the statements in relation to enzalutamide. It appeared that participants were only assessing the impact of potential promotional claims. The second exercise was another group workmat based exercise. The workmat was headed 'Place in patient pathway: Progression on ADT, chemotherapy naïve'. A workmat was to be completed for four treatments. At the end of each exercise the facilitator was instructed to ask whether any other features of enzalutamide that had not been covered were particularly relevant to the UK. There was no mention on any of the materials submitted for the national meeting that the information provided or the data was for an unlicensed indication.

The Panel considered that as the exercises were to be completed by the UK attendees as a group, consensus would have to be reached to complete the workmats. As such, the views of some of the participants might not be documented or taken into consideration. Further, the Panel noted the exercises could perhaps be carried out individually or prepared individually prior to a joint discussion. Given its comments above, the Panel did not consider that attending the presentations constituted a valid and cogent reason for holding the meeting outside the UK. The Panel was concerned that the time spent obtaining advice was low, less than 50% of the total meeting time and further no preparation was needed. The attendees worked as a group to provide one view. The Panel noted its comments above about the arrangements, content and feedback for the meeting. The Panel did not consider that the arrangements were such that the UK health professionals had attended a genuine advisory board meeting and therefore ruled a breach of the Code.

The Panel considered that, as it had ruled the arrangements did not meet the criteria for advisory boards, UK health professionals had been paid to attend a meeting where an unlicensed indication was promoted. As Xtandi was licensed in the UK the Panel considered that the arrangements constituted promotion of an unlicensed indication and not promotion of an unlicensed medicine. It therefore ruled no breach of the Code in this regard. It could not make a ruling regarding the promotion of an unlicensed indication as the relevant clause had not been cited by the case preparation manager.

The Panel noted that UK health professionals had received payment to attend a meeting which the Panel considered promoted the medicine and a breach of the Code was ruled. The Panel considered that the requirement that promotional material and activities must not be disguised had not been met and ruled a breach of the Code.

High standards had not been maintained and the Panel ruled a breach of the Code.

The Panel noted that Clause 2 was reserved for use as a sign of particular censure. The health professionals had attended the meeting believing it was a legitimate advisory board meeting, which was not so. In addition, they had received a payment for attending a promotional meeting for an indication which at the time did not have marketing authorization. The Panel noted that unacceptable payments was listed in the supplementary information to Clause 2 as an example of an activity likely to be in breach of that clause. The Panel considered that the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted its comments and rulings above and considered that its concerns about the arrangements and the company's procedures warranted consideration by the Appeal Board. The Panel thus reported Astellas Europe to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board noted the Panel's ruling that the Astellas Europe's Pan-European Uro-oncology Advisory Board Meeting was not a genuine advisory board meeting. The Appeal Board noted that the meeting clearly promoted Xtandi for an unlicensed indication to UK health professionals. In response to a question Astellas Europe stated that the

meeting at issue had been held within a few days of the first presentation of the data at a conference. Astellas Europe accepted that the meeting had not met the criteria for advisory boards as required by the Code or its own standard operating procedures (SOPs), and in that regard the Appeal Board was very concerned that either the company's SOPs were not sufficiently clear or had not been followed. The arrangements and material had been certified by Astellas Europe rather than the UK affiliate and in that regard the Appeal Board questioned the rigour of the company's processes and procedures. Improvements needed to be made and should be a priority. The Appeal Board noted that the representatives from Astellas Europe referred on a number of occasions to recognising, with hindsight that its activities could be seen as promotional. The Appeal Board noted Astellas Europe's submission that it had undertaken a number of measures to address the issues. The Appeal Board also noted that the company had accepted all the Panel's rulings of breaches of the Code including Clause 2.

The Appeal Board was concerned that the UK health professionals had attended the meeting on the understanding that it was an advisory board and had been paid to do so. This was unacceptable. Consequently, the Appeal Board decided, in accordance with Paragraph 11.3 of the Constitution and Procedure to require Astellas Europe to issue a corrective statement to all the UK attendees at the meeting. The corrective statement should refer to the case report. Under Paragraph 11.3 details of the proposed content and mode and timing of dissemination of the corrective statement must be provided to the Appeal Board for approval prior to use.

An anonymous, non-contactable health professional complained about the arrangements for a meeting organised by Astellas Pharma Europe, in Milan, in February 2014.

COMPLAINT

The complainant stated that he/she worked with a number of pharmaceutical companies and wished for all of them to act honestly and ethically and in the interests of patients not only profit. He/she understood that pharmaceutical companies should not promote a medicine before they had full go-ahead from the regulators with a licence to operate.

The complainant noted that Astellas had invited him/her and his/her colleagues to a meeting at an airport hotel in Milan, Italy on 28 and 29 February 2014 to get their advice at an advisory meeting about prostate cancer. More than 100 other clinicians were at this large meeting and crucially, Astellas presented the benefits of its new medicine enzalutamide in pre-chemotherapy indication. The complainant stated that the medicine was not licensed yet by the European Medicines Agency (EMA).

The complainant alleged that with regard to the meeting, Astellas was not truthful as to why delegates had been invited and also the company promoted something it should not have done.

When writing to Astellas, the Authority asked it to consider the requirements of Clauses 2, 3.1, 9.1, 12.1, 18.1 and 20 of the 2014 Code.

RESPONSE

Astellas explained that the meeting at issue was the Pan-European Uro-oncology Advisory Board Meeting. It was arranged and conducted by Astellas Pharma Europe Ltd which was the regional organisation of Astellas and covered countries in Europe, Middle East and Africa (EMEA). The European organisation was located on the same site as the UK organisation. The companies operated as separate legal entities and the response to this complaint was provided by the European organisation.

Astellas Europe stated that it took its commitments with regard to the Code very seriously, and was disappointed that a health professional had complained. Astellas Europe was committed to addressing all aspects of the complaint and in cooperating fully with the PMCPA to resolve the matter.

The meeting at issue was held on 27/28 February 2014 rather than 28/29 and was the Pan-European Uro-oncology Advisory Board Meeting which consisted of an introductory session and 16 national advisory board meetings. An agenda was provided.

1 Regulatory status

Astellas Europe submitted that it held the marketing authorization for enzalutamide (Xtandi) which was approved for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy in the EU, 21 June 2013, based on the results of the AFFIRM study. This indication was licensed via the EMA centralised procedure when the invitations were issued and when the meeting took place.

The role of enzalutamide had since been evaluated earlier in the natural history of prostate cancer in the PREVAIL study and results were first reported at the American Society of Clinical Oncology Genitourinary (ASCO-GU) meeting January 2014 in the USA. These results led to a Type II variation to include an additional indication which was granted a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) on 23 October 2014 and approved by the European Commission on 2 December 2014, '… for the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated'. The meeting at issue took place after the publication of the PREVAIL results and within the anticipated 6-month window in which the Type II variation adding the chemo-naive indication for enzalutamide was expected to be approved.

The summary of product characteristics (SPC) current when the invitations were issued and the meeting held was provided. The current SPC was also provided.

2 Objectives of the advisory board meetings

Astellas Europe stated that the objectives of the advisory board meetings were to:

- Present data on enzalutamide in metastatic castration-resistant prostate cancer (mCRPC) in the context of other available and emerging therapies, in order to ensure the experts at the meeting had a consistent level of knowledge of the data and thus could provide Astellas with advice, insight and feedback

- Provide Astellas with further insight into the current and likely future clinical management of mCRPC at a Pan-European level

- Seek expert insight and feedback regarding the potential opportunities and challenges facing enzalutamide as a therapeutic option for mCRPC in a complex market environment in Europe with fundamental questions in each country.

To achieve these objectives the advisory board meetings were set up with a preceding introductory data presentation so that all advisors had a common understanding of new treatment options followed by national advisory boards to enable in-depth understanding of country and sub-national differences.

3 Arrangements and logistics

The meeting took place at an airport hotel in Milan, on 27/28 February 2014. Milan airport was chosen because it was a central location within a short flight time for the majority of European countries. The 4 star airport hotel helped ensure ease of access for the majority of advisors, as opposed to travelling to an inner city hotel; the meeting facilities and capacity available at the hotel were essential to meet the logistical requirements of the meeting.

As stated previously, enzalutamide was already licensed in Europe for a sub-group of men with prostate cancer when the advisory board meetings took place, based on the AFFIRM study. Following the results of the PREVAIL study, Astellas had around 6 months in which to gather expert advice with regard to local market access for the additional indication before this indication would likely be approved. Treatment of prostate cancer was complex with the recent or impending introduction of a number of new therapies and expanded licences which made treatment pathways in each country uncertain. Astellas invited the European principal investigator of the PREVAIL study and another European expert to present data to the advisors from each country. Both speakers were global experts with busy schedules and limited availability.

The most practical, effective and expedient way to quickly gather a group of advising urologists, oncologists and uro-oncologists from a number of countries with the two expert speakers was to hold the advisory board meetings in one European location, rather than to organise separate advisory boards in individual countries. It would not have been logistically viable to have separate meetings with the same expert speakers within the required timeframe. The arrangements of these advisory board meetings allowed Astellas to ensure the availability of the independent expert speakers. The arrangements also reduced the burden on the speakers and their clinical commitments by allowing them to make one presentation to each country as part of the introductory session as opposed to attending separate meetings in each country. Astellas realised that conducting multiple, simultaneous advisory boards was innovative and complex and that any such new approach might attract comment.

The advisory board meetings started on the 28 February with registration from 7:30am and the introductory session commenced at 8:45am. To avoid the risk of travel disruption and to ensure all advisors were present at the start of the meeting, advisors travelled to arrive by 27 February. Economy flights were offered to advisors as required, with the exception of those from South Africa who were offered premium economy due to the long travel time. One expert speaker travelled business class and the other travelled economy in accordance with local compliance requirements. Train travel was provided as necessary to a few Italian advisors and some Italian and Slovenian advisors travelled by car. Accommodation was provided for all advisors and speakers in the 4 star venue as necessary to meet travel arrangements.

Dinner (€60/head) for the advisors on 27 February was preceded by a 15 minute introduction to Astellas in order to prepare them for the next day. This was held in a private room at a restaurant, and they were seated in advisory board/country tables so that the advisors could meet their respective peers and country facilitators. Arrangements were reviewed and approved locally by each affiliate's local compliance reviewer.

4 Participants

Astellas Europe stated that two hundred and eighty two advisors received a 'save the date' email and of these, 143 received the invitation letter (including the speakers). The 16 national advisory board meetings were attended by 108 advisors (including speakers) from 23 countries (including 5 UK advisors). Each advisor was identified by the local affiliate.

Countries outside the EU, in which Astellas Europe affiliates operated and that were involved in the meeting, included Turkey, Russia and South Africa. These countries were included because all were considering fast track approval options, encompassing the AFFIRM and PREVAIL data.

Affiliates were asked to identify 30 local experts with personal experience of treating patients with mCRPC, and the names of these were grouped based on their clinical expertise into first 10 (15 for Nordic and South East Europe affiliates that cover more than one country), second 10 and third 10 advisors.

- First 10 invitees for each country (15 for Nordic and South East Europe affiliates that cover more than one country) were sent the 'save the date' email.

- For each decline, the next name from the list was sent the 'save the date' email until 10 potential invitees registered interest in participating in the meetings.

- 10 potential invitees were each sent an invitation letter and a copy of the draft agenda for the meetings. The emailed invitation clearly stated the objectives of the meetings and the requirements of their participation.

- When experts confirmed their participation, each had to sign a written contract, clearly outlining the requirements of their participation. A copy of a signed advisory board agreement with a UK health professional was provided.

Astellas Europe provided details of the number of potential invitees, actual recipients of the 'save the date' email/ invitation and the actual number of attendees by country.

All advisors were paid €1,000 with the exception of those from South East Europe who were paid €500. These amounts were commensurate with fair market value assessment by country, following approval by the local compliance reviewer and in accordance with the level of advice and contribution required. The two expert speakers were each paid €1,500 which included preparation time and the delivery of the services at the advisory board meetings.

The Astellas attendees were from Astellas Europe, Astellas Pharma Global Development (APGD) and the local country affiliates. Details were provided of Astellas attendees and their respective roles at the event.

Each advisory board meeting was attended by no more than 10 advisors and no more than 3 Astellas employees which consisted of; a facilitator from the relevant affiliate, a data expert and a support person from Astellas, where appropriate and feasible. The local country affiliate attendees facilitated the individual national groups in their local language. The data experts provided input concerning the new data on enzalutamide, where requested. The additional Astellas Europe attendees were present to provide clarification if needed.

5 Content of the advisory board meetings

On the evening of 27 February 2014, a brief introduction to Astellas was presented to prepare the advisors for the next day. A copy of the presentation was provided.

The advisory board meetings on 28 February 2014 consisted of two key parts, an introductory session and national advisory board meetings.

The introductory session welcomed the advisors and presented the objectives of the meeting. As stated above, there were two speaker presentations in which data, relevant to the treatment of mCRPC was presented for the purpose of contextualisation so each advisor could provide informed advice in his/ her national advisory board meeting.

The first presentation, 'Enzalutamide: The role of the androgen receptor signalling in mCRPC' gave an overview of the mechanism and the importance of the androgen receptor in mCRPC, as well as current and future therapeutic options for CRPC. The second presentation, 'Enzalutamide in mCRPC' covered the epidemiology and natural history of CRPC, the evolution of treatment over time and the current and future treatments available; including enzalutamide (PREVAIL data). Copies of the presentations were provided.

The data presentations by the speakers were followed by a question and answer session to allow for clarification. Tablet computers were provided as part of the introductory session in order to facilitate the question and answer session and feedback at the end of the event. These tablets were restricted and no access was provided to any applications or the Internet and they were returned at the end of the meeting.

The introductory session concluded with a short break before the 16 individual advisory board meetings which accommodated all countries, as well as multi-country groups where appropriate eg countries in South East Europe were grouped where geographically appropriate (Romania, Croatia, Slovenia, Serbia, Bosnia/Herzegovina) and as would normally happen with an advisory board conducted in that region.

In the individual national advisory board meetings, two workmats were provided to facilitate the collection of advice. There were clear objectives for the advisory board meetings and these were detailed in the staff briefing slides (copy provided) as below:

Session 1 (differentiating enzalutamide in mCRPC):

- To gain advice on key clinical features and evidence differentiating enzalutamide from competitors in the proposed target patient population

Session 2 (mCRPC patient journey and profiles):

- To determine current treatment prescribing practice across the patient pathway in mCRPC
- To identify where enzalutamide might fit into that pathway, now and in the future.

These were essential outputs of these advisory board meetings and advisors would not have been paid without active participation.

The programme on 28 February consisted of 5 hours in total (including a break of 30 minutes). Presentation time was 1 hour, 30 minutes and advice seeking/discussion time was 3 hours. Two thirds of the total time (excluding break) was dedicated to seeking advice.

The meeting closed at 1:45pm which allowed the advisors to return home in good time to be back at work as soon as possible in order to limit the burden on their workload and patient care responsibilities.

6 Response to complaint

Astellas Europe noted that the complaint had been submitted almost a year after the non-promotional advisory board meetings and outlined four areas of concern:

- '... to act in an honest and ethical way and in the interests of patients not only profit ...'
- '... that pharmaceutical companies should not promote a medicine before they have full go-ahead from the regulators with a licence to operate'.
- The arrangements of the meeting were inappropriate.
- The invitation was misleading '... Astellas was not truthful as to why delegates had been invited and also the company promoted something it should not have done'.

Clause 3.1 – A medicine must not be promoted prior to the grant of the marketing authorization which permits its sale or supply

Astellas Europe submitted that the advisory board meetings were non-promotional, scientific/medical-led meetings with an agenda focussed on legitimate scientific exchange about the treatment of mCRPC.

The rationale and objectives for the advisory board meetings were outlined above. The advice gained was critical given the dynamic nature of mCRPC with recent approval of three new treatments, representing three different treatment modalities namely a chemotherapeutic agent, an androgen-synthesis inhibitor and a radio-pharmaceutical agent. The meeting approval form for the advisory board meetings and the agenda confirmed the intent and purpose of the meetings, namely scientific exchange prior to the pending additional indication of enzalutamide. This exchange was essential given the variation in the management of prostate cancer across Europe, the Middle East and Africa eg in Germany the care was led by urologists, whereas in other countries such as the UK, guidelines advocated close cooperation between urologists and oncologists as part of multi-disciplinary teams. The AFFIRM study was an oncologist-led study whereas PREVAIL was a urologist-led study. It behoved Astellas, as the marketing authorization holder, to understand the clinical practice patterns across countries and be guided as how to responsibly engage with the lead clinicians and ensure seamless patient transition from urologists to oncologists as appropriate to the stage of the disease.

As stated above, clinical data on enzalutamide and other treatments (abiraterone, radium-223, docetaxel) was provided in the introductory session for the purpose of contextualisation so each advisor could provide informed advice in the individual national advisory board meetings. This was essential in order to achieve the objectives of the national advisory board meetings.

The meetings structure and medical leadership were further evidence that this was not, and should not be perceived as a promotional meeting. The workshop materials and outputs (copies provided) were examples of the input/advice gathered from the advisors.

For the reasons stated above Astellas Europe denied a breach of Clause 3.1.

Clause 12.1 – Promotional material and activities must not be disguised

Astellas Europe submitted that the meeting invitation was clear in terms of intention, and outlined the objectives of the advisory board meetings which were non-promotional. The advice given was captured and was the basis for the fee for service. The scientific exchange at the advisory board meetings was essential, given the variation in the management of prostate cancer across the EMEA region.

The format consisted of 16 separate national advisory board meetings, which provided answers unique to practices within each country regarding the treatment of mCRPC and market access needs. Each advisory board was held in a separate room with no more than 10 advisors.

As stated above, the most practical, effective and expedient way to quickly gather a group of urologists, oncologists and uro-oncologists from a number countries with the two expert speakers was to hold the advisory board meetings in one European location, rather than organise separate advisory boards in individual countries. The arrangements were reviewed and approved by the affiliate local compliance reviewers.

On 27 February 2014 a brief historical overview of Astellas and its background, structure, therapy areas and products was provided to the participants. This also continued on 28 February with 'Welcome, Objectives and Agenda' from Astellas.

Both presentations made by the speakers on 28 February were based on *bona fide* medical and scientific subject matter and were accurate, balanced, fair and objective for the purpose of the advisory boards. The clinical data presented was essential to meet the stated objectives of the advisory board meetings and was thus acceptable in this setting.

For the reasons stated above, Astellas Europe submitted that the advisory board meetings were not in breach of Clause 12.1.

Clause 18.1 – Payments to individuals and Clause 20 – The Use of Consultants

Astellas Europe submitted that the advisory board meetings were a *bona fide* non-promotional activity as explained under Clause 12.1 above and each advisor was paid a fee commensurate with fair market value within their local country. The fees were based on the time to perform services, the technical complexity of services and responsibility assumed by the advisors. The services provided were preparing for and attending the advisory board,

performing the duties of an advisory board member such as to actively participate in the discussion during the advisory board meeting and periodic and ancillary consultancy as required for clarification following the event.

Each advisor had a written contract and was selected based on the criteria outlined above. There was a legitimate need for the advisors' services based on the objectives of the advisory board meetings and above.

The format consisted of 16 separate national advisory board meetings which provided answers unique to practices within each country regarding the treatment of mCRPC and market access needs. Each advisory board meeting was held in a separate room with no more than 10 advisors.

The country affiliate facilitators wrote reports following the individual advisory boards to inform their market access plans and local treatment pathways and options by considering how the data from the enzalutamide, abiraterone and radium-223 Phase III trials could impact everyday clinical practice decisions. At a regional level the reports highlighted differences across countries (eg treating physician and pathway, treatment options and clinical definition of progression, market access conditions) which assisted in customising regional support to the local affiliates (eg provision of supporting medical materials, answers to frequently asked questions).

Astellas Europe thus submitted that the advisory board meetings were not an inducement to prescribe and they met the requirements of Clause 20 and thus were not in breach of Clauses 18.1 or 20.

Clause 9.1 – High standards must be maintained at all times and
Clause 2 – Discredit to and reduction of confidence in the Industry

Based on the above, Astellas Europe submitted that high standards had been maintained. The advisory board meetings were not an inducement to prescribe, nor were they promotion prior to the grant of a marketing authorization. Astellas thus denied a breach of Clauses 9.1 or 2.

Summary

Astellas Europe recognised that as with any innovation, there might be areas open to interpretation. However, it strove for continuous improvement in order to ensure that its business operations were carried out in a robust, efficient and compliant manner.

The company's intention was to achieve a pragmatic approach to a complex challenge, to seek and obtain high quality advice in a complicated and rapidly changing clinical environment across a number of European and a few key non-EU countries as efficiently as possible, given the estimated regulatory timelines. It believed that it achieved this in a compliant manner and it was disappointing to receive a complaint. Astellas Europe took its responsibilities with regard to the Code very seriously and it hoped that the Panel agreed that it had not breached any of the stated clauses of the Code.

Astellas Europe responded to a request for further information as follows.

1 What preparation work was required of the attendees prior to the meeting?

Astellas Europe stated it was expected that the advisors would review the objectives outlined in the invitation and come to the meeting prepared to participate and contribute to the meeting with advice pertinent to the practice in their country. On this occasion, no preparatory materials were provided and advisors were compensated in consideration for their participation and contribution to the meeting. The amounts were commensurate with fair market value assessment by country, following approval by the local compliance reviewer and in accordance with the level of advice and contribution required.

The expert speakers prepared slides and presented at the meeting. In addition, they both participated in their respective national advisory board meetings. The expert speakers were compensated in consideration for their preparation time, participation and contribution to the meeting. The amounts were commensurate with fair market value assessment by country, following approval by the local compliance reviewer and in accordance with the level of advice and contribution required.

2 Information about the objective, content, arrangements and attendees of the two meetings previously held, Barcelona, November 2012 and Frankfurt July 2013

Astellas Europe stated it in-licensed enzalutamide in October 2009 and tivozanib in February 2011. These products were Astellas' first products launched in oncology.

The Astellas Europe EMEA regional oncology business unit was formed in May 2011 and the organisation was building capabilities in anticipation of these two new in-licensed products being launched in 2014. The oncology organisation in the local affiliates was being scaled-up in line with the anticipated original approval and launch timescale. Original assumptions were for approval and then launches starting in Q2 2014 for enzalutamide in the post-chemotherapy indication. Tivozanib was estimated for approval in Q4 2013. Based on statistically significant improvement in overall survival shown in the interim results of the enzalutamide AFFIRM phase III study in November 2011, the independent data monitoring committee recommended the study be stopped early. This allowed Astellas to apply for regulatory approval of the post-chemotherapy indication earlier than anticipated. A schematic showing the outline of timings related to enzalutamide and tivozanib was provided.

Astellas Europe submitted it took a pragmatic and efficient approach in leading the preparation across

the EMEA region to seek advice through these innovative advisory board meetings in a consistent and compliant way, as mentioned above the affiliates were being scaled up.

The comment on a briefing slide that this was the third meeting of this type related to the fact that this was the third time this framework (namely introductory expert presentations followed by parallel individual advisory boards) had been used and not that there were three meetings with identical content. The topics for each meeting were different and summarised as follows:

Meeting November 2012 – to seek advice on best practice in clinical management of advanced renal cell carcinoma (RCC) and castrate resistant prostate cancer relating to tivozanib and enzalutamide respectively.

Meeting July 2013 – to seek advice on enzalutamide in metastatic castrate resistant prostate cancer following the first approval of enzalutamide in the post-chemotherapy indication and how enzalutamide could be introduced into clinical practice in the light of the changing treatment landscape.

Meeting February 2014 – to seek advice on enzalutamide in metastatic castrate resistant prostate cancer relating to the additional chemo-naive indication. This meeting was the subject of the complaint.

These were distinct and separate meetings with a common format. The objectives, content and attendees were different and further details were provided. The overall intention of Astellas was to act in a responsible manner in the best interests of physicians and patients.

a) Pan-European Uro-oncology Advisory Board - 15 November 2012, Barcelona

Astellas Europe stated that this advisory board covered renal cell carcinoma (RCC) and prostate cancer with the objective to receive initial advice regarding the challenges facing tivozanib and enzalutamide in Europe in the run up to and immediately post launch. This advice was critical at that time as these products would be Astellas' first products launched to the oncology healthcare community and Astellas needed to understand the impact of these alongside currently available and new therapies in the major countries in Europe.

Objectives

- To help Astellas put data on enzalutamide in castrate-resistant prostate cancer (CRPC) and tivozanib in advanced renal cell carcinoma in context of other available and emerging therapies
- To help Astellas gain further insight into the current and likely future clinical management of CRPC and advanced RCC at a European level
- To receive advice regarding the challenges facing enzalutamide and tivozanib in Europe in the run up to and immediately post launch.

Arrangements

The meeting was held in Barcelona, Spain, in a 4 star hotel, which was one of the congress hotels for the European Multidisciplinary Meeting on Urological Cancers (EMUC) congress which took place in Barcelona immediately following this meeting. The meeting ran from 5pm to 9pm followed by a dinner. Accommodation and subsistence were provided.

Economy flights, or train travel were provided, with the exception of one speaker who flew business class from Germany.

Introductory session expert speakers were paid a fee for service of €1750 each, whilst the advisors received fees of €1000, with the exception of the UK advisors who received €750. In the cases where there was a co-chair in the individual country advisory boards, these received a fee of €1500, with the exception of the UK who received €1000. The fees were commensurate with country fair market value and approved by local compliance reviewers.

Attendees

The expert speakers were named. A total of 53 advisors attended from UK, Germany, Italy, France and Spain. These were oncologists, uro-oncologists and clinical researchers. These advisors were selected from countries that represented Astellas' five major European affiliates.

Astellas attendees were from the UK, Germany, Italy, France and Spain affiliates and Astellas Europe. Astellas Europe attendees did not participate in the affiliate advisory boards.

Content

The subject of the meeting was RCC and metastatic CRPC, and the country working group advisors attended an introductory session with presentations on two different pipeline products in the therapy areas stated above, prior to country-specific workshops in their local language led by the local Astellas affiliate and a local expert co-chair.

The workshops covered both cancer types and were designed for the advisors to provide advice on the key issues and challenges Astellas would face in launching these two products in oncology, both from a product perspective and as a company new to this area.

The meeting consisted of a total duration of 240 minutes, including a break of 20 minutes, with an introductory session and individual country workshop sessions.

The introductory session consisted of a welcome and agenda overview, an introduction to Astellas and two external speaker presentations, one on enzalutamide

in CRPC in the post-chemotherapy indication based on the results of the AFFIRM study, and the other on tivozanib in advanced RCC, plus two short Q&A sessions for clarification on the presentations.

The national workshop sessions consisted of 5 separate individual country-specific workshops consisting of a short introduction and objectives prior to seeking advice on the above topics.

b) Pan-European Uro-oncology Expert Meeting - 3-4 July 2013, Frankfurt

Astellas Europe stated that this advisory board was conducted in order to receive advice specifically regarding the potential opportunities and challenges facing enzalutamide in Europe following first EMA approval in June 2013 for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease had progressed on or after docetaxel therapy (the post-chemotherapy indication based on the results of the AFFIRM study).

Objectives

- To enable Astellas to frame the data on enzalutamide in CRPC in the context of other available and emerging therapies
- To provide Astellas with further insight into the current and likely future clinical management of CRPC at a European level
- To receive advice regarding the potential opportunities and challenges facing enzalutamide in Europe following EMA approval.

Arrangements

The meeting was held at a 4 star Frankfurt Airport Hotel, due to the city's central location and the hotel's proximity to the airport, to help ensure ease of access for the advisors. Overnight accommodation and subsistence were provided.

The advisors arrived on 3 July in order to avoid the risk of travel disruption and to ensure all advisors were present at the start of the meeting. The meeting on 4 July started at 8.40am following registration and collection of iPads (for Q&A sessions) and closed at 1:30pm.

Economy flights, or train travel were provided, with the exception of the two speakers who travelled business class.

The introductory session speakers were paid a fee for service of €1500 each, whilst the advisors received fees of €1000. These fees were commensurate with country fair market value and approved by local compliance reviewers.

Attendees

The expert speakers were named. A total of 61 advisors attended from Austria, Czech Republic & Slovakia, Germany, Greece/Cyprus, Ireland, Netherlands, Nordics, Poland, Switzerland and UK. These advisors were oncologists and uro-oncologists and were selected for their expertise in prostate cancer from the countries that would be first to launch enzalutamide in the post-chemotherapy setting.

Astellas attendees were from the affiliates in Austria, Czech Republic & Slovakia, Germany, Greece, Netherlands, Nordics, Poland, Switzerland, UK and Astellas Europe.

Content

The meeting consisted of a total duration of 290 minutes, including a break of 15 minutes, with an introductory session and international working group sessions.

The introductory session consisted of a welcome and agenda, an introduction to Astellas and two external speaker presentations, one on the biology of androgen receptor signalling ('CRPC: the rationale for targeting the androgen receptor') and the other on 'Enzalutamide: directly targeting the androgen receptor in mCRPC', plus two Q&A sessions for clarification on the presentations.

There were 5 international working group sessions, each consisting of a selection of advisors from Austria, Czech Republic & Slovakia, Germany, Greece/Cyprus, Ireland, Netherlands, Nordics, Poland, Switzerland and UK, seeking advice on the above topics.

The international working group sessions began with a short introduction and objectives prior to the advisors carrying out an analysis for enzalutamide in the post-chemotherapy setting and providing an understanding of the differences and similarities across multiple European countries. This was followed by an exercise where the advisors were asked to consolidate this analysis and decide which of the components listed were most important and should be taken through to the implementation exercise. This exercise sought advice on practical activities/programmes that Astellas could use to support the launch of enzalutamide across Europe taking into consideration the opportunities and challenges identified previously.

3 **Briefing materials for one of the speakers at the meeting in question**

Astellas Europe stated that one of the speakers was provided with a verbal briefing similar to the slide deck presented to the other speaker.

4 How did attendees from South Africa contribute to the opportunities and challenges within Europe?

APEL, the regional headquarters organisation of Astellas, covered countries in Europe, Middle East and Africa (EMEA). Countries outside the EU, in which Astellas EMEA affiliates operated and that were involved in the meeting, included South Africa. The rationale for including South Africa was because the country was considering fast track

approval options, encompassing the AFFIRM (post-chemotherapy) and PREVAIL (chemo-naïve) data. Launch timings of enzalutamide in South Africa had the potential to be accelerated by approximately 2 years based on a new electronic regulatory submission process. Astellas therefore required the same considerations and advice from South African health professionals as from its other European advisors at that time.

At a regional level the final report highlighted differences across countries (eg treating physician and pathway, treatment options and clinical definition of progression, market access conditions) which assisted in customising regional support to the local affiliates (eg provision of supporting medical materials, answers to frequently asked questions) including South Africa.

5 Was a summary or outputs provided to the attendees following the meeting?

Astellas Europe stated that no meeting summary or outputs were provided to the advisors.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedures such 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 it was acceptable for companies to pay health professionals and others for relevant advice. Nonetheless, the arrangements for such meetings had to comply with the Code, particularly Clause 20. To be considered a legitimate advisory board the choice and number of participants should stand up to independent scrutiny; each should be chosen according to their expertise such that they would be able to contribute meaningfully to the purpose and expected outcomes of the advisory board. The number of participants should be limited so as to allow active participation by all. The agenda should allow adequate time for discussion. The number of meetings and the number of participants should be driven by need and not the invitees' willingness to attend. Invitations to participate should state the purpose of the advisory board meeting, the expected advisory role and the amount of work to be undertaken. If an honorarium was offered it should be made clear that it was a payment for such work and advice. Honoraria must be reasonable and reflect the fair market value of the time and effort involved.

The Panel noted the complainant alleged that he/she had been invited to attend an advisory board meeting on prostate cancer however, the advisory board was attended by more than 100 other clinicians and was more like a large meeting than an advisory board. Astellas Europe submitted that the most practical, effective and expedient way to quickly gather a group of advising urologists, oncologists and uro-oncologists from a number of countries with the two expert speakers was to hold the advisory board meetings in one European location, rather than to organise separate advisory boards in individual countries. Astellas stated that it would not have been logistically viable to have separate meetings with the same expert speakers within the required timeframe. Astellas stated that the arrangements allowed it to ensure the availability of the expert speakers and reduce the burden on them. The Panel considered that holding multiple simultaneous local advisory board meetings overseas, in one central location would not necessarily be unacceptable providing all the aspects complied with the Code. As stated in the supplementary information to Clause 19, Meetings and Hospitality, there had to be valid and cogent reasons for holding meetings at venues outside the UK. In this regard, the Panel noted that the UK health professionals were not otherwise attending an international meeting or other event in Milan. In the particular circumstances of this case, the Panel queried whether the availability of the two speakers was an adequate justification given the nature of the meeting and that local experts on the data were available for each advisory board. The Panel was only considering the overall acceptability of the arrangements for the meeting in February 2014 in relation to UK health professionals.

The Panel noted this was the third such meeting held by Astellas. The previous two meetings had taken place before and immediately after the initial marketing authorization of Xtandi in the treatment of adult men with metastatic castration-resistant prostate cancer whose disease had progressed on or after docetaxel therapy. The meeting at issue was held prior to the grant of the marketing authorization for a new indication for the treatment of adult men with metastatic castration-resistant prostate cancer who were asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy was not yet clinically indicated.

The Panel queried whether the contents of the two previous meetings held in 2012 and 2013 were as distinct as submitted by Astellas. The objectives of both included enabling Astellas to frame data on enzalutamide in CRPC in the context of other available and emerging therapies and to provide insight into the current and likely future clinical management of CRPC at a European level and advice on the potential European opportunities and challenges. Whilst one advisory board was in the post-chemotherapy indication, the objectives were, nonetheless, similar to the advisory board at issue. Given the advice previously received, the Panel queried whether there remained a *bona fide* need for advice such as to justify the meeting in question.

The Panel noted the criteria and process for the selection of experts. Affiliates were asked to identify 30 local experts with personal experience of treating patients with mCRPC, and the names of these were grouped, based on their clinical expertise. The first 10 participants for each country (15 for Nordic and South East Europe affiliates that covered more than one country) were sent a 'save the date' email. For each decline, the next name on the list for the respective country was invited until 10 participants registered interest in attending from each country

who were each sent an email invitation letter, including information on the honorarium and a copy of the draft agenda. Upon confirmation each advisor was required to sign a contract which stated that advisors were required to actively participate in the discussion during the advisory board meeting. The Panel noted that participants at advisory board meetings would reasonably be expected to have sufficient expertise and experience in the relevant disease area that their contribution would be beyond that of simply having experience of treating patients for that particular disease and certainly be relevant to the advice sought by the company. The Panel considered that the number of local experts identified seemed quite large and queried whether participation was driven by who could attend as opposed to who should attend to provide Astellas with appropriate advice.

The Panel examined the agenda. Participants were not required to do any pre-reading or other preparation. The meeting had two distinct sections; the first section lasted just over 2 hours and included presentations from the two speakers on 'The role of the androgen receptor signalling pathway in mCRPC' and 'Enzalutamide in mCRPC'. Astellas submitted these ensured all advisors had a common understanding of new treatment options and the Phase 3 data for enzalutamide. Both presentations were followed by 25 minute Q&A sessions. The second section of the meeting lasted for 2 hours and 25 minutes. Attendees were split into their respective country/regional advisory board meetings where they completed two exercises. Firstly, to differentiate enzalutamide from competitors in the proposed target patient population and secondly, to look at current prescribing practice across the patient pathway in mCRPC including where enzalutamide might fit into that pathway now and in the future. The total time allowed for the two exercises was 2 hours and 10 minutes.

The Panel noted Astellas' submission that two thirds of the total time (excluding breaks) was dedicated to seeking advice. This included the two Q&A sessions, which followed the presentations. The Panel considered that the Q&A sessions were for the attendees to ask questions such that they were equipped to participate in the advisory boards rather than a means of providing advice to the company. The time allocated for the attendees to provide advice was therefore less than fifty percent of the total meeting time.

The Panel considered that it would have been helpful if the data, or a summary thereof, could have been sent in advance as pre-reading so that participants could have come prepared to provide advice at the outset. The Panel further noted that Astellas' company attendees included, *inter alia*, a data expert for each national advisory board meeting and noted its comments above in this regard about the availability of the speakers. The Panel accepted that it was important that participants understood the data and this might be particularly relevant given the different approaches to treating prostate cancer be that by urologists or oncologists. It was concerned that this was listed as one of the three objectives for the meeting. The Panel noted, however, that the sole purpose of advisory board meetings should be to gain advice from the participants; the presentation of current data by eminent speakers should not be the primary reason participants wanted to attend.

The Panel noted that all attendees were asked to complete a survey evaluating the meeting. The Panel examined the meeting report and was concerned to note that 75 questions were raised following the presentations and many of these did not appear to be related to Astellas' submission of the need for a common understanding of the data. Further, the plenary session was rated as the most useful/valuable aspect of the meeting by 38.8% of health professional respondents with the panel discussion scoring 27.1% and the discussion with colleagues from the same country scoring 34.1%. The audience was asked to suggest interesting topics that could be the focus of future meetings. Company feedback included 'ideal opportunity to be with KOLs', '… the advisers provided useful insights', 'they … want to know more relevant information about enzalutamide and research with it' and 'working groups are not always well accepted'. The feedback from both groups included a comment about sending material for pre-reading and further time for discussion.

The Panel noted that the provision of advice related to the completion of the two exercises. The information provided to each group for the first exercise consisted of a document entitled 'Differentiating enzalutamide in mCRPC' below the heading was the sentence 'Please see below statements, based on the PREVAIL data, to be used as reference during the ranking exercise'. A table was provided with ten categories; these being Mechanism of action, Overall survival, Radiographic Progression-Free Survival (PFS), Time to Prostate-Specific Antigen (PSA) progression, Prostate-Specific Antigen response, Objective soft tissue response, Quality of life, Adverse events, Time to chemotherapy and Convenience. For each of the categories a positive statement for enzalutamide, based on the PREVAIL study, was provided. The participants were to complete group workmats ranking each of the categories and associated statements as having high, moderate or low impact to differentiate enzalutamide from competitors in the proposed target population. The Panel was concerned about the universally positive nature of the statements. It appeared that participants were only assessing the impact of potential promotional claims.

The second exercise was another group workmat based exercise. The workmat was headed 'Place in patient pathway: Progression on ADT, chemotherapy naïve'. A workmat was to be completed for each of the following treatments (in the following order), docetaxel/cabazitaxel, enzalutamide, abiraterone and radium-223 (if time allowed). The workmat consisted of five sections: patient factors that would make them a candidate for the treatment, disease factors; factors concerning the patient's disease state that would make them a candidate for this treatment. Both of these sections also required the group to rank the factors given. The other three sections were: exclusions; factors which would

exclude a patient from treatment with this agent if the above criteria were met, and two sections for competitor considerations; to add two factors which would preclude this alternative treatment from being used in the patient described above. At the end of each exercise the facilitator was instructed to ask whether any other features of enzalutamide that had not been covered were particularly relevant to the UK healthcare system. The Panel noted there was no mention on any of the materials submitted for the national advisory board meetings that the information provided or the data was for an unlicensed indication.

The Panel considered that as the exercises were to be completed by the UK attendees as a group, consensus would have to be reached to complete the workmats. As such, the views of some of the participants might not be documented or taken into consideration. Further, the Panel noted the exercises could perhaps be carried out individually or prepared individually prior to a joint discussion.

The meeting for UK health professionals was held outside the UK and, as noted above, there had to be valid and cogent reasons for holding such meetings outside the UK. Given its comments above, the Panel did not consider that attending the presentations constituted a valid and cogent reason for holding the meeting outside the UK. The Panel was concerned that the time spent obtaining advice was low, less than 50% of the total meeting time and further no preparation was needed. The attendees worked as a group to provide one view. The Panel noted its comments above about the arrangements, content and feedback for the meeting. Taking all the factors into account the Panel did not consider that the arrangements were such that the UK health professionals had attended a genuine advisory board meeting. It therefore ruled a breach of Clause 20.1.

The Panel considered that, as it had ruled the arrangements did not meet the criteria for advisory boards, UK health professionals had been paid to attend a meeting where an unlicensed indication was promoted. As Xtandi was licensed in the UK the Panel considered that the arrangements constituted promotion of an unlicensed indication and not promotion of an unlicensed medicine. It therefore ruled no breach of Clause 3.1. It could not make a ruling regarding Clause 3.2 which prohibited promotion of an unlicensed indication as this had not been cited by the case preparation manager.

The Panel noted that UK health professionals had received payment to attend a meeting which the Panel considered promoted the medicine. This was contrary to requirements of Clause 18.1 and a breach of that Clause was ruled. The Panel considered that the requirement that promotional material and activities must not be disguised had not been met and ruled a breach of Clause 12.1.

The Panel considered that, overall, high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that Clause 2 was reserved for use as a sign of particular censure. The health professionals had attended the meeting believing it was a legitimate advisory board meeting, which was not so. In addition, they had received a payment for attending a promotional meeting for an indication which at the time did not have marketing authorization. The Panel noted that unacceptable payments was listed in the supplementary information to Clause 2 as an example of an activity likely to be in breach of that Clause. The Panel considered that the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted its comments and rulings above and considered that its concerns about the arrangements and the company's procedures warranted consideration by the Appeal Board. The Panel thus reported Astellas Europe to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

COMMENTS FROM ASTELLAS EUROPE ON THE REPORT FROM THE PANEL

At the consideration of the report the representatives from Astellas Europe stated that the company recognised that the execution of the Pan-European Advisory Board should have been conducted to a higher standard and it did not meet the criteria for advisory boards, as required by the Code and documented in its standard operating procedures (SOPs). Astellas Europe accepted the Panel's rulings of breaches of the Code and deeply regretted that it had brought disrepute on the pharmaceutical industry.

The company stated that it had already undertaken a number of measures and gave details of its key compliance activities since 2014. These included the move of healthcare compliance to the legal department to become the Legal and Compliance Department; growth of the compliance team; updated/new regional policies and procedures including advisory boards; rollout of a global policy for review of materials used to promote to health professionals; Legal and Compliance day; quarterly compliance updates; final signatory training; in-house PMCPA seminar; 2015 Code update; revised ZINC process and system training; regional Healthcare Compliance and reporting workshop; face-to-face/on-line training on new regional policies and SOPs; internal monitoring of compliance review and approval process; communication cascade of the Panel's ruling including the affiliate teams; further case review at quarterly compliance updates; planned training on advisory boards including details of this case including the UK affiliate and the agencies involved in the meeting at issue. Astellas Europe stated it was committed to continual improvement of compliance activities and standards.

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board noted the Panel's ruling that the Astellas Europe's Pan-European Uro-oncology Advisory Board Meeting was not a genuine advisory board meeting. The Appeal Board noted that the meeting clearly promoted Xtandi for an unlicensed

indication to UK health professionals. In response to a question the representatives from Astellas Europe stated that the meeting at issue had been held within a few days of the first presentation of the data at a conference. Astellas Europe accepted that the meeting had not met the criteria for advisory boards as required by the Code or its own SOPs, and in that regard the Appeal Board was very concerned that either the company's SOPs were not sufficiently clear or had not been followed. The arrangements and material had been certified by Astellas Europe rather than the UK affiliate and in that regard the Appeal Board questioned the rigour of the company's processes and procedures. Improvements needed to be made and should be a priority. The Appeal Board noted that the representatives from Astellas Europe referred on a number of occasions to recognising, with hindsight that its activities could be seen as promotional. The Appeal Board noted Astellas Europe's submission that it had undertaken a number of measures to address the issues. The Appeal Board also noted that the company had accepted all the Panel's rulings of breaches of the Code including Clause 2.

The Appeal Board was concerned that the UK health professionals had attended the meeting on the understanding that it was an advisory board and had been paid to do so. This was unacceptable. Consequently, the Appeal Board decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require Astellas Europe to issue a corrective statement to all the UK attendees at the meeting. The corrective statement should refer to the case report. Under Paragraph 11.3 details of the proposed content and mode and timing of dissemination of the corrective statement must be provided to the Appeal Board for approval prior to use.

Complaint received	**14 January 2015**
Undertaking received	**14 April 2015**
Appeal Board consideration	**14 May 2015**
Corrective statement issued	**1 July 2015**
Case completed	**14 May 2015**

CASE AUTH/2748/2/15

BAYER v NOVARTIS

Promotion of Lucentis

Bayer plc submitted a complaint about claims made by Novartis Pharmaceuticals UK at two symposia which Novartis Pharma AG had sponsored at a European ophthalmology congress held in the UK in 2014. The claims related to the comparative safety profiles of Bayer's product Eylea (aflibercept) vs Novartis' product Lucentis (ranibizumab).

Eylea and Lucentis were intravitreal injections indicated, *inter alia*, for the treatment of neovascular (wet) age-related macular degeneration (AMD) and visual impairment due to diabetic macular oedema (DME).

The detailed response from Novartis Pharmaceuticals UK is given below.

Bayer noted that the first symposium in question was entitled 'Forging the future in nAMD [neovascular age-related macular degeneration]: The role of anti-VEGF [anti-vascular endothelial growth factor] and novel therapeutic targets' and submitted that in inter-company dialogue, Novartis had acknowledged the promotional intent of this symposium.

Data from two studies were presented to claim a statistically, significantly increased risk of endophthalmitis following injection of Eylea compared with injection of Lucentis (Kelly *et al* 2014 and Kiss *et al* 2014). However, the conclusions were based on a retrospective analysis of insurance claims. Neither study was a scientifically valid retrospective cohort study, nor did either try to obtain clinical data to confirm the alleged incidents of endophthalmitis. No standardised definition of endophthalmitis was applied so the events could not be validated as truly inflammatory in nature. Given the heterogenicity of these data, the confidence intervals and p-value reported in slides 44 and 47 clearly lacked scientific validity and did not represent the balance of the evidence for the two medicines.

Bayer alleged that Novartis did not try to balance the discussion of data from Kelly *et al* and Kiss *et al* (and the conclusions it drew from them) with data from the large, robust, randomised and double-masked phase 3 studies (VIEW 1 and VIEW 2) which compared Eylea and Lucentis in the treatment of wet AMD (Heier *et al* 2012). These studies concluded that Eylea was generally well tolerated and had a profile of ocular treatment-emergent adverse experiences, including serious ocular adverse events, similar to that for Lucentis. The results at 52 and 96 weeks of follow-up showed no difference in rates of endophthalmitis between Lucentis and Eylea (Heier *et al*, Schmidt-Erfurth *et al* 2014). Relevant sections (4.4 and 4.8) of the Eylea summary of product characteristics (SPC) did not mention any difference in risk of endophthalmitis compared with Lucentis; it just stated that endophthalmitis was a known risk with all intravitreal injections.

Bayer submitted that there was selective presentation of data of weak scientific validity in the absence of data from robust, large, randomised controlled trials with follow-up to 2 years, which showed a very different conclusion. In addition, it was not disclosed in the symposium that Kiss *et al* was funded and co-authored by Genentech, the manufacturer of Lucentis and a business partner of Novartis. Bayer alleged that the overall representation of the safety profile of Eylea at this promotional symposium was unbalanced, inaccurate, misleading and did not fairly represent the totality of available evidence, in breach of the Code.

The Panel noted that the presentation at issue focussed on endophthalmitis which was described as a rare but feared complication of intraocular surgery and intravitreal injection, its pathogenesis, management and new data on safety signals. The new data were from two database studies, Kelly *et al* (VERO) and Kiss *et al* which looked at retrospective analysis of insurance claims taken from two different US payor claims databases. The studies were based on two separate databases although slide 44 stated, as did the speaker, that the database source data would overlap so that the same injection data might be included in both analyses. The Panel noted slide 43 was headed '"Big data" is of merit to explore safety signals'.

The Panel noted Novartis' submission that the presentation made it clear that it was difficult to obtain robust information on endophthalmitis as pivotal studies such as VIEW 1 and 2 were not powered to detect differences in the frequency of such rare adverse events; this information could only be provided by very large data sets. A point not covered within the slides although stated by the speaker. In this regard, however, the Panel also noted Novartis' submission that although data from patient populations which were broader than those in phase 3 studies could be better for evaluating rare events, such data was not as confirmatory as phase 3 data. The Panel thus queried the claim '*Robust* information on rare safety events can only be provided by very large data sets' (emphasis added).

The Panel noted the limitations of the retrospective study of insurance claims. In the conclusion of his presentation the speaker noted that such data might show a difference between the treatments but 'that without doubt' clinical studies were needed to confirm such differences. The speaker stressed that the data in Kelly *et al* and Kiss *et al* was based on claims, payments and requests for payments; it was not clinical data. The Panel noted that Kelly *et*

al concluded that all sensitivity analysis undertaken also supported the differences and that data from this retrospective analysis should be interpreted with caution, because of the inherent limitations of this type of study and limited understanding of mechanisms to explain the apparent difference in endophthalmitis risk with Eylea. Additional studies would be required to further explore the implications for clinical practice.

The Panel noted the potential benefit and limitations of Kelly *et al* and Kiss *et al*. However the presentation did not contextualise the results presented for Kelly *et al* and Kiss *et al* with the limitations of that data, the clinical data on endophthalmitis or the frequency of endophthalmitis documented in each medicine's SPC. In that regard the presentation was not sufficiently complete to enable the delegates to form their own opinion of the therapeutic value of the medicines. A breach of the Code was ruled. The comparison of the two products was misleading. A breach of the Code was ruled. The Panel noted the limitations of the retrospective analysis of insurance claims taken from US payor claims databases including the possible variability of potential disease coding and physician experience. It did not consider that the presentation reflected all the available evidence. A breach of the Code was ruled.

Bayer alleged that slide 13 significantly overstated the dosing flexibility permitted by the new Lucentis label; it implied that physicians could use Lucentis as they pleased with no restrictions with regard to treatment intervals or follow-up/monitoring requirements. Bayer stated that the Lucentis SPC clearly stated that treatment must be initiated with one injection a month until maximum visual acuity was achieved and/or there were no signs of disease activity, and specified that there was also a minimum treatment interval. A treat-and-extend regimen could only be followed when monthly treatment was established, and the patient stabilised, but even then the SPC gave clear guidance on the degree of flexibility permitted, with extensions for wet AMD limited to two weeks at a time.

The Panel noted the Lucentis SPC only permitted flexibility in monitoring and treatment intervals once maximum visual acuity was achieved and/or there were no signs of disease activity. The Panel considered that this was not clear from slide 13. A breach of the Code was ruled.

Bayer alleged that the claim on slide 13 that Lucentis dosing was: 'Personalized' 'Physicians determine monitoring and treatment intervals* for optimal outcomes ....' was in conflict with the Lucentis SPC as regards its flexibility. In addition the claim that the new posology would deliver 'optimal outcomes' was a superlative which could not be substantiated. The claim of 'optimal outcomes' was a hanging comparison and thus the exact comparison made by Novartis was unclear, but there was no evidence that the current Lucentis posology offered clinical outcomes which were optimal compared with either proactive treatment with Eylea or reactive use of Lucentis with monthly monitoring (as per the previous Lucentis SPC).

The Panel noted the claim 'optimal outcomes' was part of the first stab point on slide 13 under the heading 'Introducing the new ranibizumab EU label, which supports a personalized treatment approach'. The Panel did not consider that the claim at issue was a superlative as alleged. In that regard the Panel noted that the claim at issue did not exclude the possibility that other treatment regimens could also provide optimal outcomes. The changes to the Lucentis SPC enabled prescribers to determine monitoring and treatment intervals such as to optimise treatment with Lucentis. In that regard the Panel did not consider that the claim was a hanging comparison as alleged. It was substantiated by the Lucentis SPC. The Panel ruled no breach of the Code.

Bayer stated that with regard to the retrospective US health insurance data, slide 13 clearly stated that Kelly *et al*, (the VERO study) was sponsored by Novartis; this implied that the other retrospective study (Kiss *et al*) was independent. However, Kiss *et al* was supported by Genentech, the company which manufactured Lucentis and marketed it in the US. Further, from the abstract it appeared that one author was employed by Genentech Inc. Genentech was in commercial partnership with Novartis, which marketed Lucentis on its behalf outside the US. The disclosure was therefore incomplete and misleading about the independence of the data presented at the meeting. Bayer did not accept Novartis' assertion that it was reasonable to only disclose that it had supported Kelly *et al* as the author was also the presenter. Bayer stated that this was a promotional symposium, sponsored by Novartis, in which Novartis claimed comparatively greater safety for Lucentis vs Eylea based wholly on two studies which were both funded by companies which marketed Lucentis in their respective territories. This information would have been highly relevant to the audience in assessing any potential bias in these data. Accordingly, it was not acceptable for the funding details of both studies not to be made transparent; simply referencing the studies on the slide deck was insufficient. Bayer alleged a breach of the Code.

The Panel noted that the presenter was involved with one of the studies, which was mentioned on the disclosures made at the beginning of his presentation (slide 38) which included 'VERO study was sponsored by Novartis'. When presenting this he stated that as he was going to be talking about this study and it was a Novartis event, his involvement should be made clear.

The Panel noted that the second of the studies, Kiss *et al*, was sponsored by Genentech which marketed Lucentis in the US. The Panel noted that these two studies of US medical claims databases were used by the presenter to compare the event rate of endophthalmitis/severe intraocular inflammation for Lucentis and Eylea. The Panel considered that disclosing that VERO was sponsored by Novartis but remaining silent about Kiss *et al* might lead

the audience to assume that Kiss *et al* was not sponsored by a commercially interested party. This was not so. The Panel considered the presentation was misleading in this regard. A breach of the Code was ruled.

Bayer alleged that the second symposium in question, entitled 'Optimizing benefits and risks in DME [diabetic macular oedema]', built a picture of a worse adverse event profile for Eylea vs Lucentis in diabetic macular oedema (DME); many of the most contentious statements were made by presenters rather than on the slides.

Bayer alleged that data were presented selectively from published studies to minimise the apparent risk of arterio-thrombotic events with Lucentis and to support the incorrect assertion that Eylea had a worse safety profile than Lucentis in DME. Overall, the symposium misrepresented the safety profile of Eylea compared with Lucentis. Given the 'take-home' impact on the audience, Bayer, alleged that the impression given about the safety profile of Eylea in DME was in breach of the Code.

The Panel noted that Bayer complained about the overall impression created of the safety profile of Eylea in diabetic macular oedema. In that regard, although the symposium had consisted of three presentations and a question and answer session, the Panel considered the symposium as a whole and not each of its component parts separately.

The Panel noted that both Lucentis and Eylea were antineovascularisation agents, they prevented endothelial cell proliferation and the formation of microvascular vessels as well as vascular leakage, all of which were thought to contribute, *inter alia*, to diabetic macular oedema. The medicines did this by inhibiting vascular endothelial growth factor (VEGF). Lucentis inhibited VEGF A whilst Eylea inhibited VEGF A and the related placental growth factor (PlGF). Slide 30 compared the products. Eylea was a larger molecule than Lucentis and its structure contained an Fc (fragment crystallisable) fragment of a human immunoglobulin. Lucentis had no Fc fragment. The potential side-effect of systemic administration of anti-VEGF treatment in oncology patients was discussed. From the SPCs for Lucentis and Eylea (both administered intravitreally) it appeared that systemic effects from the inhibition of VEGF was a possibility. In a question and answer session the Panel noted that speakers stressed that ideally an anti-VEGF agent which would stay in the eye, and thus not cause systemic side-effects, would be one without an Fc portion ie Lucentis and not Eylea. The speakers also referred to the fact that there was 5 year data for Lucentis but only 2 year data for Eylea.

The Panel noted the data presented and that there was longer term data for Lucentis as it was available before Eylea. The Panel considered that much had been made of the differences between the molecules and the impression was given that this might impact on safety. This difference was not set in the context of the information in the SPC which was similar for Eylea and Lucentis.

Overall, the Panel considered that the take home message was, as alleged, that the safety profile for Lucentis was more favourable than that for Eylea and that real differences in that regard would be seen in the clinic. On balance that Panel considered that there was insufficient data to show that this was so and that the symposium overall was misleading in that regard. A breach of the Code was ruled. The comparison of the two medicines was thus misleading and a breach of the Code was ruled. The impression of a significant clinical difference between Eylea and Lucentis could not be substantiated and breaches of the Code were ruled.

In summary, Bayer was concerned that two Novartis-sponsored symposia at the ophthalmology congress misleadingly compared the safety profiles of Lucentis and Eylea. In the first symposium the misrepresentation of safety occurred in the context of superlative promotional claims which related to the efficacy of Lucentis and exaggerated claims about the flexibility of its new posology. In the second symposium implications based upon data irrelevant to the dosages and indications under discussion, verbal comment and the misleading presentation of Lucentis safety data combined to build a false picture of the comparative safety of Eylea vs Lucentis and to raise unfounded concerns in the minds of prescribers about the safety of Eylea in its newest indication.

In addition, Bayer considered that there was clear evidence in the examples given above of repeated, serious misrepresentations of safety data and disregard for the Code, such that Novartis had failed to maintain high standards and had brought the industry into disrepute. Taking everything into consideration, Bayer alleged breaches of the Code including Clause 2.

The Panel noted its rulings above. It considered that the misleading presentation of the data meant that high standards had not been maintained and a breach of the Code was ruled.

The Panel noted that the supplementary information to Clause 2 referred to examples of activities likely to be in breach of Clause 2 and these included prejudicing patient safety. The Panel noted that although it considered that the symposium had presented a misleading impression of the comparative safety profiles of Lucentis and Eylea, patient safety would not have been put at risk. The Panel noted its rulings above but nonetheless did not consider that its rulings of breaches of the Code in this case amounted to a breach of Clause 2 and no breach was ruled.

Bayer plc complained about claims made by Novartis Pharmaceuticals UK Ltd at two symposia which Novartis Pharma AG had sponsored as part of the EURetina Ophthalmology congress in London, 11-14 September 2014. The claims related to the comparative safety profiles of Bayer's product Eylea (aflibercept) vs Novartis' product Lucentis (ranibizumab).

Eylea and Lucentis were intravitreal injections (ie into the eye). Both products were indicated, *inter alia*,

for the treatment of neovascular (wet) age-related macular degeneration (AMD) and visual impairment due to diabetic macular oedema (DME).

A recording of the symposium was provided by Novartis. The slide numbering used in this case was as provided by Novartis. Bayer's numbering has been changed to Novartis' numbering. There were a couple of instances where the photographs provided by Bayer provided more details than the slides provided by Novartis and this was noted in the minute.

The case was considered under the 2014 Code using the 2015 Constitution and Procedure.

A Symposium 'Forging the future in nAMD [neovascular age-related macular degeneration]: The role of anti-VEGF [anti-vascular endothelial growth factor] and novel therapeutic targets' 13 September 2014, 1-2pm, attended by 965 conference delegates

1 Use of insurance claims data

COMPLAINT

Bayer submitted that in inter-company dialogue, Novartis had acknowledged the promotional intent of this symposium.

Data from two studies were presented to claim a statistically, significantly increased risk of endophthalmitis following injection of Eylea compared with injection of Lucentis (Kelly *et al* 2014 and Kiss *et al* 2014). However, the conclusions were based solely on retrospective analysis of insurance claims. Neither study was a scientifically valid retrospective cohort study, nor did either try to obtain clinical data to confirm the alleged incidents of endophthalmitis. No standardised definition of endophthalmitis was applied to the data so the events could not be validated as truly inflammatory in nature. Given the heterogenicity of these data, the confidence intervals and p-value reported in slides 44 and 47 of the presentation clearly lacked scientific validity and did not represent the balance of the evidence for these two medicines.

Bayer acknowledged that large datasets based on uncontrolled observation might sometimes provide relevant information regarding the post-marketing safety profile of medicines. However, the Code required that promotional, comparative safety claims must present an evaluation of all the evidence and must not mislead either directly or implicitly. Thus, when claims were based on uncontrolled observational data it was important to present the limitations of such datasets, including any potential sources of bias (such as study funding – see Point A3 below) and also to present any relevant data from large, randomised, controlled studies. This last point was especially important if the results of the controlled and uncontrolled data differed.

Bayer alleged that Novartis did not try to balance the discussion of data from Kelly *et al* and Kiss *et al* (and the conclusions it drew from them) with data from the large, robust, randomised and double-masked phase 3 studies (VIEW 1 and VIEW 2) which compared Eylea and Lucentis in the treatment of wet AMD (Heier *et al* 2012). These studies (n=2,419) concluded that 'Intravitreal [Eylea] was generally well tolerated and had a profile of ocular treatment-emergent adverse experiences, including serious ocular adverse events, similar to those for monthly [Lucentis]'. The results at 52 and 96 weeks of follow-up showed no difference in rates of endophthalmitis between Lucentis and Eylea (Heier *et al*, Schmidt-Erfurth *et al* 2014). Neither Sections 4.4 (special warnings and precautions for use) nor 4.8 (undesirable effects) of the Eylea summary of product characteristics (SPC) mentioned any difference in risk of endophthalmitis compared with Lucentis; it just stated that endophthalmitis was a known risk with all intravitreal injections.

In the Novartis wet AMD symposium there was selective presentation of data of weak scientific validity in the absence of data from robust, large, randomised controlled trials with follow-up to 2 years, which showed a very different conclusion. In addition, it was not disclosed in the symposium that Kiss *et al* was funded and co-authored by Genentech, the manufacturer of Lucentis and a business partner of Novartis (see Point 4 below).

Bayer alleged that the overall representation of the safety profile of Eylea at this promotional symposium was unbalanced, inaccurate, misleading and did not fairly represent the totality of available evidence, in breach of Clauses 7.2, 7.3 and 7.9.

RESPONSE

Novartis submitted that the aim of the presentation was to present new data on an important single aspect of ocular safety – endophthalmitis, which was accepted as a known potential, but fortunately rare, complication of intravitreal injection. This data was of interest to the audience at EURetina as there had been a cluster of endophthalmitis cases in the US which prompted the Therapeutic Surveillance Subcommittee of the American Society of Retinal Specialists (ASRS) to publish by way of a letter and associated tables on this particular adverse event (Hahn *et al*, 2013).

The presentation made it clear that it was difficult to obtain robust information on safety events such as endophthalmitis since even the pivotal, randomized, controlled, comparative studies in ophthalmology, such as VIEW 1 and 2, were not powered to detect differences in the frequency of such rare events (slide 43). Therefore, numbers for these adverse events could only be provided by very large data sets. Novartis noted that the VIEW studies involved 2,419 patients whereas the database studies referred to in the symposia involved 431,518 (VERO study, slide 45) and 339,046 (slide 47 and Kiss *et al*) injections.

Retrospective database studies were standard research tools that allowed medical evidence from the real world to be evaluated using pre-specified protocols; the retrospective nature of the data and the study were acknowledged several times during the symposium. The data was based on a specific actual event (endophthalmitis) which

occurred and resulted in a claim for treatment or a claim for time for that adverse event. The data came from independent insurance claims and not claims submitted to either pharmaceutical company, which eliminated any possibility of bias. With regard to Bayer's allegation that there was no standardised definition of endophthalmitis applied to the data Novartis noted that in the VERO study the definitions of endophthalmitis were pre-specified and agreed with clinicians in an unbiased way, prior to conducting the analyses; the algorithms to identify diagnoses of endophthalmitis were applied consistently and independently of Novartis (by IMS). Kiss *et al* used a standardised diagnostic code for endophthalmitis, ICD-9-CM, which was the current medical coding standard used in US hospitals.

Novartis submitted that database studies were standard tools to use to understand treatment and effects in real world use, away from the strict protocols of phase 3 studies which might exclude many patients by focusing on naive patients. It was accepted that broader and more representative populations than phase 3 studies, were better to evaluate rare events (Stein 2014 and Hess 2004) but of course not as confirmatory as phase 3 studies, just additional evidence generation. Stein specifically mentioned 'Large sample sizes can be particularly useful for studying uncommon conditions, such as endophthalmitis. For example, 424 enrolees in one of these databases received a diagnosis of endophthalmitis in a single year, providing a potential sample size that is considerably larger than those of most other studies of endophthalmitis'.

Novartis noted that rofecoxib was a well recognised example of where only the use of large claims and managed care databases provided the necessary power to show adverse events ie the increased risk of acute myocardial infarction and sudden cardiac death

Novartis submitted that the symposium was consistent with the Eylea and Lucentis SPCs which clearly documented that endophthalmitis was an uncommon complication of each medicine. The symposium demonstrated additional data in keeping with the adverse event profile which reflected that there might be a difference in the real world incidence of these adverse events between the products.

For the VERO and Kiss *et al* analyses which were presented, the limitations were clearly defined as being obtained from data taken from US payor claims databases, which were one source of such large datasets. The limitations of such data were made explicit both by the speaker and on the slides several times throughout the presentation:

- 18.45 – These are database studies of claims following claims for endophthalmitis or severe intra ocular inflammation for patients with neovascular AMD in the US who received ranibizumab or aflibercept

- 19.05 – the definition of a claim is a medical care use for treatment or time spent associated with the payment information which is the bill or the payment that comes out. So you might send the bill in and you might get the cheque out by a number of different sources of payment

After an event of a claim for intravitreal anti-VEGF injection with either of the two licensed agents where in another claim for payment for treatment for the same patient for an eye condition for endophthalmitis or severe intraocular inflammation follows the first injection

- 20.56 – I stress these are not actually patients these are statements of claims being submitted to the IMS database for payments.'

In addition to the statements above the concluding slide (slide 48) stated 'Further studies and additional data are required to better understand inflammation following anti-VEGF injections' and the speaker discussed the following:

- 24.10 – and without a doubt given that safety is paramount further studies are needed to try and get to the bottom of this and find out what's going wrong or what the issues are because this is only a study of claims, payments and request for payments. This is not clinically confirmed information and we need clinical data to ascertain if there is something happening or not following anti-VEGF injections.'

Novartis thus rejected Bayer's claim that the overall representation of the safety profile of Eylea at the symposium was unbalanced, inaccurate, misleading and did not represent the totality of available evidence and therefore there was no breach of Clauses 7.2, 7.3, and 7.9.

PANEL RULING

The Panel noted that the symposium in question was entitled 'Forging the future in nAMD: the role of anti-VEGF and novel therapeutic targets'. The welcome and introduction slides included slide 6 which stated 'This symposium will seek to answer the following questions: What evidence supports flexible dosing of ranibizumab for a personalized treatment approach? What are the current data on ocular safety and endophthalmitis with anti-VEGF therapies? What is the evidence supporting the efficacy of ranibizumab in nAMD patients with PED [pigment epithelial detachment]? How can we build on the success of ranibizumab therapy for nAMD?' The following slide provided the symposium flow which consisted of five presentations; 'Evidence for flexible dosing of ranibizumab in neovascular AMD', 'New data on ocular safety', 'PEDs: evidence for the best anatomical outcome', 'Mapping the future with novel pathways' and 'Closing statements and conclusions'. The Panel considered that the symposium promoted Lucentis.

The Panel noted the section of the symposium at issue was 'New data on ocular safety' (slides 37-48). Novartis' rationale for this section was in part due to the audience's interest in the topic since there had been a cluster of endophthalmitis cases in the US which had prompted the Therapeutic Surveillance Subcommittee of the American Society

of Retinal Specialists (ASRS) to publish a letter and associated tables on this particular adverse event. This letter published in May 2013 (16 months before the symposium at issue) was headed 'Aflibercept-Related Sterile Inflammation'. The Panel noted that the final paragraph stated *inter alia* 'Small sample size, clinical variation, and the limitations of voluntary reporting preclude definitive conclusions. Subgroup analysis did not detect any variables significantly affecting visual outcome or number of days to resolution'. It further stated that the frequency of the sterile inflammation reported by the manufacturer in the reporting period (approximately 30,000 injections administered, corresponding to a sterile inflammation rate of approximately 0.05%) was 'within the range documented by pivotal, prospective trials for aflibercept and other intravitreal agents and by retrospective analysis'.

The presentation at issue focussed on endophthalmitis which was described as a rare but feared complication of intraocular surgery and intravitreal injection, its pathogenesis, management and new data on safety signals. The new data were from two database studies, Kelly *et al* (VERO) and Kiss *et al* which looked at retrospective analysis of insurance claims taken from two different US payor claims databases. The studies were based on two separate databases although slide 44 stated, as did the speaker, that the database source data would overlap so that the same injection data might be included in both analyses. The Panel noted slide 43 was headed '"Big data" is of merit to explore safety signals'. Followed by:

- Cases of endophthalmitis have been reported following intravitreal anti-VEGF therapy in clinical practice
- Robust information on rare safety events can only be provided by very large data sets
- Two retrospective, database studies compared endophthalmitis/severe intraocular inflammation claims for patients with nAMD who received ranibizumab or aflibercept in the US
- Claim definition: medical care use (treatment or time spent) and associated payment information used for adjudication of payment by payers.

The Panel noted Novartis' submission that the presentation made it clear that it was difficult to obtain robust information on rare safety events such as endophthalmitis as pivotal, randomized, controlled, comparative studies in ophthalmology, such as VIEW 1 and 2, were not powered to detect differences in the frequency of such rare adverse events; this information could only be provided by very large data sets. A point not covered within the slides although stated by the speaker. In this regard, however, the Panel also noted Novartis' submission that although data from patient populations which were broader than those in phase 3 studies could be better for evaluating rare events, such data was not as confirmatory as phase 3 data. The Panel thus queried the claim '*Robust* information on rare safety events can only be provided by very large data sets' (emphasis added) above.

Slides 44-47 set out the objectives and timelines of both studies and provided an analysis of the of endophthalmitis/severe intraocular inflammation claims for Lucentis and Eylea in Kelly *et al* (VERO) and Kiss *et al* and event rates were shown. Slide 45 was headed 'VERO: endophthalmitis/severe intraocular inflammation claims from the US IMS Health retrospective database and was followed by a graphical representation of the results. The graph stated that the number of Lucentis injections administered was 252,864; the number of Eylea injections administered was 178,654. The event rate per 1,000 injections for Lucentis was 0.64 (1 in 1,561 injections) and for Eylea it was 1.06 (1 in 945 injections); the adjusted relative risk was 1.65 ($p<0.0001$). Slide 47 was headed 'WK data': endophthalmitis/severe intraocular inflammation claims from the WK retrospective US database' and set out the results from Kiss *et al*. In this study the number of Lucentis injections administered was 202,225; the number of Eylea injections was 136,821. The event rate per 1,000 injections in this study for Lucentis was 0.8 (1 in 1,279 injections) and 1.7 (1 in 575 injections) for Eylea; the odds ratio was 2.7 ($p<0.001$). Novartis submitted the symposium was consistent with the SPCs of both medicines.

The Panel noted the SPC for both Lucentis and Eylea listed endophthalmitis as an uncommon adverse reaction (frequency of ≥1/1000 to <1/100). The Lucentis SPC stated that adverse reactions were defined as adverse events (in at least 0.5 percentage points of patients) which occurred at a higher rate (at least 2 percentage points) in patients receiving treatment with Lucentis than those receiving control treatment. The Panel noted that no reference appeared on the slides or was mentioned by the speaker to remind the audience of the frequency of endophthalmitis for each medicine as set out in the respective SPCs and demonstrated in clinical studies. The Panel queried Novartis' submission that these data were consistent with the SPCs for the medicines given that the data in slides 45 and 47 showed a statistically significant difference for Lucentis compared with Eylea. Further it appeared that the event rate for endophthalmitis/severe intraocular inflammation for Lucentis (0.64 and 0.8 per 1,000 injections) was lower than in the range specified in the SPC for an uncommon adverse event and in that respect suggested that the reaction was rare (> 1/10,000 to < 1/1,000). It was not entirely clear whether the event rates in the SPCs were per injection or per patient.

Slide 48 conclusions included that 'Further studies and additional data are required to better understand inflammation following anti-VEGF injections'.

The Panel examined the two references provided by Novartis to support the use of the data analysis from retrospective analysis of insurance claims taken from US payor claims. Stein 2014 stated that:

> 'Large sample sizes can be particularly useful for studying uncommon conditions, such as endophthalmitis'

and that

> 'randomised controlled trials allow researchers to identify causal relationships between 2 variables

of interest while controlling for known and unknown confounding factors. Although a well-designed randomized trial is undoubtedly more informative than other types of study designs, including retrospective analyses using claims data, such clinical trials can be prohibitively expensive, can take years to recruit adequate numbers… to answer the research question… Before investing considerable resources…to provide a more definitive answer… researchers may find it valuable to first perform initial analyses to test their hypothesis using claims data'.

Stein also stated that:

'…because claims data exist primarily for billing and reimbursement purposes, some of the data may incompletely capture the conditions and outcomes documented in the medical records' and 'When interpreting analyses using claims data, one must consider that multiple providers with different levels of experience and expertise are contributing patient data'.

The Panel noted the limitations of this type of retrospective study of insurance claims. In conclusion of his presentation the speaker noted that such data might show a difference between the treatments but 'that without doubt' clinical studies were needed to confirm such differences. The speaker stressed that the data in Kelly *et al* and Kiss *et al* was based on claims, payments and requests for payments; it was not clinical data. The Panel noted that Kelly *et al* concluded that all sensitivity analysis undertaken also supported the differences and that data from this retrospective analysis should be interpreted with caution, because of the inherent limitations of this type of study and limited understanding of mechanisms to explain the apparent difference in endophthalmitis risk with Eylea. Additional studies would be required to further explore the differences in risk of endophthalmitis identified by this study and the implications for clinical practice.

The Panel considered the information above and noted the potential benefit and limitations of Kelly *et al* and Kiss *et al*. However the presentation did not contextualise the results presented for Kelly *et al* and Kiss *et al* with the limitations of that data, the clinical data on endophthalmitis or the frequency of endophthalmitis documented in each medicine's SPC. In that regard the presentation was not sufficiently complete to enable the delegates to form their own opinion of the therapeutic value of the medicines. A breach of Clause 7.2 was ruled. The comparison of the two products was misleading. A breach of Clause 7.3 was ruled. The Panel noted the limitations of the retrospective analysis of insurance claims taken from US payor claims databases including the possible variability of potential disease coding and physician experience. It did not consider that the presentation reflected all the available evidence. A breach of Clause 7.9 was ruled.

2 Claims alleged to be inconsistent with the SPC

The introductory section of the symposium, slide 13 was headed 'Introducing the new ranibizumab EU [European] label, which supports a personalized treatment approach'. This slide stated that the new regimen was:

'Personalized treatment	*Physicians determine monitoring and intervals* for optimal outcomes…'; and*
Flexible	*Mandatory monthly monitoring no longer required; now based on clinical need.*
Right treatment, right time	*Retreatment decisions based on [visual acuity] and/or anatomical parameters [optical coherence tomography or fluorescein angiography] help avoid under or overtreatment.*

**Interval between two doses injected in the same eye should be at least four weeks.'*

COMPLAINT

Bayer alleged that slide 13 significantly overstated the dosing flexibility permitted by the new Lucentis label; it implied that physicians could use Lucentis as they pleased with no restrictions with regard to treatment intervals or follow-up/monitoring requirements.

The Lucentis SPC stated:

'The recommended dose for Lucentis is 0.5mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05ml. The interval between two doses injected into the same eye should be at least four weeks.

Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity ie no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed.

Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.

If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Lucentis should be discontinued.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (eg optical coherence tomography or fluorescein angiography).

If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD and may be extended by up to one month at a time for DME. For RVO, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened accordingly.

In the treatment of visual impairment due to CNV secondary to PM, many patients may only need one or two injections during the first year, while some patients may need more frequent treatment.'

Bayer stated that the Lucentis SPC therefore clearly stated that treatment must be initiated with one injection a month until maximum visual acuity was achieved and/or there were no signs of disease activity, and specified that there was also a minimum treatment interval. A treat-and-extend regimen could only be followed when monthly treatment was established, and the patient stabilised, but even then the SPC gave clear guidance on the degree of flexibility permitted, with extensions for wet AMD limited to two weeks at a time.

In inter-company dialogue Novartis submitted that the slide did not provide full details of the new posology because this was stated in the prescribing information available at the meeting. Bayer, however, submitted that pharmaceutical companies could not make claims in the body of promotional material which might mislead the prescriber as to the precise requirements of the SPC and rely on the prescribing information as a disclaimer in the event of a complaint.

The Lucentis SPC did not permit total flexibility in monitoring and treatment intervals and thus Bayer alleged a breach of Clause 3.2.

RESPONSE

Novartis submitted that slide 13 was intended to communicate the very recent changes to the Lucentis EU dosing posology from mandatory monthly monitoring to physician-led assessment, rather than to provide an in-depth description of the posology in its entirety. The requirement for initial monthly dosing had not changed.

Rather, as the key changes to the posology referred to the maintenance phase of treatment this was the area of focus, the minimum treatment interval was clearly described on the slide. It was clearly stated in the opening disclaimer slide (slide 4) that local labels might differ and that for complete information the local label should be consulted.

Novartis did not accept that slide 13 overstated the dosing flexibility of the new Lucentis label. As Lucentis had been on the market since 2007, it was incongruous to suggest that clinicians were unaware of the need for initial monthly dosing. Novartis thus denied a breach of Clause 3.2.

PANEL RULING

The Panel examined slide 13 and noted that the same slide was used at the end of the symposium during the summary and conclusions section (slide 79).

The Panel noted Novartis' submission that as the key changes to the posology referred to the maintenance phase of treatment this was the area of focus, and that the minimum treatment interval was clearly described on the slide. In that regard the Panel noted that the statement referring to a minimum treatment interval was included as a footnote in small print on slide 13 and was not referred to by the speaker. The Panel noted the Lucentis SPC, Section 4.2 (posology and method of administration) stated 'Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity' and that 'In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed'. The SPC further stated: 'The treatment interval should be extended by no more than two weeks at a time for wet AMD ...'. Slide 13 did not make it clear that the personalized treatment approach was only in relation to the maintenance phase of treatment and not its initiation.

The Panel did not agree with Novartis' submission that as Lucentis had been available since 2007, all clinicians would know about the need for initial monthly dosing. Slide 13 referred to a new EU label with no reference to the fact that the difference in dosing from that previously used was only in the maintenance phase.

The Panel noted Clause 3.2 required the promotion of a medicine to be in accordance with the terms of its marketing authorization and not inconsistent with the particulars listed in its SPC. The Lucentis SPC only permitted flexibility in monitoring and treatment intervals once maximum visual acuity was achieved and/or there were no signs of disease activity. The Panel considered that this was not clear from slide 13. A breach of Clause 3.2 was ruled.

The Panel noted Novartis' submission that clear information had been provided at the beginning of the symposium, slide 4, which was headed 'Disclaimer' which included the statement 'These presentations are intended for educational purposes only and are based on the EU SmPC. Product registrations may vary country to country, so please check your local label for complete information'. The next bullet point on the slide was 'The recently

updated ranibizumab abbreviated UK prescribing information has been inserted into your abstract book for information'. The Panel noted that Clause 7.2 required material to be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. Relying on other materials to provide context and balance was not sufficient to correct an otherwise misleading impression. The Panel requested that Novartis be advised of its views.

3 Alleged superlative claim

COMPLAINT

Bayer alleged that the claim on slide 13 that Lucentis dosing was: 'Personalized' 'Physicians determine monitoring and treatment intervals* for optimal outcomes ....' was in conflict with the exact terms of the Lucentis SPC as regards its flexibility. In addition the claim that the new posology would deliver 'optimal outcomes' was a superlative which could not be substantiated. In inter-company dialogue, Novartis stated that it meant optimal in terms of individualizing treatment to ensure the best chance of achieving optimal outcomes in that specific patient, but Bayer stated that the slide appeared to claim that the personalized treatment strategy would in itself deliver outcomes which were optimal. The claim of 'optimal outcomes' was a hanging comparison and thus the exact comparison made by Novartis was unclear, but there was no evidence that the current Lucentis posology offered clinical outcomes which were optimal compared with either proactive treatment with Eylea or reactive use of Lucentis with monthly monitoring (as per the previous Lucentis SPC).

Bayer alleged that the use of the superlative 'optimal' in a promotional symposium, without substantiation, was in breach of Clauses 7.2, 7.4 and 7.10.

RESPONSE

Novartis submitted that the phrase 'optimal outcomes' on slide 13 referred to the label supporting the ability of the physician to determine the treatment and monitoring frequency on a patient-by-patient-basis, dependent on their disease activity. Thus the physician could tailor treatment to an individual rather than treat all patients with a single approach. Giving physicians this flexibility ensured the best chance of optimal outcomes for patients.

Novartis submitted that 'optimal outcomes' was not a superlative. No comparisons were drawn between Lucentis or any other product on the slide; the slide encouraged the rational use of Lucentis by presenting it objectively without exaggerating any properties. Novartis thus denied that slide 13 breached Clauses 7.2, 7.4 or 7.10.

PANEL RULING

The Panel noted the claim 'optimal outcomes' was part of the first stab point on slide 13 under the heading 'Introducing the new ranibizumab EU label, which supports a personalized treatment approach'. The Panel considered that the claim at issue was not a superlative as alleged by Bayer. The supplementary information to Clause 7.10 Superlatives was clear that superlatives were grammatical expressions of the highest quality or degree such as best, strongest etc. In that regard the Panel noted that the claim at issue did not exclude the possibility that other treatment regimens could also provide optimal outcomes. The changes to the Lucentis SPC enabled prescribers of Lucentis to determine monitoring and treatment intervals such as to optimise treatment with Lucentis. In that regard the Panel did not consider that the claim was a hanging comparison as alleged. It was substantiated by the Lucentis SPC. The Panel therefore ruled no breach of Clauses 7.2, 7.4 and 7.10.

4 Slide 38 – disclosures and alleged misleading source data

Slide 38 was part of a presentation headed 'Disclosures' and stated 'Advisory board/consultant to Bayer and Novartis', 'Speaker fees: Novartis' and 'Conference and travel: Alcon, Bayer and Novartis'. Slide 38 also stated that a hospital was involved in research supported by Allergan, Bayer and Novartis and the final bullet point was 'VERO study was sponsored by Novartis'.

COMPLAINT

Bayer noted that, as stated above, the symposium included a section presented on 'New data on ocular safety' (slides 37-48) which discussed the relative risks of Lucentis and Eylea in causing endophthalmitis and severe intraocular inflammation, based solely on data from two retrospective studies of data collated in US health insurance databases.

Bayer stated that it was clear from slide 13 that Kelly *et al*, (the VERO study) was sponsored by Novartis; this implied that the other retrospective study (Kiss *et al*) was independent. However, Kiss *et al* was supported by Genentech, the company which manufactured Lucentis and marketed it in the US. Further, from the abstract it appeared that one author was employed by Genentech Inc. Genentech was in commercial partnership with Novartis, which marketed Lucentis on its behalf outside the US. The disclosure was therefore incomplete and misleading about the independence of the data presented at the meeting.

Bayer did not accept Novartis' assertion that it was reasonable to only disclose that it had supported Kelly *et al*, as one of the authors was also a presenter. Bayer stated that this was a promotional symposium, sponsored by Novartis, in which Novartis claimed comparatively greater safety for Lucentis vs Eylea based wholly on two studies which were both funded by companies which marketed Lucentis in their respective territories. This information would have been highly relevant to the audience in assessing any potential bias in these data. Accordingly, it was not acceptable in these circumstances for the funding details of both studies

not to be made transparent; simply referencing the studies on the slide deck was insufficient. Bayer alleged a breach of Clause 7.2.

RESPONSE

Novartis submitted that in keeping with Clause 23.1 that 'in their written contracts or agreements with consultants, companies must include provisions regarding the obligation of the consultant to declare that he/she is a consultant to the company whenever he speaks in public about a matter that is the subject of the agreement', the speaker disclosed that he was involved with the VERO study and that this was a Novartis sponsored study.

Novartis submitted that as the speaker was not involved in Kiss *et al* there was no need for him to declare this to the audience. The speaker disclosed that VERO was a Novartis sponsored study in order to be transparent that he was also the author of a poster on VERO at the same meeting where the symposium was being held. Therefore this was the basis for this specific disclosure on his slide rather than any other intention as implied by Bayer.

Kiss *et al* was presented at the Association for Research in Vision and Ophthalmology (ARVO) conference in 2014 and Novartis had no access to additional data beyond that which was in the public domain. The ARVO conference was a scientific conference of high regard and as such all ARVO data was peer reviewed and then published in the Investigative Ophthalmology & Visual Science (IOVS) journal.

The reference for this study was clearly cited on slides 43, 44, 47 and 48 all of which referred to Kiss *et al*. Novartis therefore refuted the allegation that there was an intention to mislead the audience about the level of disclosure and it denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the presenter was involved with one of the studies, which was mentioned on the disclosures made at the beginning of his presentation (slide 38) which included 'VERO study was sponsored by Novartis'. The presenter stated that as he was going to be talking about this study and it was a Novartis event, his involvement should be made clear.

The Panel noted that the second of the studies, Kiss *et al*, was sponsored by Genentech Inc. which marketed Lucentis in the US. The Panel noted that these two studies of US medical claims databases were used by the presenter to compare the event rate of endophthalmitis/severe intraocular inflammation for Lucentis and Eylea. The Panel considered that disclosing that VERO was sponsored by Novartis but remaining silent about Kiss *et al* might lead the audience to assume that Kiss *et al* was not sponsored by a commercially interested party. This was not so. The Panel considered the presentation was misleading in this regard. A breach of Clause 7.2 was ruled.

B Symposium 'Optimizing benefits and risks in DME [diabetic macular oedema]' 11 September 2014, 1-2pm, attended by 633 conference delegates

Alleged misleading, unbalanced and inaccurate claims

COMPLAINT

Bayer stated that this symposium was carefully designed by Novartis to build a picture of a worse adverse event profile for Eylea vs Lucentis in diabetic macular oedema (DME); many of the most contentious statements were made by presenters rather than on the slides.

Bayer stated there was no proven link to an increased risk of vascular adverse events (arterio-thrombotic events) with Eylea compared with Lucentis at the doses used intravitreally in any indication, and yet the overall construction of the symposium deliberately questioned the safety record of Eylea compared with Lucentis in DME. Of particular concern was that many of the alleged safety issues were raised indirectly and were implied by reference to different medicines administered in different indications, at vastly different doses and by a different route, without recourse to any clinical data to support the propositions.

The first presentation set out the high risk of cardiovascular complications in diabetic patients as a result of their disease, and the dangers of systemic inhibition of growth factors such as vascular endothelial growth factors A and B (VEGF A and B) and placental growth factor (PlGF). Bayer noted that Eylea inhibited VEGF A, B and PlGF whereas Lucentis only bound to VEGF A. Particular emphasis was placed on the potential protective effect of VEGF B and PlGF in vascular disease (slide 25) and the dangers of inhibiting these factors, particularly PlGF inhibition in pregnancy – an irrelevant statement as Eylea, like other anti-VEGF therapies, was not recommended in pregnancy. In inter-company dialogue, Novartis denied that its symposium included information on the risks of PlGF inhibition in pregnancy, based on the fact that nothing about pregnancy was on any of the slides, but Bayer stated that the recording confirmed that this denial was not true. PlGF was discussed starting from time point 14.07 minutes in the recording, and at 14.47 the presenter noted the risks of 'severe disregulation' in pregnancy and an increased risk of eclampsia and pre-eclampsia in pregnancy related to PlGF inhibition.

The second presenter then presented on the risks of systemic VEGF inhibition (slides 29-45). Bayer stated this was based mainly on evidence from use of high dose intravenous anti-VEGF agents in oncology, as opposed to intravitreal use (ie Lucentis and Eylea) from which systemic circulation was minimal. Bayer noted that Novartis included a disclaimer relating to difference in dose and side-effect profile on this slide, but the overall impression was of a high risk of serious adverse events related to systemic availability of the medicine. Slide 28 summarised that 'systemic VEGF inhibition could lead to serious side effects' and slide 30 illustrated differences in

molecular structure between different anti-VEGF agents, including Lucentis and Eylea.

The presenter then discussed the theoretical relationship between molecular structure and safety profile for anti-VEGF medicines. The molecular differences highlighted on Slide 30, most notably the presence of an Fc fragment in Eylea, were used to imply a greater risk of systemic availability of Eylea vs Lucentis, with the further suggestion that this might increase the risk in DME patients of the kinds of systemic adverse events seen in cancer patients. There were no data presented to support this contention, as none existed – the argument was built entirely on implication. The observed 2 year death rate for Lucentis 0.5mg in its phase 3 studies RISE and RIDE was 4% and 4.8% respectively (Nguyen *et al* 2012) which were very similar values (indeed numerically slightly higher) than the death rates of 3.7% and 3.9% seen at 100 weeks with Eylea in the phase 3 DME studies, VIVID/VISTA, respectively. The Eylea and Lucentis SPCs did not differ with respect to their use in diabetic patients at risk of vascular disease, nor in any other respect regarding the risk of systemic vascular adverse events in any licensed indication. Indeed, although not applicable in the EU, Section 6 of the US prescribing information for Lucentis carried a specific warning of 'fatal events in DME patients', whereas Section 6 of the US prescribing information for Eylea had no such warning. Within the US, Lucentis was licensed at a lower dose (0.3mg) in DME than its licensed dose in other US indications or any indications in the EU (0.5mg) because of concerns over the risk-benefit profile of the 0.5mg dose in diabetic patients.

Bayer alleged that data in this section were presented selectively from published studies to minimise the apparent risk of arterio-thrombotic events with Lucentis, and to support the incorrect assertion that Eylea had a worse safety profile than Lucentis in DME. Specifically:

- Pooled arterio-thrombotic events safety data were presented from the RESOLVE, RESTORE and RETAIN studies, which used a flexible dosing regimen of Lucentis (slides 37-39). However, non-myocardial arterio-thrombotic events and myocardial arterio-thrombotic events from the RISE/RIDE phase 3 studies of Lucentis in DME were presented separately (slides 33/34), which made the total numbers of arterio-thrombotic events with the 0.5mg dose of Lucentis look smaller in these studies (5.2% and 2.8%) than was actually the case (8%). Myocardial infarction was not even labelled as an arterio-thrombotic event on slide 33, when it clearly was such an event.

- Following the discussion of the long-term safety profile of Lucentis, week 100 safety data from Bayer's VIVID/VISTA trials (slide 41) were shown to imply that questions remained around relevance of higher death rates in Eylea arms compared with laser. And this was also implied by the speaker (time point 26.20) ie 'results for Eylea demonstrating differences in number, particularly concerning deaths…and we look forward to seeing the 5 year data where we can conclude even more definitely if this is relevant to our treatments'. This built up to a comparison of the length of safety data available in DME for Lucentis (5 years) vs Eylea (2 years) on slide 42, a comparison made by the speaker at time point 26.54 of the recording used the trade names of both products: 'So again not only are efficacy data available for 5 years….and also the safety data available now for 5 years for Lucentis and 2 years for Eylea…'.

Bayer stated that in the final section of this symposium, from time point 50.30 to 54.00 in the recording, there was a discussion and question and answer session during which the speakers made strong promotional statements for Lucentis none of which were based in evidence. It was stated that there was 'a real big difference' in systemic exposure related to presence of an Fc portion, a statement for which there was no evidence and in addition a series of statements were made to the effect that only Lucentis and not Eylea should be used in eye disease. Specifically, the third presenter stated:

> 'Yes you are right, I think the size of the molecule matters. What really matters is the Fc portion… recirculation maximises the amount of drug exposure systemically. So if you think about that, if you want a drug which maximises the amount of systemic exposure, you want the Fc portion – like a cancer drug, like Avastin - but if you want a drug that's only going to go to the eye and nowhere else, and not be exposed to systemic circulation, then you do not want an Fc portion. So if you are looking for an eye drug that goes in the eye but doesn't go anywhere else, then you really want to look for a drug without an Fc portion and that's what Lucentis, Lucentis, does have, it has no Fc portion at all, unlike Eylea and unlike Avastin, and that's an important point.'

Bayer stated that Eylea was the only medicine licensed in ophthalmology which had an Fc portion in its molecule, and so the closing message of the Novartis symposium effectively recommended that Eylea not be used because of its Fc portion, based on unproven allegations of safety risks relating to increased systemic circulation. Indeed it appeared that the entire symposium was designed to build up to this message. Bayer repeated that there were no data to support increased adverse events, or any risk arising specifically from an Fc portion, in patients treated with Eylea compared with Lucentis, in any of its licensed indications.

Although a couple of slides were included elsewhere in the symposium which correctly stated that Lucentis and Eylea had 'well documented' safety profiles, slides 42 and 44 (Bayer incorrectly referred to slide 45 in its complaint as this was a slide of the third speaker) and there was an additional correct comment on slide 42 that no new safety concerns had been identified with Eylea, the inclusion of these comments did not mitigate the overwhelming promotional take-home message that there were serious questions over the vascular safety of Eylea, particularly in the DME population at high risk of vascular events, and that Eylea was unsafe to use and only Lucentis should be considered in this population.

Bayer alleged that the cumulative effect of the symposium misrepresented the safety profile of Eylea compared with Lucentis. Given the 'take-home' impact on the audience, Bayer, alleged that the overall impression given by this symposium about the safety profile of Eylea in DME breached Clauses 7.2, 7.3, 7.4 and 7.9.

RESPONSE

Novartis noted that Bayer included a video recording of the symposium with its complaint. Slide 5 (Novartis incorrectly referred to slide 2 as this was a welcome slide) of the symposium presentation clearly requested that the symposium not be videoed and that it would be available as a live stream. Novartis further noted that Clause 10.3 stated that symposia were 'private occasions' and advised companies that quotations from such activities must not be used without the formal permission of the speaker. Novartis stated that in making the video Bayer had not fully respected the professional standing of the speakers (Clauses 9.1 and 9.2).

Novartis also noted that Bayer had decided not to include the symposium slide entitled 'Housekeeping' (slide 5) which contained the following information:

- This symposium is being broadcast live on the EURETINA website
- Please mute mobile phones
- Videoing the symposium is not permitted
- Questions to the audience will be asked throughout – please respond using the keypads provided
- A Q&A session will be held at the end of the session – please use the question card provided in your abstract book to submit a question
- Please return completed evaluation forms before you leave. Forms can be found in the back of the program book
- Please do participate!'

Novartis stated that it had provided the full slide deck for the presentation – to highlight the omission of some slides by Bayer and aid legibility of the ones provided to the PMCPA; there were thus differences in the slide numbering as referenced by Novartis. (This case used Novartis' numbering). In addition, Novartis noted that Bayer sometimes incorrectly referenced slides even in accordance with the reference material it had provided.

Novartis refuted Bayer's assertion that the symposium was designed to build a picture of a worse adverse event profile for Eylea vs Lucentis in diabetic macular oedema (DMO also known as DME). The symposium was designed to look at the very valid considerations that an ophthalmologist might face when treating diabetics with DMO and also the additional possible comorbidities. It reviewed the current data available for all the anti-VEGF inhibitors which might be used to treat DMO.

Novartis submitted that the SPC excerpts presented below demonstrated a well recognised theoretical risk associated with the use of anti-VEGF inhibitors. As a VEGF inhibitor and a medicine used off-licence, bevacizumab (Avastin) was a valid molecule to include in this scientific debate. The content of the symposium was of interest to the audience and warranted legitimate scientific debate on the theoretical impact of VEGF on arterial thromboembolic events. It was therefore consistent with the information contained within both SPCs:

Eylea SPC	**Lucentis SPC**
Section 4.4 **Systemic effects**	**Section 4.4** **Systemic effects following intravitreal use**
Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in the treatment of patients with CRVO or DME with a history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients.	Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors. There are limited data on safety in the treatment of DME, macular oedema due to RVO and CNV secondary to PM patients with prior history of stroke or transient ischaemic attacks. Caution should be exercised when treating such patients (see Section 4.8).
Section 4.8 **Description of selected adverse reactions**	**Section 4.8** **Product-class-related adverse reactions**
Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.	There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors.

Section 5.1 Mechanism of action	Section 5.1
Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PIGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PIGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PIGF can synergize with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation.	Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (eg VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO.

Novartis submitted that the symposium was therefore clearly designed to enable debate to enhance the current scientific knowledge in this area. As with all treatments for a condition the clinician was required to weigh up the risks and benefits of treatment when making decisions and in line with the title of the symposium the benefits and risks of medicines were reviewed.

Novartis stated that speaker 1 was a world renowned expert in his field as a diabetologist and also a researcher into microcirculation. His presentation was entitled 'The importance of systemic safety in patients with DME: a diabetologist's viewpoint'. He was therefore well positioned to lead such a debate on the microvascular and macrovascular complications associated with hyperglycaemia and also the additional cardiovascular risk seen in such patients.

Novartis stated that Bayer first raised a concern that this speaker had made a statement about placental growth factor in its letter of 10 December when it stated that 'the speaker drew attention to potential problems with inhibition of placental growth factor (PIGF), notably pregnancy'. However, no further details were provided unlike the level of detail provided in the letter to the PMCPA. Novartis responded to this complaint based on the information made available by Bayer at the time.

This speaker in slides 22-25 generally spoke about the VEGF family which included PIGF. He talked about what was known about the VEGF family in general and therefore Novartis could not understand how the statements he made about PIGF were derogatory to Eylea. In addition, there was no link made for any anti-VEGF inhibitors (including PIGF) in treatment of DMO. Further, Novartis agreed with Bayer that anti-VEGF inhibitors were not recommended in pregnancy but it did not consider that the contribution to the debate as provided by this speaker was negative as suggested by Bayer. Novartis referred to this speaker's transcript in relation to his comments for PIGF below to demonstrate that Bayer had cherry picked phrases which suggested the speaker spoke solely about the negative effects of PIGF on pregnancy:

> '14.42 - Placental Growth Factor (PIGF) is actually one of the most interesting. Until very recently we thought PIGF was nothing more than a decoy. PIGF will bind to the decoy receptor and therefore make your VEGF-A more responsive.
>
> 15.00 - We've recently demonstrated however that PIGF is its own endothelial stimulant. In HUVEC cells, it promotes nitrous oxide dependent vasodilatation. It appears to have protective properties.
>
> 15.15 - We know that if the absence of placental growth factor pregnancy is severely deregulated we know that low placental growth factor is very strongly associated with preeclampsia and eclampsia in pregnancy.

A lot of what we know comes from administration of VEGF receptor antagonists or VEGF inhibition. Before I go on I want to emphasise that most the data, these data I'm showing here come from systemic administration of VEGF. This is when VEGF inhibitors were used to treat cancers and clearly in cancer where the alternative is dying, then a slight increase in vascular risk is something that can be accepted.'

Novartis stated that confusingly Bayer attributed parts of speaker 1's presentation to speaker 2. Novartis noted that slides 26 and 28 were presented by speaker 1; slide 28 (Bayer reference 2) was his last slide. Novartis reiterated that speaker 1 spoke from his experience as a diabetologist and his understanding from his research of the impact of VEGF inhibition. The theoretical risk of VEGF inhibition for systemic adverse events including arterial thromboembolic events was clearly documented as it was included in the SPC. Therefore the statement highlighted by Bayer 'Systemic VEGF suppression could potentially lead to serious side effects' (Slide 28) was in keeping with the SPCs for the products.

Novartis refuted Bayer's assertion as modified in the reference material it provided to the PMCPA that slide 28 was 'immediately' followed by a slide illustrating differences in molecular structure between different anti-VEGF agents (slide 30).

Slide 30 was actually presented by speaker 2 and separated by an introductory slide, slide 29.

Speaker 2 then spoke about 'Balancing efficacy with safety considerations in DME'. The slide (Novartis stated slide 20 but this was incorrect; the relevant slide appeared to be slide 30, slide 20 was presented by speaker 1 not speaker 2) presented by this speaker looked at the molecular and pharmacodynamic properties of the three medicines which might be used to treat DMO. Novartis disagreed with Bayer's assertion that this speaker specifically drew attention to the Fc fragment as a cause for a greater risk of systemic availability with a further suggestion that this might increase the risk in DMO patients of the kind of systemic adverse events seen in cancer patients.

Novartis submitted that this speaker therefore legitimately looked at the differing elements of the different products, including Avastin and the first slide focused on the legitimate place for the use of anti-VEGF inhibitors in DMO by showing the wealth of evidence supporting the efficacy of anti-VEGF treatments.

Further slides then looked at the systemic safety of anti-VEGF agents. This then focused on the safety analyses of arterial thromboembolic events from available clinical trial data which, as Bayer highlighted, showed data for vascular events from RISE/RIDE, RESOLVE/RESTORE/RETAIN. There were several slides which presented the data for Lucentis but this was because there were more clinical data available for Lucentis than for Eylea – studies VISTA/VIVID.

Novartis considered that the US labelling for Lucentis in the area of DMO, as referred to by Bayer, was not relevant to the European market to which this congress was specifically focused and therefore it did not accept that cherry picking statements from the US labelling for these products was relevant where there was specific European labelling.

Novartis did not accept that the data presented in this section minimised the apparent risk of arterial thromboembolic events with one medicine over another nor did it understand Bayer's point that myocardial infarction was not labelled as an arterial thromboembolic event on slide 33. Novartis submitted that the material was appropriately labelled and suitable for the specialist audience who would know that a myocardial infarction was an arterial thromboembolic event.

Novartis further noted that Bayer raised the fact that a speaker referred to trade names of products. Novartis did not ask the speaker to refer to products by brand name, but considered that the speaker used language and terms that he was at ease with. Novartis submitted that the speaker was balanced and fair in his use of brand names such that he did not refer to Bayer's product generically but by brand name for Novartis' product. The speaker also reflected the availability of amount of safety data accurately and reported that there were 5 year data for Lucentis and 2 year data for Eylea.

The speaker acknowledged that there was a difference in perception for the RISE and RIDE data vs data collected from studies in non-US populations. As there had been some debate in the scientific community on whether these studies showed a dose dependent safety profile it was decided that this was entirely relevant to look at in some more detail. Therefore the speaker looked at the safety profile as seen in these studies. Slide 35 showed the two-year incidence of vascular deaths with Lucentis 0.3/0.5 mg in RISE and RIDE. Deaths during the 24-month study period in RISE/RIDE had shown overall deaths as 11 (4.2%) at the 0.5mg dose group vs 7 (2.8%) at the 0.3mg dose group and 3 (1.2%) in the sham (placebo) group.

Slide 35 was headed 'Two year incidence of vascular deaths with ranibizumab 0.3/0.5mg in RISE and RIDE' and was referenced to Nguyen *et al* (2012).

Deaths during the 24-month study period	**[Placebo] (n = 250)**	**[Lucentis] 0.3 mg (n = 250)**	**[Lucentis] 0.5 mg (n = 250)**
Overall, n (%)	3 (1.2)	7 (2.8)	11 (4.2)
Vascular	3 (1.2)	5 (2.0)	6 (2.4)
Non-vascular	0	2 (0.8)	4 (1.6)
Unknown cause	0	0	1 (0.4)

Novartis submitted that it was relevant to the debate to reflect that the total numbers had come from both vascular and non-vascular deaths. However when the vascular deaths were looked at specifically there was a difference between the two doses.

Novartis noted Bayer's reference to comments that were made in the discussion and question and answer section at the end of the symposium. Answers given by the panelists were their personal view, understanding and expertise in this area. To highlight the differences in what was said, Novartis provided a more detailed transcript as opposed to the cherry-picked transcript presented by Bayer:

> 'Q: What determines the PK in the blood stream with different anti-VEGF agents?'
>
> 'A: Actually it's difficult to say because we don't know all the answers to this but there are various properties of different substances which all end up in different behaviour in the body and one of this different behaviour is the systemic concentration over time actually and one of the aspects may well be size of the molecule; smaller molecules are eliminated from the systemic circulation very fast, larger molecules need some more time and this may be part of the explanation why there is a real big difference in systemic exposure of the different drugs.'

This was the 'real big difference' statement that Bayer incorrectly attributed to having been linked to the presence of an Fc portion. As demonstrated by the transcript from the presentation there clearly was no such statement which linked the statement 'real big difference' to the Fc portion.

Speaker 3 who led the question and answer session then followed up with his perspective and related the differences in size to the Fc portion. This text had been provided by Bayer and, other than a few minor words, Novartis submitted it accurately reflected the follow-up answer given by speaker 3 to the question and answer session.

Novartis stated that the presence of an Fc portion was clearly a key difference between the medicines as highlighted on slide 30 which showed their various molecular and pharmacokinetic attributes. This was a statement made by speaker 3 in relation to possible reasons for a longer systemic exposure. Novartis did not accept that responses to a question and answer session supported Bayer's allegation that the entire symposium had been designed to build up to this message. As acknowledged by Bayer there were multiple safety profile slides which clearly gave a balanced view of the safety data available for the medicines.

Novartis vigorously rejected Bayer's assertion that the 'take-home' message of this symposium was that Eylea had a poor safety profile because:

- The symposium was set up to invite debate on the factors which might be taken into account when treating diabetes patients with macular oedema
- The factor relating to the active medicinal ingredient and the pharmacodynamic factors were all presented in a balanced and factual manner
- The theoretical risks in relation to systemic effect were recognised and outlined in the SPCs of the two licensed medicines
- The presentation looked at the practical considerations for the three products which might be used in this condition – one of which could be used as an unlicensed treatment
- All data presented was presented in full and with balance where available
- It was clearly presented that there was a potential class effect which was relevant for all the medicines discussed
- The data presented was for the registration trials on the products which had a licence and reflected the comparators used in those trials.
- There were no promotional claims made in the symposium about any licensed indication nor were specific efficacy claims made for Lucentis.

Novartis denied the allegation that the symposium was set up to present a poorer safety profile for Eylea vs Lucentis and noted that summary slides after presenting the available data from clinical studies clearly reflected that both had good safety profiles by the statement 'There is a well-documented safety profile in DMO for [Eylea] (2 years) and [Lucentis] (5 years)', so Novartis did not accept that an overall negative 'take-home' impression was created. Novartis accepted that the data reflected that there was 5 year safety data for Lucentis which was longer than that shown for Eylea but this was a statement of fact and an accurate evaluation of the current data.

Novartis refuted a breach of Clause 7.9 in that information and claims about adverse events must reflect the available evidence or be capable of substantiation by clinical experience.

As Novartis disagreed that the symposium was promotional in nature or that it was set up to make comparisons of the adverse events data for arterial thromboembolic events and that as such it was misleading – it did not therefore accept that this was in breach of Clause 7.3.

The company considered that the data presented under this scientific symposium was accurate, balanced, fair and objective. That it did not mislead directly or by implication, by distortion, exaggeration or undue emphasis and that consequently it was not in breach of Clause 7.2 nor Clause 7.4.

PANEL RULING

The Panel noted that Bayer complained about the overall impression created of the safety profile of Eylea in diabetic macular oedema (DME) by the symposium. In that regard, although the symposium had consisted of three presentations and a question and answer session, the Panel considered the symposium as a whole and not each of its component parts separately. The symposium was organised by Novartis and referred in detail to its medicine. The Panel considered that the symposium promoted Lucentis.

The Panel noted that both Lucentis and Eylea were antineovascularisation agents, they prevented endothelial cell proliferation and the formation of microvascular vessels as well as vascular leakage, all of which were thought to contribute, *inter alia*, to diabetic macular oedema. The medicines did this by inhibiting vascular endothelial growth factor (VEGF). Lucentis inhibited VEGF A whilst Eylea inhibited VEGF A and the related placental growth factor (PlGF). Slide 30 compared the products. Eylea was a larger molecule than Lucentis and its structure contained an Fc (fragment crystallisable) fragment of a human immunoglobulin. Lucentis had no Fc fragment.

The symposium in question was entitled 'Optimizing benefits and risks in DME management'. In that regard the Panel considered that attendees would expect the presentations to be about the practical and clinical aspects of managing DME. The first section of the symposium was about systemic safety in DME patients. The speaker set out the complications associated with diabetes and in particular that diabetic patients with DME had an even greater risk of co-morbid complications than those without DME. The presentation then focussed on the role of the VEGF family of growth factors and the beneficial effects of VEGF A, VEGF B and PlGF in animal studies. Slide 25 was entitled 'The role of VEGF-B and PlGF has been explored in animal studies' and stated that PlGF had protective properties in preclinical models of heart, retinal and neural diseases. The following slide (26) was headed 'Potential side-effects of systemic administration of anti-VEGF treatment in oncology patients'. Such side effects included hypertension, thromboembolic events and cardiac dysfunction. Slide 26 included 'The dosage, route of administration and side effect profile of anti-VEGF therapies in oncology patients are different to those in ophthalmology patients'. The next slide (27) was headed 'audience participation' and was blank. The slide set provided by Bayer gave the detail (page 21 of Bayer's pdf) which made it clear that participants were asked to use voting buttons to answer the question 'Do you think that systemic VEGF inhibition is clinically relevant in patients with DME?'; Almost 69% thought yes, 22% thought no and 9% did not know. The concluding slide to this section of the symposium ended with the statement that 'Systemic VEGF suppression could potentially lead to serious side effects'.

The Panel noted that Section 5.2, pharmacokinetic properties, of the Lucentis SPC stated that following monthly intravitreal administration of the medicine, serum concentrations of ranibizumab were generally low, with maximum levels generally below those needed to inhibit the biological activity of VEGF by 50% as assessed in an in vitro assay. The Eylea SPC stated in Section 5.2 that aflibercept was slowly absorbed from the eye into the systemic circulation after intravitreal administration, predominantly as an inactive, stable complex with VEGF; only free Eylea was able to bind with endogenous VEGF. The mean maximum plasma concentration of free aflibercept was approximately 50 to 500 times below that required to inhibit systemic VEGF by 50% in animal models. Section 4.4 of both SPCs stated that systemic adverse events, including non-ocular haemorrhages and arterial thromboembolic events, had been reported following intravitreal injection of VEGF inhibitors. Similarly both SPCs advised that caution should be exercised when treating patients with a history of stroke or transient ischaemic attacks or myocardial infarction. Section 4.8 of both SPCs stated that there was a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction following intravitreal use of VEGF inhibitors. It thus appeared for both medicines, that systemic effects from the inhibition of VEGF was a possibility. There was five year data for Lucentis and two year data for Eylea.

The second part of the symposium was entitled 'Balancing efficacy with safety considerations in DME'. The speaker started by explaining that 'there are various substances we have available for treating our patients with DME and the other disease that responds to anti-VEGF treatment. However all these substances are not all exactly the same'. They might have different efficacy, risks and side effects. The first slide in this section (slide 30) compared the molecular weight, structure etc of Lucentis, Eylea and Avastin. It was noted on the slide that Eylea and Avastin unlike Lucentis, contained an Fc portion. The speaker drew attention to the differences in systemic elimination half-life (around 2 hours for Lucentis, 5-6 days for Eylea and 20 days for Avastin) and mean serum exposure after one injection (area under curve, days nM) after one injection (0.2, 3.3 and 14.1 for Lucentis, Eylea and Avastin respectively). The speaker continued by talking about 'Systemic safety of anti-VEGF agents' and explained there had been extensive discussions in the US with respect to the differences in various doses of Lucentis particularly 0.3 and 0.5mg and that he would summarise why this was not seen as such an issue in Europe. He presented seven slides relating to arterio-thrombotic events (ATEs) for Lucentis and concluded, (slide 40), *inter alia*, that 'No differences in event rates of MIs, non-myocardial ATEs (including cerebrovascular events) and vascular deaths were observed…' and 'Based on currently available data there is no evidence to suggest differences in safety between Lucentis 0.5mg, 0.3mg and control'. Data on the safety of Eylea was then presented (slide 41). The speaker referred to 'similar results' for Eylea but pointed to 'differences in number particularly concerning death'. The speaker noted that the data shown was 2 year data and that 'we will be happy to see the 5 year results where we can conclude even more definitely if this is of any relevance for our treatments'.

The speaker summarised the data for Lucentis and Eylea with slide 42, entitled 'Consistent and well-documented long-term safety profile of anti-VEGF agents in DME', beneath which was the statement: 'Incidences of ocular and non-ocular events similar across groups, and similar to previous trials in other indications; no new safety findings or increased safety concerns reported'. At the end of this section of the symposium slide 43 (page 37 of Bayer's pdf which had the detail) asked delegates whether molecular and pharmacokinetic differences influenced their choice of anti-VEGF agent (for DME patients); 63% voted yes and 33% voted

no (3.6% did not know). The speaker concluded (slide 44) by noting that there were molecular and pharmacokinetic differences between anti-VEGF agents, repeating that there was a well documented safety profile in DME for Eylea (2 years) and Lucentis (5 years) and that treatment considerations should balance the benefits of treatment and the risk and severity of adverse effects.

In the closing comments the speaker presented two slides (82 and 83) to conclude. Slide 82 stated, 'Anti-VEGF therapy provides similar VA [visual acuity] scores in patients with DME at 12 months, regardless of the agent or dosing regimen used. Both agents provide sustained VA gains – aflibercept (2 years) and ranibizumab (5 years)' and that there was a wealth of phase 3 data to support the safety of anti-VEGF agents in DME and that Lucentis had a consistent, well-documented long-term safety profile in this indication. With regard to the question and answer session the Panel noted that the speakers stressed that ideally an anti-VEGF agent which would stay in the eye and thus not cause systemic side effects would be one without an Fc portion ie Lucentis and not Eylea or Avastin. One speaker stated that a medicine without an Fc portion ie Lucentis would enable him to give his patients the best vision possible as safely as possible.

The Panel noted the data presented and that there was longer term data for Lucentis as it was available before Eylea. The Panel considered that much had been made of the differences between the molecules and the impression was given that this might impact on safety. This difference was not set in the context of the information in the SPC which was similar for Eylea and Lucentis. In considering the data as a whole the Panel noted that according to Bayer there were differences between the US labelling for Lucentis in DME which referred to fatal events in DME. This was not in the Lucentis SPC. The Panel also noted Novartis' submission that this was not relevant in Europe.

Overall, the Panel considered that the take home message was, as alleged, that the safety profile for Lucentis was more favourable than that for Eylea and that real differences in that regard would be seen in the clinic. On balance that Panel considered that there was insufficient data to show that this was so and that the symposium overall was misleading in that regard. A breach of Clause 7.2 was ruled. The comparison of the two medicines was thus misleading and a breach of Clause 7.3 was ruled. The impression of a significant clinical difference between Eylea and Lucentis could not be substantiated and breaches of Clause 7.4 and 7.9 were ruled.

C Summary

COMPLAINT

Bayer stated that it was gravely concerned that two Novartis-sponsored symposia at the London EURetina congress misleadingly compared the safety profiles of Lucentis and Eylea.

In the case of the wet AMD symposium, (A above), the misrepresentation of safety occurred in the context of superlative promotional claims which related to the efficacy of Lucentis and exaggerated claims about the flexibility of its new posology. In the case of the DME symposium, (B above), implication based upon data irrelevant to the dosages and indications under discussion, verbal comment and misleading presentation of Lucentis safety data combined to build a false picture of the comparative safety of Eylea vs Lucentis and to raise unfounded concerns in the minds of prescribers about the safety of Eylea in its newest indication.

In addition, Bayer considered that there was clear evidence in the examples given above of repeated, serious misrepresentations of safety data and disregard for the Code, such that Novartis had failed to maintain high standards and had brought the industry into disrepute. Taking all of Novartis' activities at EURetina into consideration, Bayer alleged breaches of Clauses 9.1 and 2.

RESPONSE

Novartis submitted that Bayer had not proven its allegations as set out in its complaint which contained multiple inaccuracies of fact and misrepresented the content of the symposium by selectively presenting slides or by misrepresenting the order of slides used in the presentation. Furthermore, Bayer repeated this with inaccuracies of quotations, which could be easily disproven, or selective use of those sections of speaker statements which supported its argument of imbalance without presentation or use of the full statement in context.

As clearly outlined above the symposia took place in the context of debate to further scientific knowledge; neither symposium misrepresented the overall safety profiles for the two medicines as alleged either favourably for Lucentis or negatively for Eylea.

Finally, Novartis did not accept that Bayer had, provided clear evidence in the examples given in its complaint of repeated, serious misrepresentation of safety data and disregard for the Code such that Novartis had failed to maintain high standards and had brought the industry into disrepute. Consequently, Novartis did not consider that there had been a failure to maintain high standards such as to warrant a breach of Clause 9.1 nor that it had brought the industry into disrepute such as to warrant a breach of Clause 2.

PANEL RULING

The Panel noted its rulings in Points A and B above. It considered that the misleading presentation of the data meant that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure. The Panel noted that the supplementary information to Clause 2 referred to examples of activities likely to be in

breach of Clause 2 and these included prejudicing patient safety. The Panel noted that although it considered that the symposium had presented a misleading impression of the comparative safety profiles of Lucentis and Eylea, patient safety would not have been put at risk. The Panel noted its rulings above but nonetheless did not consider that its rulings of breaches of the Code in this case amounted to a breach of Clause 2 and no breach was ruled.

Complaint received **12 February 2015**

Case completed **24 June 2015**

CASE AUTH/2749/2/15

ANONYMOUS NON CONTACTABLE v CHUGAI

Consultancy arrangements and general Code compliance

An anonymous, uncontactable ex-employee of Chugai Pharma complained about the company's appointment of a consultant and its general attitude towards Code compliance.

The complainant noted that Chugai contracted a lot of work to a pharmacist at an NHS hospital trust. The pharmacist owned a company and also worked for a number of external agencies which Chugai used on projects. A senior Chugai manager and the pharmacist were socially very close and often went on nights out. The manager often boasted of his/her relationship with the pharmacist and of how information could be obtained by 'bringing [the pharmacist] for a few drinks'. The complainant stated that he/she had heard the two favourably discussing the prescribing of Chugai medicines and had also heard the senior manager promise the pharmacist extra business by putting him/her in touch with Chugai's business partners. The complainant was uncomfortable with the closeness of the relationship but feared his/her job might be at risk if he/she highlighted it to Chugai senior management.

The detailed response from Chugai is given below.

The Panel noted that the health professional in question was engaged as a consultant by Chugai on a number of occasions between December 2011 and December 2014. Chugai had only been asked to consider activities which had taken place since March 2012. The relevant Codes were thus the 2012 and 2014 editions.

The Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. The complainant was non-contactable and so could not be asked to provide further details; he/she had provided no evidence to show that the health professional had not been suitably qualified to provide the services contracted or that the engagement of the health professional had been an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. The complainant stated that he/she had been uncomfortable with the closeness of the relationship between the health professional and the senior manager and had not felt able to bring it to the attention of other senior managers – who, it seemed from Chugai's submission, appeared to have been unaware of the closeness of the friendship.

The Panel considered that in addition to the criteria that should be met when a company used a health professional as a consultant or advisor, the impression created by the arrangements was also very important. The Panel noted Chugai's submission that the health professional was a close, personal friend of Chugai's senior manager; their friendship pre-dated the health professional's engagement as a consultant to Chugai. In the Panel's view it was extremely important that clear distinctions were made between business and personal arrangements. Given the relationship between the health professional and the senior manager, it would be difficult for the engagement of the health professional not to be seen as a direct consequence of that relationship. The Panel noted that in many of the consultancy agreements, the senior manager had played some role, albeit that he/she did not have sole responsibility for the arrangements. Some of the senior manager's direct line reports had been responsible for selecting the health professional in question as a consultant/advisor to the company and the senior manager had then approved the budget and service fee. The Panel was concerned that despite a 'conflict of interest' register being presented to the Chugai leadership team for completion from 2013, the senior manager had not declared his/her friendship with the pharmacist. The Panel considered that the senior manager's conduct in this regard had not maintained high standards. A breach of the Code was ruled.

The Panel noted that the health professional had been paid £1,325 for services in 2012 plus £49.20 expenses; this was less than 1% of Chugai's total spend on consultants that year. In 2013 he/she had not been contracted by Chugai at all but in 2014, although he/she carried out only seven contracts for the company (less than 6% of the total number of contracts (n=123)), he was paid £28,225 plus expenses – around 29% of the company's total spend on consultants for that year (not including an additional agency project). The Panel was concerned about the impression that this might have given to those within Chugai who knew about the friendship between the health professional and the manager.

In addition to the above, in 2014 Chugai commissioned an agency to develop four projects to support the market growth of one of its medicines. The agreement between Chugai and the agency showed that the core project was to support the NHS tender for the medicine in a particular location. The total value of the project was £35,000 with some of that money (amount unknown by Chugai) being paid to the health professional via a sub-contract with the agency to build a health economic model. The Panel considered that in these circumstances it was very important that all relevant people were aware of the involvement of the health professional at issue. Further, in the Panel's view the amount paid to the health professional, if he/she was contracted personally and not via his/her company, would have to be disclosed by Chugai as part of its aggregate disclosure for 2014 given the agency had engaged him/her on behalf of Chugai.

The Panel noted its comments above and that the complainant had provided 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 thus ruled no breach of the Code. It also ruled no breach of the Code for those consultancies where the health professional had been contracted through his/her company. The Panel noted Chugai's submission that the health professional had received only limited hospitality in attending three advisory board meetings and two internal training meetings. Further, a review of expense claims by Chugai showed the company had not arranged or funded any private social occasion. The complainant provided no evidence to the contrary. No breaches of the Code were ruled.

The Panel noted its rulings above, and although it had some concerns about the consultancy arrangements it considered that Chugai had not brought discredit upon, or reduced confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

The complainant alleged that during his/her time in Chugai there was a somewhat laissez-faire attitude to ABPI compliance. A senior manager often mocked the Code and referred to it as a tick box exercise. The complainant alleged that some of the senior sales team were not ABPI certified; the company seemed to turn a blind eye to this. This attitude sometimes seemed to permeate through the company and the complainant considered that the company conveniently referred to the fact that as a Japanese company it was relationship based and that the Code was more for big pharmaceutical companies.

The Panel again noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. The complainant had not provided any evidence or cited any specific event to support his/her allegations. The Panel noted that the Code training slides provided by Chugai did not appear to be unreasonable either in tone or content. The Panel noted Chugai's submission regarding on-line training, monthly updates on the Code, the Code awareness group and the attendance of key staff at compliance conferences and considered that there was no evidence to suggest an unacceptable attitude to training or compliance. The Panel considered that on the evidence before it, there was nothing to suggest with regard to training etc, that high standards had not be maintained. No breach of the Code was ruled.

The Panel noted the allegation that senior members of the sales team, were not ABPI certified. The Panel further noted that Chugai had provided the ABPI Representatives Examination certificates for a number of its relevant senior staff and had explained why one senior manager and one director had yet to pass the examination. In that regard the Panel considered that staff had taken or would take the ABPI examination in accordance with the requirements of the Code and it ruled no breach of the Code.

The Panel noted its rulings above and ruled no breach of Clause 2.

An anonymous, uncontactable ex-employee of Chugai Pharma UK Ltd complained about the company's appointment of a consultant and general Code compliance within the organisation.

When writing to Chugai, attention was drawn with regard to consultancy arrangements, to the requirements of Clauses 2, 9.1, 18.1, 21, 22 and 23.1 of the 2015 Code and their equivalents in the 2014 and 2012 Codes. Chugai was initially asked to respond in relation to relevant activities which took place from March 2012 onwards.

On receipt of the response, which included the dates of the activities, the Panel considered that it would have to identify the relevant Codes and equivalent clause numbers. It appeared these were likely to be the 2012 and 2014 Codes and the equivalent Clauses were 2, 9.1, 18.1, 18.7 (instead of 21), 19.1 (instead of 22.1) and 20.1 (instead of 23.1).

With regard to the allegations about Code compliance, Chugai was asked to respond in relation to the requirements of Clauses 2, 9.1 and 16.1.

A Appointment of a consultant

COMPLAINT

The complainant noted that Chugai contracted a lot of work to a pharmacist at an NHS hospital trust. The pharmacist owned a company and also worked for a number of different private consultation firms which Chugai used externally on projects. The issue with the relationship was that Chugai's senior manager and the pharmacist were socially very close and often went on nights out. The senior manager often boasted of his/her relationship with the pharmacist and talked of how information could be obtained by 'bringing [the pharmacist] for a few drinks'. The complainant stated that he/she had heard the two favourably discussing the prescribing of Chugai medicines and also the senior manager promise the pharmacist extra business by putting him/her in touch with Chugai's business partners. The complainant was uncomfortable with the closeness of the relationship on occasions but feared his/her job might be in jeopardy if he/she highlighted it to Chugai senior management.

RESPONSE

Chugai stated that in common with many pharmaceutical companies, its process for contracting the provision of third party services was to use pre-approved template contracts, which were personalised for the occasion by completing facts such as the nature of the service and fee involved. Once the project received budget approval, the contract was sent to the health professional for signing. On receipt of the fully signed contract, two copies of the contract were signed by Chugai; one was returned to the service provider and the second retained and archived within Chugai.

Chugai noted that during the course of the investigation it had uncovered some administrative errors in that some of the contracts signed by the health professional had not been countersigned by Chugai. Consequently, the processes would be reviewed and staff retrained but Chugai did not consider that these errors were directly relevant to the complaint in question and they would be corrected as part of Chugai's subsequent process review.

Chugai gave a brief résumé of the pharmacist's career and noted that he/she was respected across the industry for his/her forthright views about the quality of health economic models and standards of industry-produced material and he/she worked with medical education agencies and pharmaceutical companies in this regard. Much of his/her private work was operated through his/her consultancy business established for that purpose.

Chugai stated that it had engaged the services of the pharmacist on nine occasions in the past three years. The pharmacist was engaged either personally or via his/her company as follows: as a member of three advisory boards (July 2012, September 2014 and October 2014); to deliver staff training (September 2012 and October 2014); to write a therapy area report (October 2014); to write two licensing reports (October 2012 and December 2014) and to develop material for a budget impact model and formulary pack (December 2014). Details of the time taken for each project and the fee paid was stated and a copy of each consultancy agreement was provided.

Chugai added that in April 2014, it commissioned an independent medical education agency, to develop four projects relating to one of its medicines. The agency subsequently decided, independently of Chugai to sub-contract one of these projects, the building of a health economic model, to the pharmacist. Chugai stated that it had disclosed this project for the sake of completeness as it considered that it was the only other project with which the pharmacist interacted with Chugai in a financial capacity (albeit indirectly). The total value of this project was £35,000. Chugai submitted that it did not know how much the agency had paid the pharmacist for the health economic model.

The pharmacist had been a personal friend of one of Chugai's senior managers for over ten years, which pre-dated his/her time employed by Chugai. Chugai submitted that it had played no part in arranging or funding any private social occasions and this had been verified in a review of business expense claims.

Chugai noted that the hospitality provided to the pharmacist in a business context was very limited. During the years 2012-2015, the pharmacist attended three advisory boards and spoke at two internal training meetings. Chugai submitted that the hospitality provided at these occasions was directly and proportionally related to the event during the day. Chugai had never sponsored the pharmacist to attend any national or international conference.

In summary, Chugai stated that it was confident that each of the listed engagements with the pharmacist were appropriate, payments were of fair market value, and met the requirements of Clause 23.1 (20.1 in the 2014 Code) and all other aspects of the Code. Consequently Chugai refuted any breach of that Clause. In particular, the pharmacist was selected on each occasion for his/her knowledge of the NHS, formulary processes, health economic models and for his/her views on the general medical value of potential in-licensed treatments. There was no evidence or suggestion that his/her selection was anything other than appropriate. There was nothing to suggest his/her appointments were related to any undue influence in relation to the commercial use of individual Chugai products.

Chugai stated that it could not find any evidence of the pharmacist receiving inappropriate hospitality influence or inducement; it therefore refuted any breach of Clauses 18.1, 21 (18.7 in the 2014 Code) or 23.1 (20.1 in the 2014 Code). Further, there was no evidence of the pharmacist receiving inappropriate hospitality consequently Chugai refuted any breach of Clause 22.1 (19.1 in the 2014 Code).

In the context of the allegations that the relationship between the company (and its employees) and the pharmacist were inappropriate, Chugai categorically denied any wrongdoing. There was no evidence of any inappropriate interaction. Consequently, the company denied a breach of Clauses 9.1 or 2.

In a response to a request from the Panel, Chugai provided further information.

FURTHER INFORMATION FROM CHUGAI

Chugai submitted that as it had previously provided a full and detailed response, it was concerned at the nature and number (23) of the multi-layered follow-up questions and noted that a number of them were about the relationship between the Chugai senior manager and the pharmacist. Chugai could not see the relevance of asking the involvement of the senior manager in nominating or selecting the pharmacist as the complainant had not suggested that the selection was made by individuals who did not have the relevant expertise to make such a decision. This question appeared to relate to an implication of nepotism rather than the suitability of the individual to provide the services requested. This was beyond the scope of the Code and the company was therefore surprised to see such questions. The underlying principles and wording of the Code was focused on legitimate need for the service, relevant expertise and on the appointment of a consultant not being an inducement to prescribe or recommend etc products of the engaging company. Nevertheless Chugai answered the additional questions and provided the requested documentation. At no time was the senior manager identified by the complainant responsible for the sole authorisation of any project involving the pharmacist. Several members of staff had been involved in the various interactions with the pharmacist, including several senior managers.

What was the process for choosing the pharmacist as a potential consultant to the company?

Chugai submitted that it first engaged the pharmacist in December 2011 to sit on a joint advisory board run between Chugai and another pharmaceutical company. The pharmacist's engagement included making a presentation. Details of the fee paid was given.

Chugai noted that the Code did not require a company to specifically record why each individual service provider was selected, but that: 'the criteria for selecting consultants must be directly related to the identified need and the persons responsible for selecting the consultants must have the expertise necessary to evaluate whether the particular consultants meet those criteria' (Clause 23.1, previously 20.1 in the 2014 Code). While the detailed reasoning was not recorded, the pharmacist would have been chosen for his/her experience as a senior pharmacist at a UK hospital trust.

Was the senior manager in any way involved in the pharmacist's selection and, if so, please give details?

Chugai's system, in common with those of other pharmaceutical companies, recorded the name of the originating project lead and the names of those who approved the budget spend. It did not record the names of all those involved in the decision-making process. Chugai named the originating project lead but stated that the senior manager who was the subject of this complaint signed the contract letter on behalf of Chugai and its business partner; he/she was present at this advisory board and presented to the group.

Please name the senior manager and personal friend of the pharmacist.

Chugai provided the name of the senior manager but it could not see how naming him/her, or any other individual, made any difference to the PMCPA consideration. The most recent version of the Chugai standard operating procedure (SOP) governing the selection and appointment of consultants was provided and it was in the process of being updated.

Relevant consultant expertise.

Chugai noted that a number of the Panel's questions related to the suitability of the pharmacist to provide the contracted services and the fact that he/she changed roles in June 2014. Chugai failed to see how a change in role rendered the previous experience of the service provider irrelevant and considered that the answers provided in its initial response were, to a large extent, self-evident.

As previously stated, the pharmacist had established a private company which provided services to industry. This in itself indicated an intention to provide services beyond those of any individual NHS position he/she held and reflected his/her overall experience as a pharmacist.

Chugai submitted that while the detailed reasoning for specifically selecting the pharmacist for each engagement was not always recorded, he/she was chosen for his/her experience as a senior pharmacist at a UK hospital trust. Chugai was confident that the pharmacist was an appropriate choice of consultant and the relevant expertise was self-evident and explained in every situation.

Please explain the pharmacist's particular expertise. When looking for consultants to provide the services in question, were any other candidates considered? How much influence did the senior manager have in nominating and selecting the pharmacist for each role?

Chugai submitted it was self-evident that a change in role did not suddenly negate the experience obtained in previous positions; such a contention was counter-intuitive to senior management appointments in all areas of business and medicine.

Chugai reiterated its comments above regarding nepotism and the scope and principles of the Code. However, it indicated the specific involvement of the senior manager subject to this complaint in each of the five identified engagements.

September 2014: advisory board

The senior manager did not specifically select the pharmacist, but, he/she approved his/her fee (which was in accordance with other fees paid to the other advisory board members). The fee settlement was countersigned by finance.

October 2014: Therapy area report

The senior manager did not specifically select the pharmacist, but as the line manager of the organiser he/she would have overruled any inappropriate selection and additionally he/she had a role in approving the budget and service fee.

October 2014: advisory board

The senior manager did not specifically select the pharmacist, but as the line manager of the organiser he/she would have overruled any inappropriate selection and additionally had a role in approving the budget and service fee. The fee settlement was countersigned by finance.

October 2014: Staff training

The selection of the pharmacist was made by another senior manager. The senior manager in question had a role in approving the budget and service fee and the settlement was countersigned by finance.

December 2014: Budget impact model and formulary pack

Chugai noted that other potential providers were approached for this work. One was unavailable; the other submitted an unfavourable pricing proposal; the pharmacist was selected on the combined basis of his experience, price and availability. The senior manager at issue did not select the pharmacist, but as the line manager of the person who did, he/she

would have overruled any inappropriate selection and additionally had a role in approving the budget and service fee. The fee for settlement was signed by two senior directors.

Licensing reports

Regarding the remaining two engagements for the pharmacist to write a licensing report for medicines in areas of clinically unmet need; please explain the pharmacist's relevant expertise in these therapy areas. When looking for consultants to provide the services in question, were any other candidates considered? How much influence did the senior manager have in nominating and selecting the pharmacist for each role?

Chugai repeated its comments above regarding the expertise of those who selected the pharmacist, the implication of nepotism and the scope and principles of the Code. However, Chugai indicated the specific involvement of the senior manager on each of the two identified occasions.

The questions related to the suitability of the pharmacist to provide the contracted services and particularly whether he/she had the relevant therapy area knowledge. In making decisions related to the licensing-in of a product, much of the decision was related to the commercial viability based on likely uptake rather than a detailed analysis of the therapeutic condition *per se*.

The pharmacist's whole career experience was highly relevant in providing an overview of the perceived advantages and disadvantages of new therapies from the perspective of clinical uptake and therefore commercial viability.

Chugai reiterated that the pharmacist had established a private company as the vehicle by which services were provided to industry. This indicated an interest in providing services beyond those of any individual NHS position held, and reflected his/her overall experience as a pharmacist.

October 2014: licensing report

The senior manager at issue was not involved in the nomination or selection of the pharmacist for this service. The appointment was made by another senior manager, approved by the senior manager at issue, and countersigned by finance.

November 2014: licensing report

The senior manager was not involved in the nomination or selection of the pharmacist for this service. The appointment was made by another senior manager, approved by finance, and countersigned by a senior director.

During the period that the pharmacist has worked for Chugai, have any other consultants provided similar services? What proportion of Chugai's consultancy work has been awarded to the pharmacist compared with other consultants?

Chugai did not see the relevance of these questions in relation to the Code or in relation to the complaint. The Code did not limit the number of times a consultant was selected, nor did it indicate the number of times one consultant could be used compared with any other.

Self-evidently, other consultants were used at advisory boards; typically seven other individuals at each advisory board. Other health professionals had spoken at Chugai-organised internal and external meetings.

Chugai had only commissioned two reports on licensed-in medicines; both were awarded to the pharmacist with a fee of £300 paid for each.

Other consultants and agencies had been commissioned to produce materials for Chugai during the three-year period in question.

Chugai's total spend on consultants in 2014 was provided. A variety of consultancy services were managed which included advisory board attendance, speaker fees, training and support. Of the one hundred and twenty three engagements organised in 2014, seven were contracted with the pharmacist.

Chugai's total spend on consultants in 2013 was provided. A variety of consultancy services were managed which included advisory board attendance, speaker fees, training and support. Of the eighty-nine engagements organised in 2013, none were contracted with the pharmacist.

Chugai's total spend on consultants in 2012 was provided. A variety of consultancy services were managed which included advisory board attendance, speaker fees, training and support. Of the eighty-seven engagements organised in 2012, two were contracted with the pharmacist.

When the pharmacist has been asked to participate in a meeting, has the senior manager/personal friend also been present at the meeting?

Chugai failed to see the relevance of this question to the Code the principles and wording of which, quite rightly, focused on legitimate need for the service, relevant expertise and on the appointment of a consultant not being an inducement for the consultant to prescribe or recommend etc, products of the engaging company.

While Chugai did not record the attendance of individual members of staff at every meeting, the senior manager had indicated that he/she was not present in the majority of the actual meetings. However he/she was likely to have been in the Chugai office on some occasions and would have acknowledged the pharmacist during a coffee break.

Please comment specifically on the complainant's allegation that the senior manager often boasts of his/her friendship with the pharmacist and of his/her promise to put him/her in touch with, and introduce him to, Chugai's business partners to get

some extra work. Would those business partners have included a named agency?

Chugai submitted that this question related directly to the integrity and professionalism of the company and of the individual senior manager without any direct relevance to a specific clause within the Code.

Chugai submitted that it was not possible for the company to know which business partners the complainant had referred to. The senior manager categorically denied making any such statements. Chugai refuted the allegation outright.

What has Chugai done to ensure that the relationship between the pharmacist and the company/senior manager remained wholly professional and unbiased?

Chugai stated it was unclear which specific allegation in the complaint and which clause number this question related to.

Chugai stated that it had provided a copy of the consultant engagement SOP and indicated the number and nature of all the consultant engagements with the pharmacist including details of the arrangements. It submitted that all were appropriate and within the scope of the Code.

The involvement of the senior manager in question in making the selections was limited, but was irrelevant from a Code perspective unless the health professional was chosen for his/her influence on Chugai business, which was neither the allegation nor for which was there any evidence.

A 'conflict of interest' register was presented to the Chugai leadership team for completion from 2013. At that time the senior manager did not declare the friendship as a potential conflict of interest. Chugai noted that there was no requirement in the Code for a conflict of interest register.

Did Chugai know about the personal relationship between the pharmacist and its manager before it received this complaint? Has the manager ever declared a possible conflict of interest regarding his/her personal relationship?

Chugai submitted it was unclear which specific allegation in the complaint and which clause number these questions related to.

Chugai stated that some members of staff within Chugai knew about the friendship between the senior manager and the pharmacist. The investigations for this complaint revealed that it was a close friendship. It was not formally declared or registered. As a result of this complaint, Chugai would reiterate the importance of the register and also expand its use beyond the leadership team.

Regardless, Chugai had no evidence that the friendship had influenced either the selection of service provider, or that the pharmacist made inappropriate decisions about Chugai's products or business, or that any of the engagements involving the pharmacist were in breach of the Code.

The pharmacist had not declared any conflict of interest to Chugai.

Chugai's contracts required the pharmacist to declare to his/her NHS employers any relevant interactions with Chugai. There was no requirement for Chugai to check that he/she had done so and it had not interviewed the pharmacist in the course of this investigation.

Chugai submitted it was unclear which specific allegation in the complaint and which clause number this related to.

Please provide a copy of the agreement between Chugai and its agency and any relevant correspondence between the parties relating to the pharmacist. Did Chugai provide its agency with a list of potential consultants? At what stage did Chugai know that its agent had engaged the pharmacist?

Chugai provided a copy of the agreement between Chugai and its agency.

The Chugai project was originally commissioned from a specialist agency, and the proposal provided was from the project manager. When the specialist agency was disbanded part way through the project, the project manager moved to a new agency, and transferred the project to the new company for completion. Hence the original proposal provided was signed while the project was delivered by another agency.

Chugai reiterated that its agency independently decided to secure services from the pharmacist. Chugai did not provide its agency with a list of potential consultants.

Chugai became aware of the pharmacist's involvement when the project was first proposed. The agency planned to use two consultants, the pharmacist and a second consultant. Chugai was not given the details regarding the various activities that each consultant would undertake.

In summary, Chugai stated that it stood by its original response and that it acted in good order in its selection of consultants. Chugai rejected the allegations in full.

Chugai was very concerned that the complainant was anonymous and non-contactable; he/she had not provided any evidence or material in support of the serious allegations. The company was very concerned that this allegation could damage the good reputation of the company and of the individuals concerned.

PANEL RULING

The Panel noted that the health professional in question was first engaged as a consultant by Chugai in December 2011, to sit on an advisory board, and then not again until July and September 2012 and

September, October and December 2014. Chugai had only been asked to consider activities which had taken place since March 2012. The relevant Codes were thus the 2012 and 2014 editions.

The Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. The complainant was non-contactable and so could not be asked to provide further details. The complainant had provided 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 complainant stated that he/she had been uncomfortable with the closeness of the relationship between the health professional and the senior manager and had not felt able to bring it to the attention of Chugai senior management – who, it seemed from Chugai's submission, appeared to have been unaware of the closeness of the friendship.

The Panel noted that Clause 20 of the 2012 and 2014 Codes covered the use of consultants and was identical in each Code. Clause 20.1 in each Code set out the following criteria that should be met when a company used a health professional as a consultant or advisor. A written contract or agreement must be in place before services were provided and it must specify the services to be undertaken and the basis for payment. A legitimate need for such services must be identified in advance and the criteria for selecting the consultant(s) must be directly related to the identified need; the person selecting the consultant must have the expertise necessary to evaluate whether the particular consultant met those criteria. The number of consultants must be no more than reasonably necessary to achieve the identified need and the company must retain records concerning, and make appropriate use of, the services provided by consultants. The hiring of a consultant must not be an inducement to prescribe, supply, administer, recommend, buy or sell any medicine and the compensation provided must reflect the fair market value of the services provided. Token consultancy arrangements were not acceptable. The contract with a consultant must include provisions that the consultant was obliged to disclose his/her consultancy whenever he/she wrote or spoke about a matter in public which was the subject of the agreement or any other issue relating to that company.

The Panel noted Chugai's concern about the number of questions it had been asked and that some of the questions were about matters which it submitted were beyond the scope of the Code. The Panel noted that the details requested were so that it could fully understand the relationship between the parties and the context in which the health professional had been engaged by Chugai to evaluate the complaint in relation to the criteria set out in Clause 20 of the 2012 and 2014 Codes.

The Panel considered that in addition to the criteria that should be met when a company used a health professional as a consultant or advisor, the impression created by the arrangements was also very important. The Panel noted Chugai's submission that the health professional was a close, personal friend of Chugai's senior manager; their friendship pre-dated the health professional's engagement as a consultant to Chugai. In the Panel's view it was extremely important that clear distinctions were made between business and personal arrangements. Given the relationship between the health professional and the senior manager, it would be difficult for the engagement of the health professional not to be seen as a direct consequence of that relationship. The Panel noted that in many of the consultancy agreements, the senior manager had played some role, albeit that he/she did not have sole responsibility for the arrangements. Some of the senior manager's direct line reports had been responsible for selecting the health professional in question as a consultant/advisor to the company and the senior manager had then approved the budget and service fee. The Panel was concerned that despite a 'conflict of interest' register being presented to the Chugai leadership team for completion from 2013, the senior manager had not declared his/her friendship with the health professional involved. The Panel considered that the senior manager's conduct in this regard had not maintained high standards. A breach of Clause 9.1 was ruled. Although some members of staff within Chugai knew about the friendship between the senior manager and the health professional, the closeness of the friendship had only been discovered as a result of this complaint.

The Panel noted that the health professional in question had been paid £1,325 for his/her services in 2012 plus £49.20 expenses; this was less than 1% of Chugai's total spend on consultants that year. In 2013 he/she had not been contracted by Chugai at all but in 2014, although he/she carried out only seven contracts for the company (less than 6% of the total number of contracts (n=123)), he/she was paid £28,225 plus expenses – around 29% of the company's total spend on consultants for that year (not including the agency project). The Panel was concerned about the impression that this might have been given to those within Chugai who knew about the friendship between the health professional and the senior manager.

In addition to the above in 2014, Chugai commissioned an agency to develop four projects to support the market growth of one of its medicines. The agreement between Chugai and the agency showed that the core project was to support an NHS tender for its medicine in a particular location. The total value of the project was £35,000 with some of that money (amount unknown by Chugai) being paid to the health professional via a sub-contract with the agency to build a health economic model. The Panel considered that in these circumstances it was very important that all relevant people were aware of the involvement of the health professional at issue. Further, in the Panel's view the amount paid to the health professional, if he/she was contracted personally and not via his/her company, would have to be disclosed by Chugai as part of its aggregate disclosure for 2014 given the agency had engaged him/her on behalf of Chugai.

The Panel noted its comments above and that the complainant had provided 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 thus ruled no breach of Clause 20.1 of the 2012 and 2014 Codes. It also ruled no breach of Clause 18.7 of the 2014 Code for those consultancies where the health professional had been contracted through his/her company. The Panel thus also ruled no breach of Clause 18.1 of the 2012 and 2014 Codes. The Panel noted Chugai's submission that the health professional had received only limited hospitality in attending three advisory board meetings and two internal training meetings. Further, a review of expense claims by Chugai showed the company had not arranged or funded any private social occasion. The complainant provided no evidence to the contrary. No breaches of Clause 19.1 of the 2012 and 2014 Codes were ruled.

The Panel noted its rulings above, and although it had some concerns about the consultancy arrangements it considered that Chugai had not brought discredit upon, or reduced confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

During its consideration of this matter, the Panel noted with concern that only 2 of the 9 consultancy agreements with the health professional in question had been countersigned by Chugai; one had not been signed by either party. Chugai had noted these errors and stated that procedures would be reviewed and staff retrained.

B General Code compliance

COMPLAINT

The complainant alleged that during his/her time in Chugai there was a somewhat laissez-faire attitude to ABPI compliance. A senior manager often mocked the Code and referred to it as a tick box exercise. The complainant alleged that a number of members of the senior sales team, were not ABPI certified; the company seemed to turn a blind eye to this. This laissez-faire attitude sometimes seemed to permeate through the company and the complainant stated that he/she often considered that the company conveniently referred to the fact that as a Japanese company it was relationship based and that the Code was more for big pharmaceutical companies.

Response

Chugai noted that although Clause 16.2 was not specifically listed by the case preparation manager, it would respond to the allegations concerning the ABPI Representatives Examination.

Chugai submitted that the director, referred to in the complaint, did not need to take the ABPI Representatives Examination as he/she was a national (second-line) director whose role was primarily strategic. However, Chugai decided that he/she should sit the examination and he/she had been granted a short extension. He/she sat the examination within the extended period and was expected to pass it within the required 2 years.

The only other senior manager who had not yet passed the ABPI Representatives Examination sat the examination within the required 12-month period and was expected to pass it within the required 2 years from joining the company.

Chugai provided copies of the ABPI Representatives Examination certificates for relevant senior staff.

With regard to general Code compliance, Chugai submitted that it had developed a comprehensive range of UK SOPs to ensure that processes were in place to meet the requirements of the Code. SOPs were reviewed at least annually to ensure compliance. The 13 current SOPs covered topics including meetings and hospitality, interactions with patient organisations, use of consultants and certification. During 2015, further SOPs would be developed to address the new disclosure requirements.

All employees were required to read SOPs before undertaking any new task and at least annually, sign to confirm they had read and understood the SOPs relevant to their role according to a predefined categorisation.

Compliance staff typically attended at least two specialist compliance conferences a year to ensure maintenance of appropriate knowledge and skills.

All employees attended an induction training course (ITC) day one of which included a 45 minute presentation from compliance on the importance of compliance and the Code and of personal integrity when making business decisions. There was also a 1 hour presentation from the quality assurance department on the general SOPs; the delegates subsequently undertook self-study of the relevant SOPs and received follow-up training within their departments. New starters had to complete SOP training within one month of joining the company.

Sales teams received compliance training, at least annually, for their role. Compliance provided updates to the sales teams on developments in SOPs and the Code at internal meetings. The next update was due 23 March 2015. In addition, all sales staff undertook an annual online Code course from an independent external supplier. Compliance also ran a bi-monthly internal Code awareness group where Code-related events were discussed and company-based guidance was reviewed. Changes in guidance were then distributed to all staff.

The business subscribed to a monthly update service from an independent compliance specialist to ensure that a high awareness was maintained of evolving issues and Code cases.

All employees had a training record which was checked and signed at least annually by line managers; copies were stored in head office.

All staff had to successfully complete on-line training on changes to the Code and passed the module 'ABPI Code of Practice 2015: What is New'. All staff were required to successfully complete additional on-line training on elements that were considered high risk with regard to good governance (UK Bribery Act 2010, Data Protection Act 1998, social media awareness, and IT risks).

Chugai submitted that it operated a comprehensive governance framework, including a full suite of SOPs related to Code compliance. All employees were trained annually in SOPs relevant to their role and all received regular Code training and updates. The company denied a breach of Clauses 2, 9.1 or 16.1.

FURTHER INFORMATION FROM CHUGAI

Chugai noted that it had been asked to address the complainant's statement that a senior manager often mocked the Code and referred to it as a tick box exercise and to explain what could have led the complainant to make such an allegation. Chugai submitted that these questions related directly to the integrity and professionalism of the company and its senior manager.

Chugai stated that the senior manager was interviewed by an external compliance specialist and strongly denied making any such comments about 'tick-box exercises' and most certainly did not mock the Code. The senior manager was a champion for the Code internally and was also known to the PMCPA and the ABPI as being active in compliance and sat on compliance-related working groups and spoke at international compliance congresses. A copy of the last presentation by the senior manager at an induction training course was provided.

In summary, Chugai stated that it stood by its original response and that it acted in good order in its approach to Code compliance. Chugai rejected the allegations in full.

PANEL RULING

The Panel again noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. The complainant had not provided any evidence or cited any specific event to support his/her allegations. The Panel noted that the Code training slides provided by Chugai did not appear to be unreasonable either in tone or content. The Panel noted Chugai's submission regarding on-line training, monthly updates on the Code, the Code awareness group and the attendance of key staff at compliance conferences and considered that there was no evidence to suggest that training was a 'tick box' exercise or that the company took a laissez-faire attitude to compliance. The Panel considered that on the evidence before it, there was nothing to suggest with regard to training etc, that high standards had not be maintained. No breach of Clause 9.1 was ruled.

The Panel noted the allegation that senior members of the sales team, were not ABPI certified. The Panel further noted that Chugai had provided the ABPI Representatives Examination certificates for a number of its relevant senior staff and had explained why the director and one of the senior managers had yet to pass the examination. In that regard the Panel considered that staff had taken or would take the ABPI examination in accordance with the requirements of the Code and it ruled no breach of Clause 16.1.

The Panel noted its rulings above and ruled no breach of Clause 2.

Complaint received **26 February 2015**

Case completed **12 May 2015**

ACTELION v GLAXOSMITHKLINE

Promotion of Volibris

Actelion UK and Ireland complained about two leavepieces for Volibris (ambrisentan) issued by GlaxoSmithKline UK.

A four page leavepiece headed 'Endothelin Receptor Antagonists – Drug Drug Interactions' featured a table on page 2 which listed a number of medicines down the side of the page and set out whether they could be used with bosentan (Tracleer), macitentan (Opsumit) and Volibris. These three medicines were listed across the top of the page and next to each was a reference to that medicine's summary of product characteristics (SPC). Various intersecting boxes in the table were coloured red, amber, green or grey. The grey boxes denoted that the drug drug interaction was 'Unknown' and the green boxes denoted 'No clinically relevant effect'.

Actelion noted to the requirement that when material referred to published studies, clear references must be given. The leavepiece appeared to quote the Volibris SPC as the reference for most of the information on interactions. However, Actelion could find no reference in the SPC to interactions with clarithromycin, tacrolimus and ritonavir and alleged that this information was thus unsubstantiated.

The detailed response from GlaxoSmithKline is given below.

The Panel noted that material had to be capable of substantiation and that substantiation to be provided on request. In addition references were required in certain circumstances including when promotional material referred to published studies.

The Panel noted GlaxoSmithKline's submission that the substantiation for the information regarding interactions with clarithromycin, tacrolimus and ritonavir were a number of studies and not the Volibris SPC. The Panel did not consider that the table at issue referred to a published study as such. The material provided to substantiate certain information was a number of studies but given the context there was no need to reference these studies in the leavepiece itself. Thus the Panel ruled no breach of the Code.

Actelion alleged that the leavepiece did not contain sufficient information to allow readers to make their own opinion as to the therapeutic value of the medicine. In inter-company correspondence Actelion referred to the fact that the leavepiece only provided information on drug interactions.

The Panel noted that as the leavepiece was headed 'Endothelin Receptor Antagonists – Drug Drug Interactions' readers would expect information about drug drug interactions. Health professionals would have to use other sources for information about the efficacy of the medicines listed. In the circumstances the Panel considered that only referring to interactions in the leavepiece did not mean that the leavepiece was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine as alleged. No breach was ruled.

The second piece was an A5 leavepiece headed 'Stockley's Drug Interactions Chart'. Stockley's corporate brand colours were used in the leavepiece which unfolded to an A3 sheet one side of which, in the form of a chart, was an 'at-a-glance' guide to common interactions between medicines frequency used in pulmonary arterial hypertension. A section to the right hand side of the chart advertised Stockley's Drug Interaction book. Beneath this was the GlaxoSmithKline corporate logo and a statement 'This interaction chart is produced through an educational grant from GlaxoSmithKline and is provided as an educational guide for health care professionals. The content of this material has been produced independently by the editorial team of Stockley's Drug Interactions'.

Actelion was concerned that the leavepiece was ambiguous in its purpose ie was it a promotional or educational item? Actelion noted that the sponsorship statement indicated the leavepiece was provided as an educational guide for health professionals. However, the reverse of the leavepiece included prescribing information for Volibris; this was not in line with PMCPA guidance that medical and educational goods and services must not bear the name of any medicine.

The Panel considered that the leavepiece was a piece of promotional material for Volibris which included the interaction chart. In effect the leavepiece also included several advertisements for Stockley's publications. The Panel considered that the description of GlaxoSmithKline's involvement could have been better worded but there was no prohibition under the Code to providing education as part of a promotional item. Indeed promotion should be informative and educational. The leavepiece was not a medical or educational good or service as meant by the Code and no breach was ruled.

Actelion UK and Ireland Limited submitted a complaint about two pieces of promotional material for Volibris (ambrisentan) issued by GlaxoSmithKline UK Limited. Volibris was indicated for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO (World Health Organisation) Functional Class II and III, to improve exercise capacity. The materials at issue were two charts; one chart compared the drug interactions observed with bosentan, macitentan (Actelion's

products Tracleer and Opsumit respectively) and Volibris (ref UK/ABT/0023/14) and the other, using data from a standard textbook, compared the interactions between medicines frequently used in PAH, and included ambrisentan and bosentan (ref UK/ABT/0059/13). The intended audience for each leavepiece was clinicians experienced in PAH working in one of the seven UK adult PAH reference centres and prescribing target oral therapy for PAH.

This case was considered under the 2014 Code using the 2015 Constitution and Procedure.

A Interaction Chart (ref UK/ABT/0023/14)

This four page leavepiece was used between 3 September 2014 and 28 February 2015 and was headed 'Endothelin Receptor Antagonists – Drug Drug Interactions'. Page 2 featured a table which listed a number of medicines down the side of the page and set out whether they could be used with bosentan (Tracleer), macitentan (Opsumit) and Volibris. These three medicines were listed across the top of the page and next to each was a reference to that medicine's summary of product characteristics (SPC). Various intersecting boxes in the table were coloured red, amber, green or grey. Each box included text. Grey boxes denoted that the drug drug interaction was 'Unknown' and green boxes denoted 'No clinically relevant effect'. Page 3 was headed 'safety information' and referred to adverse reactions associated with Volibris. Prescribing information for Volibris was included on the outside back page.

1 Interactions with clarithromycin, tacrolimus and ritonavir

COMPLAINT

Actelion noted that Clause 7.6 stated that when material referred to published studies, clear references must be given. In that regard, Actelion noted that the leavepiece appeared to quote the Volibris SPC as the reference for all information on interactions except for those with mycophenolate mofetil and omeprazole. However, Actelion stated that it could find no reference in the Volibris SPC to interactions with clarithromycin, tacrolimus and ritonavir and alleged that this information was thus unsubstantiated.

RESPONSE

GlaxoSmithKline noted that the Code required all claims to be capable of substantiation and that substantiation be provided promptly when requested. References were only mandatory when referring to published studies including the use of quotations, tables, graphs and artwork. GlaxoSmithKline submitted that if Actelion had asked for the information relating to clarithromycin, tacrolimus and ritonavir to be substantiated during inter-company dialogue, it would have supplied Markert *et al* (2013), Mandagere *et al* (2010a) and Gillies *et al* (2011), just as it did for mycophenolate mofetil (Mandagere *et al*, 2010b) and omeprazole (Harrison *et al*, 2009).

PANEL RULING

The Panel noted that material had to be capable of substantiation and that substantiation be provided on request (Clauses 7.4 and 7.5). In addition references were required in certain circumstances including when promotional material referred to published studies.

The Panel noted GlaxoSmithKline's submission that the substantiation for the information regarding clarithromycin, tacrolimus and ritonavir were a number of studies and not the SPC. The Panel did not consider that the table on page 2 referred to a published study as such and thus Clause 7.6 did not apply. The material provided to substantiate certain information was a number of studies but given the context there was no need under Clause 7.6 to reference these studies in the leavepiece itself. Thus the Panel ruled no breach of Clause 7.6.

The Panel considered that the impression given by the reference in the leavepiece to the Volibris SPC was that all the interactions were in that SPC and this was not so. The Panel queried whether the material met the requirements of Clause 7.2 in this regard and requested that this be drawn to GlaxoSmithKline's attention.

2 Material not sufficiently complete

COMPLAINT

Actelion alleged that the leavepiece did not contain sufficient information to allow readers to make their own opinion as to the therapeutic value of the medicine. In inter-company correspondence Actelion referred to the fact that the leavepiece only provided information on drug interactions. A breach of Clause 7.2 was alleged.

RESPONSE

GlaxoSmithKline submitted that the leavepiece was intended to cover the known drug-drug interactions of bosentan, macitentan and Volibris and was not a complete review of the safety or efficacy of the medicines. A succinct safety statement was included in the leavepiece to highlight specific safety issues and provide balance.

PANEL RULING

The Panel noted the heading on page 1 of the leavepiece 'Endothelin Receptor Antagonists – Drug Drug Interactions' and considered that readers would expect information about drug drug interactions. Page 3 of the leavepiece included safety information about Volibris. The table on page 2 included a number of red boxes which were labelled variously including 'avoid macitentan', 'concomitant use not advisable' and 'contraindicated'.

In the Panel's view the leavepiece was designed to provide information about interactions. Health professionals would have to use other sources for information about the efficacy of the medicines listed in the table on page 2. The Panel noted

that Actelion had not provided information about what was missing from the chart in question. In the circumstances the Panel considered that only referring to interactions in the leavepiece did not mean that the leavepiece was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine as alleged. No breach of Clause 7.2 was ruled.

B Stockley's Drug Interaction Chart (ref UK/PAH/0031/13)

The A5 leavepiece was headed 'Stockley's Drug Interactions Chart'. Stockley's corporate brand colours were used in the leavepiece which unfolded to an A3 sheet one side of which, in the form of a chart, was an 'at-a-glance' guide to over 350 common interactions between medicines frequently used in PAH. A section to the right hand side of the chart advertised Stockley's Drug Interaction book. Beneath this was the GlaxoSmithKline corporate logo and a statement 'This interaction chart is produced through an educational grant from GlaxoSmithKline and is provided as an educational guide for health care professionals. The content of this material has been produced independently by the editorial team of Stockley's Drug Interactions'. Three of the four quarters on the reverse of the A3 page included advertising for Stockley's publications. The fourth quarter included the prescribing information for Volibris, information about reporting adverse events and the GlaxoSmithKline corporate logo. The leavepiece was used between 27 March 2014 and October 2014.

COMPLAINT

Actelion alleged that the leavepiece breached Clause 18.4; the company was concerned that it was ambiguous in its purpose ie was it a promotional or educational item? Actelion noted that the sponsorship statement indicated the leavepiece was provided as an educational guide for health professionals. However, the reverse of the leavepiece included prescribing information for Volibris; this was not in line with PMCPA guidance that medical and educational goods and services must not bear the name of any medicine.

RESPONSE

GlaxoSmithKline submitted that the leavepiece was used by its field-based commercial team. It was not a medical or educational good or service as such items must not bear the brand name of any medicine. The leavepiece was promotional and in that regard it was clearly branded with Volibris and carried all the obligatory information including the prescribing information.

The leavepiece advertised the complete Tenth Edition of Stockley's Drug Interactions (a world-renowned resource). As GlaxoSmithKline had commissioned Stockley to produce a chart on PAH drug interactions, information on this funding was provided on the pages where the PAH chart was reproduced. It was described as an educational guide, which GlaxoSmithKline amended to a guide (copy not supplied) when it was superseded by UK/ABT/0023/14 'Endothelin Receptor Antagonists – Drug Drug Interactions' (the leavepiece at issue in A above). The use of the word educational on an item did not constitute it being a medical or educational good or service. GlaxoSmithKline submitted that it wanted prescribers to know that the company had commissioned the PAH interactions chart, but that it had had no input to the classification of the drug interactions noted in the table, which was assessed and created by Stockley. GlaxoSmithKline had no editorial input to the leavepiece but did review and certify the content. This had been clearly explained during inter-company dialogue:

'This leavepiece is not a medical educational goods or service. It is a piece of promotional material which carries the Volibris prescribing information and other obligatory information. It reproduces the interaction table from Stockley that GlaxoSmithKline commissioned and also gives the reader information on the textbook. GlaxoSmithKline do not provide the book or online access. Had we been giving away the actual text book Stockley, then we agree it would have fallen within the scope of a medical or educational good or service.'

GlaxoSmithKline had stated that the leavepiece was a promotional piece and not a medical or educational good or service and, therefore, it denied a breach of Clause 18.4 of the 2014 Code.

PANEL RULING

The Panel examined the leavepiece. It considered that it was a piece of promotional material for Volibris which included the interaction chart. In effect the leavepiece also included several advertisements for Stockley's publications including Stockley's Drug Interactions, Tenth Edition.

The Panel considered that the description of GlaxoSmithKline's involvement could have been better worded but there was no prohibition under the Code to providing education as part of a promotional item. Indeed promotion should be informative and educational. The leavepiece was not a medical or educational good or service as meant by Clause 18.4 of the Code. The Panel thus ruled no breach of Clause 18.4.

Complaint received **9 March 2015**

Case completed **5 June 2015**

ANONYMOUS GENERAL PRACTITIONER v ViiV HEALTHCARE

Promotion of Triumeq

An anonymous general practitioner complained about a Triumeq advertisement issued by ViiV Healthcare UK and published in the BMJ. Triumeq was a fixed dose combination of dolutegravir, abacavir and lamivudine as a single-tablet for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents above 12 years of age who weighed at least 40kg.

The advertisement featured the claim 'inner strength. The only single-pill regimen built with dolutegravir' above the claim 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks'. The claim was referenced, *inter alia*, to Walmsley *et al* (2013, the SINGLE study). The asterisk referred to a footnote 'In studies supporting Triumeq, [dolutegravir 50mg + abacavir 600mg/ lamivudine 300mg] were used. Bioequivalence has been demonstrated. Atripla is not licensed for initial use in treatment-naïve patients'.

The complainant alleged that 'inner strength' implied a panacea against all ills. He also considered it was unfair to compare Truimeq against Atripla outside its licensed indication and queried whether the studies cited actually used the fixed dose combination or just the individual components.

The detailed response from ViiV Healthcare is given below.

The Panel noted that 'inner strength' had the largest font size within the advertisement and was in Triumeq branded colours, directly above the less prominent claim 'The only single-pill regimen built with dolutegravir'. The first part of the claim beneath this began 'The components of Triumeq form the first HIV regimen…'. The Panel considered that it was clear from the advertisement that Triumeq was for the treatment of HIV and thus that 'inner strength' did not imply that the medicine was a panacea for all ills as alleged. No breach of the Code was ruled.

The Panel noted the allegation that it was unfair to compare Truimeq with Atripla outside its licensed indication and considered that in this regard the complainant had referred to the use of Atripla (marketed by Gilead Sciences) outside of its licensed indication although the construction of the relevant sentence in the complaint was such that this was not entirely clear. The Panel noted that ViiV Healthcare had responded on this basis.

The claim 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks', was referenced, *inter alia*, to Walmsley *et al*. The associated footnote stated, *inter alia*, that Atripla was not licensed for initial use in treatment-naïve patients. Walmsley *et al* was one of the Phase III studies upon which the licence for Triumeq had been granted. The double-blind study compared the safety and efficacy of Triumeq (as dolutegravir plus abacavir/ lamivudine ie two tablets) with that of Atripla administered as a single tablet. The patients had not previously received therapy for HIV infection. When the SINGLE study was conducted, Atripla was the only single-tablet regimen preferred in the US HIV treatment guidelines and one of the two recommended single-tablet regimens in the European treatment guidelines.

The Panel noted that Atripla was a once daily fixed dose combination indicated for the treatment of HIV infection. The SPC stated that 'No data are currently available from clinical studies with Atripla in treatment-naïve or in heavily pre-treated patients'.

The Panel noted the complainant's allegation that it was unfair to compare Triumeq with Atripla outside its licensed indication ie because Atripla had been used as initial therapy in HIV patients. The Panel considered that this was a difficult matter. The Code was clear that the promotion of a medicine must be in accordance with its marketing authorization and not be inconsistent with the particulars listed in its SPC. The company was not promoting a competitor medicine and so in that regard the Panel ruled no breach of the Code.

The Panel questioned whether comparing products using an unlicensed dose or treatment regimen of a competitor met the requirements of the Code. Readers might be misled as to the approved use of the competitor product and the company that marketed the competitor product might not be able to use or counter those claims as it might be accused of promoting an unlicensed dose etc. The Panel noted that the claim in question clearly stated that Atripla had been used in treatment-naïve patients. An asterisk next to the mention of Triumeq, rather than Atripla or the reference to treatment-naïve patients, led readers to a footnote, the third sentence of which stated that Atripla was not licensed for initial use in treatment-naïve patients; this appeared to be an acknowledgement from ViiV Healthcare that Atripla had been used outside of its licensed indication. The Panel noted that the supplementary information to the Code stated that claims must be capable of standing alone and that, in general, they should not be qualified by the use of footnotes. The Panel considered that

the claim at issue could not standalone without misleading readers as to the licensed indication for Atripla and on this very narrow point, the Panel ruled a breach of the Code. This ruling was appealed by ViiV Healthcare.

The Appeal Board noted ViiV Healthcare's submission that Atripla was a well accepted first-line treatment for HIV in the UK albeit that it was not licensed for use in treatment-naïve patients and that, given current clinical practice worldwide, Atripla had been accepted as the appropriate comparator in Walmsley *et al* which was cited in the Triumeq summary of product characteristics (SPC). In addition the use of Atripla in treatment-naïve patients was supported by independent treatment guidelines and the medicine was licensed for such use in the US.

The Appeal Board noted that HIV was a highly specialised therapy area. The SPCs for Triumeq and Atripla stated that the medicines had to be respectively 'prescribed' or 'initiated' by physicians 'experienced in the management of HIV infection'. ViiV Healthcare stated that there were currently approximately 800 such physicians in the UK. The Appeal Board considered that such a specialised audience was likely to prescribe medicines off-licence. The Appeal Board noted ViiV Healthcare's submission that such physicians would be familiar with the Atripla licence and would know that first-line use of the medicine had not been approved in the UK.

The Appeal Board noted its comments above and that the advertisement appeared only in the hospital edition of the BMJ. It therefore considered that the claim in question 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks' reflected current clinical practice and in that regard patients were not put at risk. The Appeal Board considered that given the particular set of circumstances and factors discussed above, the claim at issue was not misleading and on this narrow point it ruled no breach of the Code. The appeal was successful.

The Panel noted the complainant queried whether the studies cited had used the fixed dose combination or the individual components. The claim explicitly referred to 'The components of Triumeq…' and to the use of Atripla and not to the use of its components. The Panel considered that the complainant appeared to understand that Atripla as a fixed dose combination had been used. The Panel considered that it was sufficiently clear from the advertisement that Triumeq had been administered as its components and that Atripla had been administered as the single fixed dose tablet and so in that regard the advertisement was not misleading. No breach of the Code was ruled.

An anonymous General Practitioner complained about a Triumeq advertisement (UK/TRIM/0022/14A) issued by ViiV Healthcare UK Limited and published in the BMJ, 14 March 2015. Triumeq was a fixed dose combination of dolutegravir, abacavir and lamivudine as a single-tablet regimen for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents above 12 years of age who weighed at least 40kg.

The top three quarters of the double-page spread advertisement consisted of a visual on the left and narrative on the right-hand side; the prescribing information and other obligatory information occupied the lower quarter of the advertisement. The advertisement featured the claim 'inner strength. The only single-pill regimen built with dolutegravir' above the claim 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks'. The claim was referenced to Walmsley *et al* (2013, the SINGLE study), Walmsley *et al* (2014) and Pappa *et al* (2014). The asterisk directed readers to the footnote 'In studies supporting Triumeq, [dolutegravir 50mg + abacavir 600mg/lamivudine 300mg] were used. Bioequivalence has been demonstrated. Atripla is not licensed for initial use in treatment-naïve patients'.

COMPLAINT

The complainant alleged that 'inner strength' implied a panacea against all ills. He also considered it was unfair to compare Truimeq against Atripla outside its licensed indication and queried whether the studies cited actually used the fixed dose combination (FDC) or just the individual components.

When writing to ViiV Healthcare, the Authority asked it to consider the requirements of Clauses 3.2 and 7.2 of the 2014 Code.

RESPONSE

ViiV Healthcare stated that it was committed to complying with the Code and stated that its medical and commercial signatories were registered in accordance with Clause 14.4.

1 'inner strength'

ViiV Healthcare did not consider that the advertisement at issue implied a panacea against all ills. The Oxford dictionary defined panacea as 'a solution or remedy for all difficulties or diseases'. Individuals would interpret an advertisement in their own way but it was stated in the text immediately below that Triumeq was the 'first HIV regimen....' and ViiV Healthcare thus submitted that it was clear that the advertisement related to HIV only and that it was not ambiguous or misleading as a potential treatment for any other disease, condition or illness. There was no breach of Clause 7.2.

2 Comparison with Atripla

ViiV Healthcare noted that Atripla was the first single-tablet regimen to become available in December 2007; it gave patients a simple and more convenient way of treating their HIV with three established antiretroviral agents. The European AIDS Clinical Society (EACS) Guidelines recommended two

nucleos(t)ides with either a non-nucleoside, boosted protease inhibitor or integrase inhibitor; furthermore the guidelines specifically recommended, when appropriate, that the components of Atripla be given as the single-tablet in HIV treatment-naïve patients. Given the success of this co-formulation, recently approved HIV single-tablet regimens had compared themselves with Atripla as a gold standard; this included Triumeq and Stribild, licensed in May 2013. ViiV Healthcare submitted that the comparison of Triumeq with Atripla in the SINGLE study was appropriate and reflected clinical practice. To enable prescribers to make an informed clinical decision ViiV Healthcare believed it was important to communicate the results of the SINGLE study, whereby Triumeq was superior to Atripla.

Furthermore, the advertisement focussed on Triumeq and communicated the results of the SINGLE study and therefore could not be deemed to promote another company's product. As Triumeq was licensed for the treatment of HIV infected adults and adolescents above 12 years of age weighing at least 40kg, ViiV Healthcare submitted that the advertisement was not in breach of Clause 3.2.

3 Fixed dose combination or individual components?

ViiV Healthcare noted that the advertisement explicitly stated that 'In studies supporting Triumeq, [dolutegravir with abacavir/lamivudine] were used. Bioequivalence has been demonstrated'.

The European Medicines Agency (EMA) approved Triumeq based on the clinical trial data from three large Phase III studies (Walmsley *et al* (SINGLE), Raffi *et al* 2013 (SPRING-2) and Clotet *et al* 2014 (FLAMINGO)) and the results of a bioequivalence study (Weller *et al* 2014). ViiV Healthcare submitted that the advertisement was consistent with Clause 7.2 given that the information was based on the Triumeq summary of product characteristics (SPC) dated September 2014.

Summary

ViiV Healthcare did not consider that the advertisement was misleading or ambiguous or that it promoted outside the Triumeq licence and as such did not breach Clauses 3.2 and 7.2.

PANEL RULING

The Panel noted that the complainant's allegation that the claim 'inner strength' implied that Triumeq was a panacea for all ills. The Panel noted that 'inner strength' had the largest font size within the advertisement and was in Triumeq branded colours, directly above the less prominent claim 'The only single-pill regimen built with dolutegravir'. The first part of the claim beneath this began 'The components of Triumeq form the first HIV regimen…'. The Panel considered that it was clear from the advertisement that Triumeq was for the treatment of HIV and thus the claim in question, 'inner strength', did not imply that the medicine was a panacea for all ills as alleged. There was no direct or indirect reference to any other medical condition. No breach of Clause 7.2 was ruled.

The Panel noted the allegation that it was unfair to compare Truimeq with Atripla outside its licensed indication and considered that in this regard the complainant had referred to the use of Atripla (marketed by Gilead Sciences) outside of its licensed indication although the construction of the relevant sentence in the complaint was such that this was not entirely clear. The Panel noted that ViiV Healthcare had responded on this basis.

The claim 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks', was referenced, *inter alia*, to Walmsley *et al*. The asterisk led to a footnote which stated, *inter alia*, that Atripla was not licensed for initial use in treatment-naïve patients. Walmsley *et al* was one of the Phase III studies upon which the licence for Triumeq had been granted. The study compared the safety and efficacy of Triumeq (as dolutegravir plus abacavir/lamivudine ie two tablets) with that of Atripla administered as a single tablet (placebo tablets were used to double-blind the study and all patients received three tablets a day). The patients had not previously received therapy for HIV infection. The investigators noted that when they conducted the SINGLE study, the comparator, Atripla, was the only single-tablet regimen preferred in the US HIV treatment guidelines and it was also one of the two recommended single-tablet regimens in the European treatment guidelines.

The Panel noted that Atripla was a once daily fixed dose combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate which according to its SPC was 'indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Atripla prior to initiation of their first antiretroviral treatment regimen'. The SPC also stated, *inter alia*, that 'No data are currently available from clinical studies with Atripla in treatment-naïve or in heavily pre-treated patients'.

The Panel noted the complainant's allegation that it was unfair to compare Triumeq with Atripla outside its licensed indication ie because Atripla had been used as initial therapy in HIV patients. The Panel considered that this was a difficult matter. Clause 3 of the Code was clear that the promotion of a medicine must be in accordance with its marketing authorization and not be inconsistent with the particulars listed in its SPC. A company would not be promoting a competitor medicine and so in that regard the Panel considered that Clause 3 would not apply and so it ruled no breach of Clause 3.2.

Clause 7.2 of the Code required that information, claims and comparisons be accurate balanced, fair, objective, unambiguous and based on an up-to-

date evaluation of all the evidence and reflect that evidence clearly. Claims must not mislead either directly or by implication. The Panel questioned whether comparing products using an unlicensed dose or treatment regimen of a competitor met the requirements of Clause 7.2. Readers might be misled as to the approved use of the competitor product and the company that marketed the competitor product might not be able to use or counter those claims as it might be open to accusations of promoting an unlicensed dose etc. The Panel noted that the claim in question clearly stated that Atripla had been used in treatment-naïve patients. An asterisk next to the mention of Triumeq, rather than Atripla or the reference to treatment-naïve patients, led readers to a footnote, the third sentence of which stated that Atripla was not licensed for initial use in treatment-naïve patients; this appeared to be an acknowledgement from ViiV Healthcare that Atripla had been used outside of its licensed indication. The Panel noted that the supplementary information to Clause 7 stated that claims must be capable of standing alone and that, in general, they should not be qualified by the use of footnotes. The Panel considered that the claim at issue could not standalone without misleading readers as to the licensed indication for Atripla and on this very narrow point, the Panel ruled a breach of Clause 7.2. This ruling was appealed.

The Panel noted the complainant queried whether the studies cited had used the fixed dose combination or just the individual components. The Panel noted that the central claim explicitly referred to 'The components of Triumeq…' and to the use of Atripla and not to the use of its components. The Panel considered that given the complainant's concerns about the comparison of Triumeq with Atripla, he had appeared to understand that Atripla as a fixed dose combination had been used. The Panel considered that it was sufficiently clear from the advertisement that Triumeq had been administered as its components and that Atripla had been administered as the single fixed dose tablet and so in that regard the advertisement was not misleading. No breach of Clause 7.2 was ruled.

APPEAL BY VIIV HEALTHCARE

ViiV Healthcare noted that the Panel had ruled a breach of Clause 7.2 on the very narrow point that the claim could not stand alone without misleading the readers as to the licensed indication of Atripla. ViiV Healthcare submitted that UK HIV physicians would not be misled by the claim at issue as they were extremely familiar with Atripla and had used it as an initial regimen for the treatment of HIV for nearly eight years.

ViiV Healthcare stated that its appeal against the Panel's ruling was based on four interlinked elements:

1 HIV treatment regimens must be prescribed by expert physicians only

ViiV Healthcare noted that both the Triumeq and Atripla SPCs stated that treatment should be initiated by a physician experienced in the management of HIV infection and thus the audience for this advertisement were experts in the field of HIV. Those who were not HIV experts should not initiate treatment.

ViiV Healthcare noted that the advertisement was placed in the hospital edition of the BMJ, which reached over 70,000 hospital doctors in the UK who were members of the BMA. The journal was chosen as it was read by approximately 52% of senior infectious disease specialists in the UK. The advertisement did not appear in the version of the BMJ which was sent to GPs only.

2 Atripla was well known to the HIV expert audience and known to be prescribed as initial HIV treatment

ViiV Healthcare noted that the components of Atripla had been licensed for initial treatment of HIV in the UK for over a decade: efavirenz (EFV) in 1999, tenofovir disoproxil fumarate (TDF) in 2002 and emtricitabine (FTC) in 2003; the fixed dose combination of FTC/TDF was licensed in 2005. (Sastiva, Viread and Emtrivia SPCs). ViiV Healthcare submitted that HIV physicians were very familiar with the combination of EFV/TDF/FTC and the three components had been recommended as a preferred initial regimen by the British HIV Association (BHIVA) since 2005 (BHIVA Guidelines 2005 and 2014).

ViiV Healthcare noted that the first single tablet regimen, Atripla (EFV/TDF/FTC), was licensed in Europe in 2007 and established itself as the standard of care for treatment-naïve patients with HIV in the UK despite its licensed indication requiring initial suppression by another regimen. ViiV Healthcare submitted that it must be mindful that prescribers were not bound by licensed indications and could prescribe any treatment for any condition if they considered it was in the best interests of their patients and were prepared to justify that decision if need be; this was endorsed by treatment guidelines which highlighted the importance of individualising therapy (BHIVA Guidelines 2014, EACS Guidelines (version 7.1), November 2014, International AntiViral Society (IAS) USA Guidelines 2014, Department of Health and Human Services (DHHS) Guidelines, April 2015).

ViiV Healthcare provided a letter dated 1 May 2015 from an HIV specialist which verified that HIV physicians in the UK clearly considered there was adequate evidence of the efficacy and safety of using Atripla in this way, as did the US regulators where it was licensed for initial treatment (Atripla US prescribing information (January 2015). Current practice supported the use of Atripla outside the terms of its UK licence as it was still the most commonly used first-line regimen for HIV in the UK, with nearly eight years' experience. Thus it was clear that UK HIV physicians were extremely familiar with Atripla and would not be misled by the claim at issue or need any further information to enable them to understand the relevance of the claim to their clinical practice.

3 Atripla was used as the comparator arm in treatment-naïve studies as the current standard of care

ViiV Healthcare submitted that the EMA acknowledged and accepted Atripla as the appropriate comparator in the registrational trial, SINGLE, which was used to support regulatory submissions for both Tivicay and Triumeq (Tivicay and Triumeq SPCs); Atripla was also used by Gilead for the Stribild submission (Stribild SPC). All of these medicines used the data from their registration studies in their promotional campaigns. In all of these studies, Atripla was used outside the terms of its European licence as initial therapy and the EMA had accepted the results of these studies and included details of them in the respective SPCs. There were no caveats or qualifications around the use of Atripla as the comparator in the therapy-naïve population in the Triumeq SPC where the SINGLE study was discussed:

> 'The efficacy of Triumeq in HIV-infected, therapy naïve subjects is based on the analyses of data from two randomized, international, double-blind, active-controlled trials, SINGLE (ING114467) and SPRING-2 (ING113086) and the international, open-label, active-controlled trial FLAMINGO (ING114915).'
>
> 'In SINGLE, 833 patients were treated with dolutegravir 50mg once daily plus fixed-dose abacavir-lamivudine (DTG + ABC/3TC) or fixed-dose efavirenz-tenofovir-emtricitabine (EFV/TDF/FTC).'
>
> 'EFV/TDF/FTC = efavirenz 600mg, tenofovir 300mg, emtricitabine 200mg in the form of Atripla FDC.'

Consequently, ViiV Healthcare submitted that as it was important to promote Triumeq appropriately and in a manner wholly consistent with its SPC, the comparison with Atripla from SINGLE was both fair and clinically relevant and reflected current UK practice. ViiV Healthcare submitted that if it was unable to include balanced and objective references to Atripla (as an acceptable comparator arm) in dolutegravir's key registration study, it would restrict communication of critical information about HIV medicines to health professionals; this could indirectly impact health professionals' decision-making, rationale prescribing choices and optimal selection of individual antiretroviral agents thereby reducing the benefits to patients.

4 The claim stood alone and was not qualified by a footnote

ViiV Healthcare noted, as the Panel acknowledged, a company would not promote a competitor product and the claim at issue clearly promoted Triumeq, not Atripla, and the study upon which the claim was based reflected the current use of Atripla in the UK and thus it was a fair comparison and was not misleading.

ViiV Healthcare submitted that the claim related to the superiority of Triumeq over Atripla, a commonly prescribed initial treatment for HIV in the UK. HIV physicians would not be misled as to the approved use of Atripla as this was how they had used it for nearly eight years. However, as this was off-label use of Atripla, a statement to this effect should be included and was added as a final line in the advertisement to ensure transparency. It did not qualify the claim, but acknowledged the licence status of Atripla; not to do so could be considered misleading.

COMMENTS FROM THE COMPLAINANT

There were no comments from the complainant.

APPEAL BOARD RULING

The Appeal Board noted ViiV Healthcare's submission that Atripla was a well accepted first-line treatment for HIV in the UK albeit that it was not licensed for use in treatment-naïve patients and that, given current clinical practice worldwide, Atripla had been accepted as the appropriate comparator in the Phase III pivotal, SINGLE study (Walmsley *et al*). The SINGLE study was cited in the Triumeq SPC. In addition the use of Atripla in treatment-naïve patients was supported by independent treatment guidelines and the medicine was licensed for such use in the US.

The Appeal Board noted that HIV was a highly specialised therapy area. The SPCs for Triumeq and Atripla stated that the medicines had to be respectively 'prescribed' or 'initiated' by physicians 'experienced in the management of HIV infection'. In response to a question the representatives from ViiV Healthcare stated that there were currently approximately 800 such physicians in the UK. The Appeal Board considered that such a specialised audience was likely to prescribe medicines off-licence. The Appeal Board noted ViiV Healthcare's submission that such physicians would be familiar with the Atripla licence and would know that first-line use of the medicine had not been approved in the UK.

The Appeal Board noted its comments above and that the advertisement appeared only in the hospital edition of the BMJ. It therefore considered that the claim in question 'The components of Triumeq* form the first HIV regimen to have demonstrated statistically superior efficacy vs Atripla in treatment-naïve patients at 48, 96 and 144 weeks' reflected current clinical practice and in that regard patients were not put at risk. The Appeal Board considered that given the particular set of circumstances and factors discussed above, the claim at issue was not misleading and on this narrow point it ruled no breach of Clause 7.2. The appeal was successful.

Complaint received	**13 March 2015**
Case completed	**17 June 2015**

CASE AUTH/2757/5/15

ANONYMOUS v BOEHRINGER INGELHEIM

Congress stand presentation

An anonymous, non-contactable complainant alleged that data within a presentation hosted by Boehringer Ingelheim on its stand at a European stroke congress held in the UK, was misleading and not in patients' best interests.

Boehringer Ingelheim marketed Pradaxa (dabigatran) a non-vitamin K antagonist oral anticoagulant (NOAC) indicated, *inter alia*, for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors such as prior stroke, transient ischemic attack, heart failure, diabetes mellitus and hypertension.

The complainant stated that the presentation discussed the relative merits of different dosage regimes for novel anticoagulants and notably the advantages of Pradaxa. Slide 16 was headed 'Consequences of a missed dose' and compared once-daily dosing with twice-daily dosing for a medicine with a half-life of 12 hours and T_{max} of 3 hours. The footnote stated 'AF, atrial fibrillation; BD, twice daily; NOAC, non-vitamin K antagonist oral anticoagulant; OD, once daily'. This was followed by two references, Vrijens and Heidbuchel (2015) and Nagarakanti *et al* (2008). Vrijens and Heidbuchel seemed to be a secondary reference taken from a primary publication Comté *et al* (2007). Graph C in Figure 2 in Vrijens and Heidbuchel was based on Figure 2 of Comté *et al*.

The complainant noted that Comté *et al* reported mathematical modelling of data for antiretroviral agents. The complainant considered that the extrapolation of conclusions based on modelling of data from these agents in a different patient group to cardiovascular patients treated with an entirely different class of medicine was highly questionable. Furthermore the graph presented differed from those in Vrijens and Heidbuchel and Comté *et al* in that it included the half-life of dabigatran and not the half-lives for lopinavir and ritonavir.

The detailed response from Boehringher Ingelheim is given below.

The Panel noted slide 13 raised the question what if a patient had been treated with a NOAC for stroke prevention in atrial fibrillation rather than a vitamin K antagonist and whether thrombolysis was an option. Slide 14 referred to low rates of ischaemic stroke in NOAC trials and showed that the lowest rates were in dabigatran 150mg and 110mg. Slide 15, headed 'Thrombolysis can be considered in a patient on a NOAC if anticoagulant activity can be ruled out', stated that the patient had missed a morning dose of a once-daily NOAC. This meant that IV thrombolysis could still be considered. The slide in question, slide 16, featured a graph which compared concentration when a dose was delivered once- and twice-daily with missed doses on day 7. Slide 17 was headed 'Thrombolysis can be considered in a patient on a NOAC if anticoagulant activity can be ruled out' and asked whether the coagulation assays had ruled out anticoagulant activity. Subsequent slides mentioned dabigatran favourably.

The Panel considered that slide 16 was not clear. Its position between two slides that referred to the clinical use of NOACs, together with the lack of clear labelling meant it was extremely difficult to understand the full context of the graph on slide 16 which had been adapted from Figure 2C of Vrijens and Heidbuchel. The Panel did not accept Boehringer Ingelheim's submission that all the assumptions for Figure 2 in Vrijens and Heidbuchel were clear on slide 16. It was not clear that the graph on slide 16 was a simulation showing a theoretical pharmacokinetic profile for a medicine with a half-life of 12 hours similar to NOACs rather than clinical data on patients taking NOACs. Nor was it clear that the graph was adapted from Figure 2C of Vrijens and Heidbuchel which was headed '1 missed QD [once-daily] dose equals 3 missed BID [twice-daily] doses'. The Panel agreed with Boehringer Ingelheim that Figure 2C in Vrijens and Heidbuchel referred to a simulation similar to what might be expected with NOACs and not to the data in Comté *et al* which was a simulation of data for HIV patients. It appeared that the difference in the half-life of NOACs (around 12 hours) and protease inhibitors (lopinavir/ritonavir 10.7hrs) had been taken into account in Figure 2C.

The Panel considered that slide 16 was misleading as it was not clear that it was simulated data. Its positioning within a promotional presentation for dabigatran together with the footnote did not help the audience understand that it was simulated data and the relevance to the clinical situation was unclear. Whilst the complainant had clearly been misled he/she was incorrect as the simulation was not of HIV patients. The Panel ruled a breach of the Code in relation to the presentation of the simulated data. The Panel noted that the graph on slide 16 was misleading and in addition did not make it clear that it was adapted from Vrijens and Heidbuchel. A breach of the Code was ruled.

With regard to the allegation that HIV data was not relevant to NOACs, the Panel ruled no breach of the Code as slide 16 was not the HIV patient data and thus it was not misleading to omit the half-lives for two HIV medicines, lopinavir and ritonavir.

An anonymous, non-contactable complainant complained about a slide within a presentation (ref UK DBG-151019b) hosted by Boehringer Ingelheim

Limited on its stand at the European Stroke Organisation Congress which was held in Glasgow, 17-19 April 2015.

The slide in question, slide 16, was provided with Boehringer Ingelheim's response. It was headed 'Consequences of a missed dose' and compared once-daily dosing with twice-daily dosing for a medicine with a half-life of 12 hours and T_{max} of 3 hours. The footnote stated 'AF, atrial fibrillation; BD, twice daily; NOAC, non-vitamin K antagonist oral anticoagulant; OD, once daily'. This was followed by two references Vrijens and Heidbuchel (2015) and Nagarakanti *et al* (2008).

Boehringer Ingelheim's product Pradaxa (dabigatran) was a non-VKA (vitamin K antagonist) oral anticoagulant (NOAC). Pradaxa's indications included the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors such as prior stroke, transient ischemic attack, heart failure, diabetes mellitus and hypertension.

COMPLAINT

The complainant stated that the presentation discussed the relative merits of different dosage regimes for novel anticoagulants and notably the advantages of that for Pradaxa. During the discussion a slide entitled 'Consequences of a missed dose' was presented [slide 16].

The complainant stated that the references cited on the slide included Vrijens and Heidbuchel and that having read that paper it seemed to be a secondary reference taken from a primary publication ie Comté *et al* (2007). The graph C in Figure 2 in Vrijens and Heidbuchel was based on Figure 2 of Comté *et al*.

The complainant noted that Comté *et al* reported mathematical modelling of data for antiretroviral agents. The complainant considered that the extrapolation of conclusions based on modelling of data from these agents in a different patient group to cardiovascular patients treated with an entirely different class of medicine was highly questionable. Furthermore the graph presented differed from those in Vrijens and Heidbuchel and Comté *et al* in that it included the half-life of dabigatran and not the half-lives for lopinavir and ritonavir. This misled clinicians and the complainant did not consider that it was in the best interests of patients.

When writing to Boehringer Ingelheim, the Authority asked it to respond in relation to Clauses 7.2 and 7.8.

RESPONSE

Boehringer Ingelheim submitted that the presentation in question was delivered by a professor of neurology with expertise in stroke. The presentation took place from the Boehringer Ingelheim promotional stand located in the area of all other pharmaceutical company exhibition stands. The projector screen faced into the exhibition area. All entry into the exhibition area was through security staff who checked congress badges so that only health professionals registered for the meeting had access to the stands and could have seen the presentation.

Boehringer Ingelheim stated that there was no restriction on who viewed it within the exhibition hall. There were a number of seats on the stand and nearby, otherwise there was room around and between stands from where people could watch the session, although the further away you were, perhaps the sound quality and the visibility of the details on the screen might have been diminished, as one would expect. Only one presentation took place at 10am on Saturday, 18 April 2015 with the opportunity for questions and answers at the end. Boehringer Ingelheim submitted that it did not keep a record or request completion of a registration form from attendees due to the open and fluid nature of the surroundings.

A copy of the presentation was provided showing that of the twenty-three slides presented, slide 16 was the one referred to by the complainant.

The title of the presentation was 'Acute ischaemic stroke in a patient with NVAF [non-valvular atrial fibrillation]: what now?'. The aim of the talk was to discuss the evidence and guideline recommendations for the management of patients with non-valvular atrial fibrillation, already receiving anticoagulant therapy who might then present with an acute ischaemic stroke. Acute treatment of stroke and secondary prevention of stroke were covered in the talk. This was an area of considerable focus currently and the topics covered were very common questions from this clinical community. Using a patient case, the topics of diagnostics, risk factors for stroke, interventional and medicinal therapies were covered. As the talk was about how to manage patients already on anticoagulation the first scenario presented was for a patient receiving warfarin, but with a subtherapeutic (low) INR [international normalised rate]. Reasons for this were discussed and the evidence and guidelines on whether to administer thrombolysis in this setting discussed. As warfarin was not the only anticoagulant available, the next scenario covered was how this management would change if the patient was receiving a NOAC. The next part of the talk went on to discuss questions and blood tests that would be useful in assessing the patient's suitability for thrombolysis. As with the example of the patient on warfarin, non-adherence to medicines was covered here too. As all NOACs had a relatively shorter half-life than warfarin (approximately twelve hours vsforty hours) the slide in question 'Consequences of a missed dose' was very relevant and important to the educational content. Adherence to this class of medicine with a short half-life had caused physicians much concern. Boehringer Ingelheim submitted that the slide in question shown in this context was entirely appropriate and not misleading. The presenter then discussed the evidence and guideline recommendations for how to manage the patient's secondary stroke prevention in light of the preceding events.

The slide mentioned by the complainant (slide 16) contained a graph taken from Vrijens and Heidbuchel. This was cited as the reference on the slide itself. Vrijens and Heidbuchel was about the importance of patient's adherence to short half-life medication and the consequences of failing to adhere. Within the section 'Superior therapeutic coverage with twice-daily dosing regimens' on page 5, the authors gave examples of two medicines (protease inhibitors for which Comté *et al* was cited as a reference, and platelet inhibitors) and from two different patient populations. These formed the basis of the theory and reasons why the authors went on to do their own simulation work.

The next section of Vrijens and Heidbuchel, titled 'A simulation of the consequences of non-adherence with once- or twice-daily dosing' was not referenced to Comté *et al* and contained four graphs in Figure 2 representing the authors own simulations.

The graph in question was C in Figure 2 and was used on slide 16 of the presentation. Boehringer Ingelheim submitted that there was a very clear explanation with the figure explaining the assumptions and background to the graphs. It stated 'These graphs illustrate the theoretical pharmacokinetic profiles of a dose X administered once-daily (QD), and a dose X/2 administered twice-daily (BID), for a drug with a half-life of about 12 h and a T_{max} of 3 h'. Since the graph illustrated the theoretical pharmacokinetic profiles of a dose X QD and a dose X/2 BID for 'a' medicine with half-life of twelve hours and a T_{max} of three hours, it did not refer to lopinavir or ritonavir. Boehringer Ingelheim noted that lopinavir and ritonavir in fact had different half-lives.

Boehringer Ingelheim submitted that all these assumptions explained above were clear on the graph in slide 16. Nothing in the graph presented suggested that it referred to dabigatran. Again, as this represented hypothetical medicines X and X/2 there had been no suggestion or implication on Boehringer Ingelheim's part or the author's part that this was the concentration of dabigatran or in fact lopinavir and ritonavir, which in fact had different half-lives.

The description for graph C in Figure 2 of Vrijens and Heidbuchel stated 'The pharmacological equivalent of missing a single dose in a once-daily regimen (blue dot) is missing three doses (red dots) of a twice-daily dosing regimen'. This explanation had been illustrated by the blue and red dots on slide 16. Boehringer Ingelheim amended the title slide as using the original description based on author's text in the setting of a promotional stand could be misconstrued.

Boehringer Ingelheim strongly contested the statement that the graph had been taken from Comté *et al* and the citation was therefore a secondary data source. Boehringer Ingelheim strongly contested the statement that the graph was used to deliberately mislead clinicians as it considered that it had accurately represented and correctly referenced the graph's source.

Boehringer Ingelheim could, however, see the similarities in shape to the graph in Comté *et al*. However this was not surprising given that pharmacokinetic principles applied to all medicines. In fact it was very clear from this graph that there was a medicine concentration on the y-axis and in the description and assumptions supporting this figure in the paper.

In summary, Boehringer Ingelheim strongly denied either deliberately or unintentionally misleading clinicians as to the source data presented (Clause 7.2) on the congress stand. Boehringer Ingelheim believed it had demonstrated above that it had been mindful of presenting graphs in a clear and balanced way (Clause 7.8) relevant to the overall scientific content of the presentation.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. Such complaints were accepted and, like all complaints, judged on the evidence submitted by the parties. The complainant had the burden of proving his/her complaint on the balance of probabilities.

The Panel examined the presentation used at the Boehringer Ingelheim exhibition stand. The material related to treating a patient who had had an ischaemic stroke and was taking warfarin for stroke prevention in atrial fibrillation (AF). Slide 13 raised the question what if the patient had been treated with a NOAC for stroke prevention in AF rather than a vitamin K antagonist and whether thrombolysis was an option. Slide 14 referred to low rates of ischaemic stroke in NOAC trials and showed that the lowest rates were in dabigatran 150mg and 110mg. Slide 15 was headed 'Thrombolysis can be considered in a patient on a NOAC if anticoagulant activity can be ruled out' and stated that the patient had missed a morning dose of a once-daily NOAC. This meant that IV thrombolysis could still be considered. The slide in question, slide 16, was headed 'Consequences of a missed dose'. It featured a graph which compared concentration when a dose was delivered once- and twice-daily with missed doses on day 7. Slide 17 was headed 'Thrombolysis can be considered in a patient on a NOAC if anticoagulant activity can be ruled out' and asked whether the coagulation assays had ruled out anticoagulant activity. Subsequent slides mentioned dabigatran favourably.

The Panel examined Vrijens and Heidbuchel which looked at NOACs and considerations of once-daily vs twice-daily regimens and the potential impact on medication adherence. NOACs were said to have plasma half-lives of around 12 hours. This meant that anticoagulation effect declined radically when doses were missed. The paper stated that a twice-daily regimen was less prone than the once-daily regimen to hazardously high peaks or hazardously low troughs in anticoagulation concentration. The paper referred to Comté *et al* which suggested (model based finding) superior therapeutic coverage with twice-daily compared with once-daily protease inhibitors for treating HIV patients. The paper also referred to the superior inhibition (model based

simulation) of platelet aggregation with twice-daily administered ticagrelor compared with a once-daily clopidogrel (Vrijens *et al* 2014).

Comté *et al* stated that the more important factor was maintenance of therapeutic levels of drug action not the concentration in the plasma.

Vrijens and Heidbuchel stated that these two examples showed that while once-daily dosing might be seen as an option to simplify the dosing regimen and increase patient adherence, it might require near-perfect adherence to achieve its intended pharmacodynamic and clinical results, whereas twice-daily dosing depending on the medicine's pharmacokinetics, was more forgiving of variations in dose-timing or occasionally missed doses. The real therapeutically relevant question was the impact of suboptimal adherence on the pharmacologic effects of the medicine.

Vrijens and Heidbuchel further stated that it was of paramount importance to investigate these elements also in detail in NOAC patients, as the consequences of suboptimal pharmacologic effects were so severe (bleeding or thrombotic events, both of which might be fatal). Clearly, the above-mentioned findings could not be just extrapolated to NOAC therapy; not only might the consequences of non-adherence differ depending on the specific characteristics of the medicine but also the patients taking NOACs were different from those taking HIV medication and might therefore have specific issues.

The graph in question, slide 16, was taken from Figure 2C of Vrijens and Heidbuchel which was a simulation to depict the typical pharmacokinetic profile for a medicine with a half-life of about 12 hours, similar to NOACs. The graph in question showed that the pharmacological equivalent of missing a single dose in a once-daily regimen was missing three consecutive doses of a twice-daily dosing regimen.

Vrijens and Heidbuchel stated that the findings from the simulation of the consequences of non adherence with once- or twice-daily dosing showed the importance of considering a twice-daily dosing regimen instead of automatically assuming that once-daily dosing would be better due to the higher percentage of doses taken. It should also be clear that there would not be one all-encompassing answer on which dosing regimen was best for NOACs; this question needed to be assessed for each NOAC and each patient separately. It remained to be proven how far these projected differences also reflected clinical outcomes with NOACs.

The Panel considered that there were two aspects to the complaint. Firstly, whether using the modelling data was misleading *per se* and secondly, whether using simulated data from one patient group in relation to a different patient group was also misleading.

The Panel considered that slide 16 was not clear. Its positioning in the presentation between two slides that referred to the clinical use of NOACs, together with the lack of clear labelling meant it was extremely difficult to understand the full context of the graph on slide 16 which had been adapted from Figure 2C of Vrijens and Heidbuchel. The Panel did not accept Boehringer Ingelheim's submission that all the assumptions for Figure 2 in Vrijens and Heidbuchel were clear on slide 16. It was not clear that the graph on slide 16 was a simulation showing a theoretical pharmacokinetic profile for a medicine with a half-life of 12 hours similar to NOACs rather than clinical data on patients taking NOACs. Nor was it clear that the graph on slide 16 was adapted from Figure 2C of Vrijens and Heidbuchel which was headed '1 missed QD dose equals 3 missed BID doses'. The Panel agreed with Boehringer Ingelheim that Figure 2C in Vrijens and Heidbuchel referred to a simulation similar to what might be expected with NOACs and not to the data in Comté *et al* which was a simulation of data for HIV patients. It appeared that the difference in the half-life of NOACs (around 12 hours) and protease inhibitors (lopinavir/ritonavir 10.7hrs) had been taken into account in Figure 2C.

The Panel considered that slide 16 was misleading as it was not clear that it was simulated data. Its positioning within a promotional presentation for dabigatran together with the footnote did not assist the audience in understanding that it was simulated data and the relevance to the clinical situation was unclear. Whilst the complainant had clearly been misled he/she was incorrect as the simulation was not of HIV patients. The Panel ruled a breach of Clause 7.2 in relation to the presentation of the simulated data. The Panel noted that the graph on slide 16 was misleading and in addition did not make it clear that it was adapted from Vrijens and Heidbuchel. A breach of Clause 7.8 was ruled.

With regard to the allegation that HIV data was not relevant to NOACs, the Panel ruled no breach of Clause 7.2 of the Code as slide 16 was not the HIV patient data and thus it was not misleading to omit the half-lives for two HIV medicines, lopinavir and ritonavir.

Complaint received **8 May 2015**

Case completed **1 July 2015**

PARAGRAPH 5.1/DIRECTOR v ASTRAZENECA

Clinical trial disclosure (Caprelsa)

A study published online in Current Medical Research & Opinion (CMRO) on 5 May 2015 was entitled 'Clinical trial transparency update: an assessment of the disclosure of results of company-sponsored trials associated with new medicines approved in Europe in 2012'. The study authors were Dr B Rawal, Former Medical Innovation and Research Director, ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and research. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2014. It covered 23 new medicines (except vaccines) from 18 companies that were approved by the European Medicines Agency (EMA) in 2012. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available in the supplemental information via a website link. Neither the study nor the supplemental information identified specific studies. The study did not assess the content of disclosure against any specific requirements.

The Deputy Director decided that the study was such that she had received information from which it appeared that AstraZeneca UK might have breached the Code and decided in accordance with Paragraph 5.1 of the Constitution and Procedure to take the matter up as a complaint.

The summary output for each medicine set out the sources for all trials found irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Caprelsa (vandetanib) and Zinforo (ceftaroline fosamil).

The detailed response from AstraZeneca is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that two Caprelsa evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 95%. The disclosure percentage at 31 July 2014 was 95%. A footnote stated that from company communication, two undisclosed Phase II trials pre-dated disclosure requirements.

The Panel noted that Caprelsa was first licensed and commercially available in April 2011. The studies completed in November 2003 and August 2006. The 2008 Code and Joint Position 2005 were thus relevant.

One study which completed in 2003 and under the Joint Position 2005 did not need to be disclosed. The results were published in May 2005. The Panel ruled no breach of the 2008 Code including Clause 2.

The second study completed in August 2006 and was described by AstraZeneca as an exploratory Phase II study which terminated early due to slow enrolment. The Panel noted AstraZeneca's submission that this exploratory study was not of significant medical importance and nor did it impact on the product's labelling. The Panel therefore ruled no breach of the 2008 Code including Clause 2.

The Panel noted the CMRO publication in that three Zinforo evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 70%. The disclosure percentage at 31 July 2014 was 90%. A footnote stated that from company communication, the undisclosed trial was a post-approval Phase I [pharmacokinetic] type study in children, therefore out of scope of the disclosure requirements.

The Panel noted ceftaroline fosamil was first approved and commercially available as Teflaro in January 2011. The Panel noted that two studies which completed in February 2009 and July 2008 were undertaken before AstraZeneca was granted a sublicence in August 2009. These were the responsibility of another pharmaceutical company and this was taken up separately with that company (Case AUTH/2772/6/15).

The Panel noted that Zinforo was first licensed in August 2012 and commercially available in Germany on October 2012.

The Panel noted that the remaining study completed in February 2013 ie after both Zinforo and Teflaro were first licensed and commercially available (August 2012 and January 2011 respectively). The Second 2012 Edition of the Code and thus the Joint Position 2009 were relevant. This stated that if trial results for an investigational product that had failed in development had significant medical importance study sponsors were encouraged to post the results if possible. The Panel noted AstraZeneca's submission that the study was sponsored, designed and conducted by another company. It had no UK involvement and was conducted in the US. AstraZeneca had reimbursed half the cost of the study in order to use it in a paediatric investigation plan for Zinforo. The Panel noted that AstraZeneca was a UK registered company. It could be argued that this meant the UK Code applied however, the Panel considered that the circumstances were

such that AstraZeneca was not responsible for the disclosure of this study under the ABPI Code. The Panel considered that as there was no UK involvement in the study, the matter did not come within the scope of the UK Code and therefore ruled no breach.

A study published online in Current Medical Research & Opinion (CMRO) on 5 May 2015 was entitled 'Clinical trial transparency update: an assessment of the disclosure of results of company-sponsored trials associated with new medicines approved in Europe in 2012'. The study authors were Dr B Rawal, Former Medical Innovation and Research Director, ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and research. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2014. It covered 23 new medicines (except vaccines) from 18 companies that were approved by the European Medicines Agency (EMA) in 2012. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available in the supplemental information via a website link. Neither the study nor the supplemental information identified specific studies. The study did not assess the content of disclosure against any specific requirements.

The Deputy Director decided that the study was such that she had received information from which it appeared that AstraZeneca UK Limited might have with Paragraph 5.1 of the Constitution and Procedure to take the matter up as a complaint.

COMPLAINT

The study assessed the proportion of trials for which results had been disclosed on a registry or in the scientific literature either within 12 months of the later of either first regulatory approval or trial completion, or by 31 July 2014 (end of survey). Of the completed trials associated with 23 new medicines licensed to 18 different companies in 2012, results of 90% (307/340) had been disclosed within 12 months and results of 92% (312/340) had been disclosed by 31 July 2014.

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

Phase	Total	Un-evaluable	Evaluable	Disclosed in 12-month timeframe	Disclosure Percentage	Complete before 31 July 2014	Disclosed at 31 July 2014	Disclosure percentage at 31 July 2014
Phase I & II	37	2	35	33	94%	35	33	94%
Phase III	6	0	6	6	100%	6	6	100%
Phase IV	1	1	0	0		0	0	
Other	1	1	0	0		0	0	
Total	**45**	**4**	**41**	**39**	**95%**	**41**	**39**	**95%**

Footnote (company communication): Two undisclosed phase II trials pre-dated disclosure requirements.

The data for Zinforo (ceftaroline fosamil) were as follows:

Phase	Total	Un-evaluable	Evaluable	Disclosed in 12-month timeframe	Disclosure Percentage	Complete before 31 July 2014	Disclosed at 31 July 2014	Disclosure percentage at 31 July 2014
Phase I & II	3	0	3	1	33%	3	3	100%
Phase III	8	3	5	5	100%	5	5	100%
Phase IV	4	3	1	0	0%	1	0	0%
Other	1	0	1	1	100%	1	1	100%
Total	**16**	**6**	**10**	**7**	**70%**	**10**	**9**	**90%**

Footnote (company communication): The single undisclosed trial is a post-approval phase I PK type study in children, therefore out of scope of disclosure requirements.

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

total	total number of company sponsored trials identified which were completed by 31 July 2014
unevaluable	trials with completion date within the last 12 months or key dates missing – excluded from the analysis
evaluable	trials with all criteria present including dates, and hence the base number of trials which could be evaluated for the assessment
results disclosed in 12 month timeframe	evaluable trials which were disclosed within the target 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
disclosure percentage	proportion of evaluable trials which were disclosed within 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
completed before 31 July 2014	number of evaluable trials completed before 31 July 2014
Disclosed at 31 July 2014	number of evaluable trials with results disclosed by 31 July 2014
disclosure percentage at 31 July 2014	proportion of evaluable trials which were disclosed by 31 July 2014

AstraZeneca was asked to respond in relation to Clauses 2, 9.1 and 13.1 of the 2015 Code. The Authority noted that previous editions of the Code would be relevant and provided details.

RESPONSE

AstraZeneca stated that it had long been committed to making information about its clinical research publicly available to enhance the scientific understanding of how its medicines worked and in the medical interest of patients. The disclosure policies exceeded the current legal requirements for disclosure.

AstraZeneca stated that investigational clinical trials were registered on the US National Library of Medicine's website (www.clinicaltrials.gov) prior to the first patient being enrolled and to other websites within timelines as required by law or policy. Additionally, basic information was on the company's publicly accessible website (www.astrazenecaclinicaltrials.com).

AstraZeneca submitted that transparency of clinical trial results and applicable information from its clinical trials contributed to public confidence in medicines and improved public health and scientific knowledge. AstraZeneca recognised that increased requirements for transparency, within the reactive and proactive disclosure contexts, must also be balanced with the protection of personal data, intellectual property and confidential information.

Thus, AstraZeneca committed to communicating accurate and meaningful information about its sponsored clinical trials in a timely, accurate, balanced and complete manner, regardless of outcome. AstraZeneca submitted that its current and planned clinical trials transparency position met or exceeded all existing legal and regulatory standards:

- AstraZeneca registered and posted results from all Phase I-IV interventional trials, including healthy volunteer trials, on ClinicalTrials.gov and other applicable legally required websites, as well as on its own website

- AstraZeneca registered non-interventional studies and disclosed the results of those trials conducted on marketed (commercially available) products on all legally required websites in addition to its own website

- AstraZeneca posted trial results, synopses and other information on its website for products approved in countries that did not legally require disclosure

- AstraZeneca's timelines for disclosure were:
  - Results of trials with already commercially available medicines were posted within one year of trial completion. Results of trials with medicines in development were posted within 30 days of first regulatory approval for the new medicine where trials had completed at least one year. When a medicine in development was discontinued, results were published within one year of the public announcement of the decision, unless analysis and interpretation of the data were not sufficiently complete, in which case the company posted an explanation for the delay and the anticipated date when the results would be posted.
  - For marketed medicines and recently approved medicines where AstraZeneca considered there to be good cause to delay posting of results, it sought necessary approval according to applicable law. Where approved, an explanation for the delay and the anticipated date when the results would be posted.

AstraZeneca submitted that, in essence, it posted the results of all its clinical trials in all stages of clinical development on several public websites – regardless of outcome (positive or negative) – including for medicines which were discontinued in development.

Scope of complaint and AstraZeneca UK response

The basis of the complaint was the recently published CMRO survey which identified from the cohort of all completed company-sponsored clinical trials, carried out in patients and relating to new medicines approved by the EMA in 2012, studies for which results were not posted in a 'timely' manner. This included, according to the survey protocol, studies identified through searching clinical trial registries and/or included in a European Public Assessment Report (EPAR) for which results had not been disclosed within twelve months of the later of either first regulatory approval or trial completion. The survey also indicated if the clinical trial results had been disclosed by the end of the survey, 31 July 2014.

The supplemental information referred to two AstraZeneca products, Caprelsa (vandetanib) and Zinforo (ceftaroline fosamil), where the researchers considered that the disclosure of some clinical trial results had not been 'timely'. The percentage of evaluable studies disclosed within the twelve-month timeframe, as set out in the survey protocol, was 95% and 70% respectively.

The authors of the article stated that there were no unevaluable trials where the key dates were missing. All unevaluable trials had completed in the last 12 months and were within the required results disclosure timeframe disclosure.

Caprelsa

Vandetanib was first licensed in the US by the Food and Drug Administration (FDA) on 6 April 2011; it became commercially available without a trade name in the US on 25 April 2011. AstraZeneca did not wait for a trade name approval because, at that time, there were no other FDA-approved medicines available for the treatment of medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. The FDA approved the trade name Caprelsa in August 2011.

The supplemental information to the CMRO article stated that there were forty-one evaluable Caprelsa studies and of these thirty-nine were disclosed in a 'timely' manner in accordance with the survey protocol. A footnote to the Caprelsa data stated 'Two undisclosed phase II trials pre-dated disclosure requirements'.

The researchers had provided AstraZeneca UK with details of the Caprelsa studies included in the survey. AstraZeneca identified the studies which, in the opinion of the researchers, were not in accordance with the survey protocol.

As Caprelsa was launched in April 2011 and the studies in question were completed before 1 November 2008, the 2008 Code applied and this referred to the Joint Position 2005 which stated:

> 'The results of all clinical trials, other than exploratory trials, conducted on a drug that is approved for marketing and is commercially available in at least one country should be publicly disclosed on a free, publicly accessible, clinical trial results database, regardless of outcome. Trial results from exploratory trials also should be publicly disclosed if they are deemed to have significant medical importance and may have an impact on a marketed product's labeling.'

Study NCT00034918 was an exploratory Phase II study; it completed in November 2003 and thus did not need to be disclosed as it predated the Joint Position 2005. The study results were published in the journal Clinical Cancer Research in May 2005.

Study D4200C00045 was an exploratory, Phase II study; it completed in August 2006. This study terminated early due to slow enrolment and, therefore, was not of significant medical importance nor did it have an impact on the product's labelling. As per the Joint Position 2005, the results were not required to be disclosed.

On the basis of the information detailed above and the information regarding the studies not disclosed within the study protocol, AstraZeneca denied breaching Clause 21.3 of the 2008 Code, as the Joint Position 2005 did not require disclosure of the two trials identified as not being disclosed in 'timely' manner.

Zinforo

AstraZeneca submitted that ceftaroline fosamil was initially synthesized by Takeda Pharmaceutical Co Ltd and developed by Cerexa Inc and Forest Laboratories, Inc. In 2006, Forest Laboratories, Inc acquired Cerexa Inc. In August 2009, Forest Laboratories, Inc granted AstraZeneca an exclusive sub-licence including worldwide commercial rights and co-exclusive development rights for ceftaroline fosamil, excluding US, Canada and Japan. On 29 October 2010, Forest Laboratories obtained FDA approval for ceftaroline fosamil in the US and it became commercially available there as Teflaro on 3 January 2011. AstraZeneca was granted a licence for Zinforo by the EMA on 23 August 2012 and first made the product commercially available in Germany on 1 October 2012.

The supplemental information to the CMRO article stated that there were ten evaluable Zinforo studies and of these seven were disclosed in accordance with the survey protocol. One of these studies remained undisclosed on 31 July 2014. A footnote to the Zinforo data stated 'The single undisclosed trial is a post-approval phase I PK type study in children, therefore out of scope of the disclosure requirements'.

The researchers provided AstraZeneca UK details of the Zinforo studies included in the survey. AstraZeneca had identified the studies which, in the opinion of the researchers, were not in accordance with the survey protocol.

Two studies (NCT00633126 and NCT00633152) were exploratory studies. As Teflaro was first licensed and commercially available in January 2011 and the

studies completed in February 2009 and July 2008 respectively, the 2008 Code and the Joint Position 2005 were relevant. The Joint Position 2005 did not require the results from exploratory studies to be disclosed. Both these studies had results disclosed before the issue of a marketing authorization and commercial availability in territories that AstraZeneca was responsible for under the licensing agreement.

AstraZeneca submitted that these studies were sponsored, designed and conducted by Cerexa Inc and/or Forest Laboratories, Inc. The studies were not conducted on behalf of AstraZeneca and were conducted entirely in the US. There was no involvement of any UK centres, investigators or patients. The decision tree developed by the PMCPA for considering a previous clinical trial disclosure complaint and the subsequent case rulings, indicated that where the clinical trial had no involvement from a UK company and there was no involvement of UK centres, investigators or patients, then the ABPI Code did not apply.

The remaining study (NCT01298843) was a pharmacokinetic study in children aged younger than 12 years. As this study completed in February 2013, the Second Edition 2012 Code of Practice and the Joint Position 2009 were relevant. AstraZeneca UK recognised that this trial did not report results within the timelines required by the Joint Position 2009. However, as both Zinforo and Teflaro were licensed for use in those 18 years and over, this study was conducted in an unlicensed population.

AstraZeneca stated that this study was sponsored, designed and conducted by Forest Laboratories in order to fulfil an FDA paediatric post-marketing requirement. AstraZeneca reimbursed Forest Laboratories half of the cost of the study, in order to use the study as part of the paediatric investigation plan (PIP) for Zinforo. However, the study was not conducted on behalf of AstraZeneca. Furthermore, there was no involvement of any UK centres, investigators or patients in this study. The study was conducted entirely in the US and therefore the ABPI Code did not apply.

AstraZeneca's Global Procedure on Disclosure of Trial Information to Public Websites stated that the company was responsible for disclosure of study information where AstraZeneca had sponsored the study. The licensing agreement between AstraZeneca and Forest Laboratories for ceftaroline fosamil stated that each party was responsible for conducting their development activities in compliance with all applicable laws and guidelines in each party's respective territory. Therefore, as clearly set out in the documents detailed above, disclosure of these studies was the responsibility of Forest Laboratories not AstraZeneca.

AstraZeneca provided details of this complaint to Actavis, which acquired Forest Laboratories in July 2014, and Actavis informed AstraZeneca that the results for study NCT01298843 would be posted on EudraCT by 21 July 2015.

AstraZeneca UK denied breaching Clause 21.3 of both the 2008 ABPI Code and Second 2012 Edition of the Code as the studies were conducted outside the UK and were not sponsored by AstraZeneca nor were they conducted by or on behalf of AstraZeneca.

Summary

AstraZeneca denied breaching Clause 13 (2015 Code) and Clause 21.3 (2008 Code and Second 2012 Edition of the Code), as the studies identified by the researchers, were in compliance with the applicable ABPI Code and Joint Position or they fell out with the jurisdiction of the ABPI Code. Consequently, AstraZeneca denied breaching Clause 9.1 and Clause 2.

General comments from the Panel

The Panel noted that all the cases would be considered under the Constitution and Procedure in the 2015 Code as this was in operation when the CMRO study was published and the complaint proceedings commenced. The Panel noted that the study concluded that of the completed trials associated with 23 new medicines licensed to 18 different companies in 2012, results of 90% had been disclosed within 12 months and results of 92% had been disclosed by 31 July 2014.

The Panel noted that the CMRO study in question was an extension of a previously reported study of trials related to new medicines approved in Europe in 2009, 2010 and 2011 which found that over three-quarters of all these trials were disclosed within 12 months and almost 90% were disclosed by the end of the study. That study was the subject of an external complaint which gave rise to 27 cases in 2013 and 2014. The present case was not the subject of external complaint. The study itself formed the basis of the complaint.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities came within the scope of the Code such as activities relating to UK health professionals or activities carried out in the UK.

Clause 13.1 of the 2015 edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patient enrolment) and the results of completed trials for medicines licensed for use and commercially available in at least one country. Further information was to be found in the current Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the current Joint Position on the Publication of Clinical Trial Results in the Scientific Literature, both at www.ifpma.org.en/ethics/clinical-trials-disclosure.html. Companies must include on the home page of their website, information as to where details of their clinical trials could be found.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed in the study were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

> **'Clause 7.5 Data from Clinical Trials**
>
> Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

> 'Companies must disclose details of clinical trials.'

The relevant supplementary information stated:

> **'Clause 21.3 Details of Clinical Trials**
>
> This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (http://clinicaltrials.ifpma.org).
>
> Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'

The relevant supplementary information stated:

'Clause 21.3 Details of Clinical Trials

This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at http://clinicaltrials.ifpma.org.

Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code came into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014. These requirements were to be found in Clause 13.1 of the 2015 Code. The relevant supplementary information had been amended in the 2015 Code to replace the year of the relevant joint positions with the word 'current', to add a reference to the medicine being licensed and 'commercially available' and to update the website address. The 2015 Code came into effect on 1 May 2015 for newly introduced requirements following a transition period from 1 January 2015 until 30 April 2015. The study at issue was posted online on 5 May 2015.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the matter for consideration related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position

2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code, and thus which joint position applied, was complicated. It noted that the 2011 Code which, taking account of the transition period, came into operation on 1 May 2011, was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 30 April 2012 under the 2011 Code and 1 May 2012 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the joint position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 and 2015 Codes). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the study referred to licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than one year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the matter for consideration was whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights.

The Panel referred to the decision tree in the previous cases (for example 2654/11/13 *et al*) which it updated to include the 2015 Code.

The Panel considered that companies would be well advised to ensure that all the clinical trial results were disclosed as required by the codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the article and thus the matter for consideration was only about whether or not study results had been disclosed and the timeframe for such disclosure. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study related to products approved for marketing by the EMA in 2012 and searched for the data between 1 May and 31 July 2014. The study was published online on 5 May 2015. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the date the product was first licensed and commercially available anywhere in the world might predate EMA approval.

PANEL RULING IN CASE AUTH/2763/5/15

Caprelsa

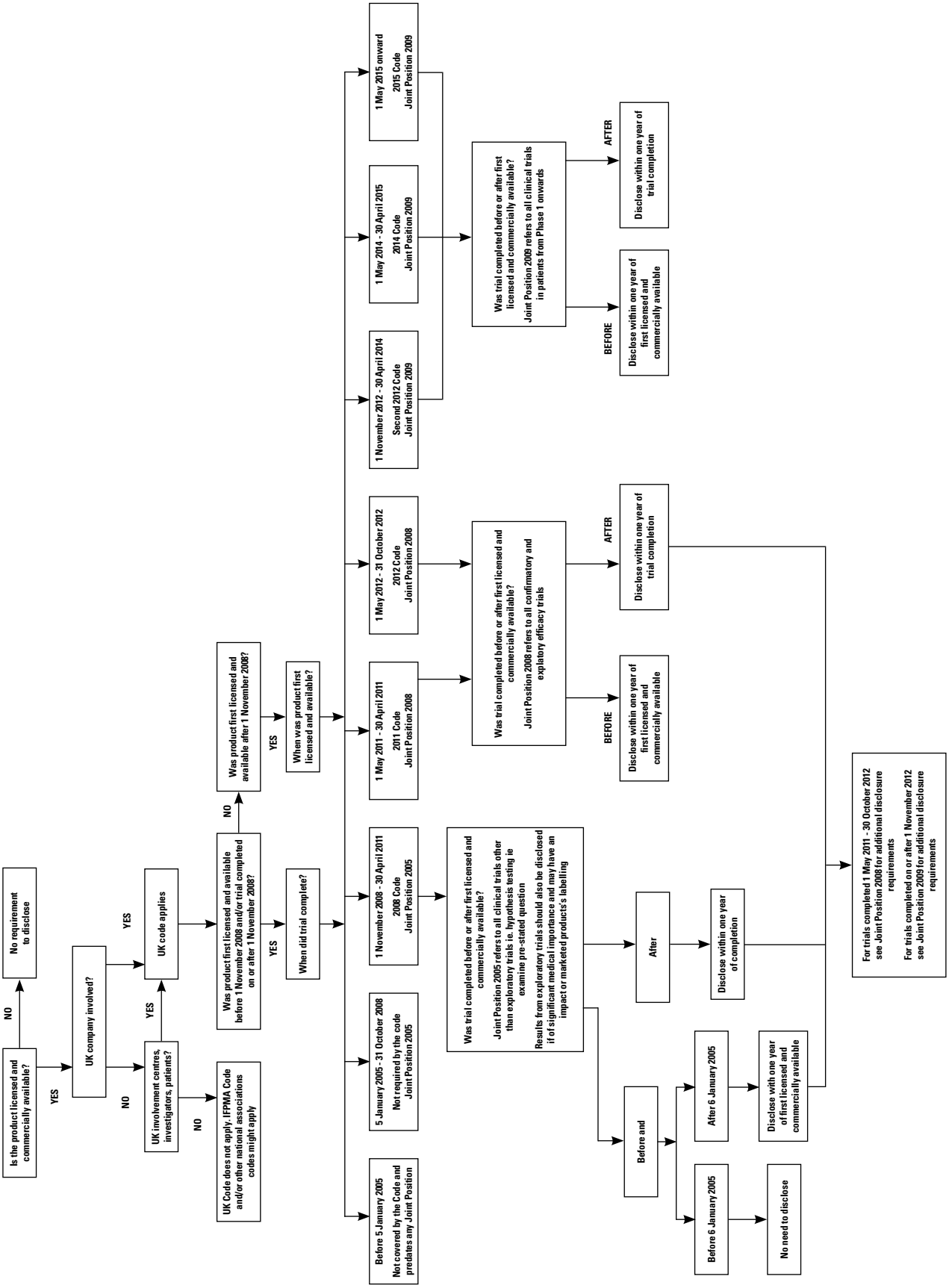
The Panel noted the CMRO publication in that two Caprelsa evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 95%. The disclosure percentage at 31 July 2014 was 95%. A footnote to the information stated that from company communication, two undisclosed Phase II trials pre-dated disclosure requirements.

The Panel noted that Caprelsa was first licensed and commercially available in April 2011. The studies completed in November 2003 and August 2006. The 2008 Code and Joint Position 2005 were thus relevant.

Study NCT00034918 completed in 2003 and under the Joint Position 2005 did not need to be disclosed. The results were published in Clinical Cancer Research in May 2005. The Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

Decision Tree

Updated Decision tree developed by the Panel



Study D4200C00045 completed in August 2006 and was described by AstraZeneca as an exploratory Phase II study which terminated early due to slow enrolment. The Panel noted AstraZeneca's submission that this exploratory study was not of significant medical importance and nor did it impact on the product's labelling. The Panel therefore ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

Zinforo

The Panel noted the CMRO publication in that three Zinforo evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 70%. The disclosure percentage at 31 July 2014 was 90%. A footnote to the information stated that from company communication, the undisclosed trial was a post-approval Phase I PK [pharmacokinetic] type study in children, therefore out of scope of the disclosure requirements.

The Panel noted ceftaroline fosamil was first approved and commercially available as Teflaro in January 2011. The Panel noted that two studies (NCT00633126 and NCT00633152) which completed in February 2009 and July 2008 were part of work undertaken before Forest Laboratories granted a sublicence to AstraZeneca in August 2009. These were the responsibility of another pharmaceutical company and this was taken up separately with that company (Case AUTH/2772/6/15).

The Panel noted that Zinforo was first licensed in August 2012 and commercially available in Germany on October 2012.

The Panel considered that it could be argued that the date a product was first approved and commercially available was not brand specific if there were a number of different brand names for the same product as for ceftaroline fosamil. The Panel noted, however, that the joint positions referred to maintaining protection for intellectual property rights. Further it was not clear whether the reference to first approved and commercially available was medicine specific or company specific.

The Panel noted that the remaining study (NCT01298843) completed in February 2013. This was after the dates that both Zinforo and Teflaro were first licensed and commercially available (August 2012 and January 2011 respectively). The Second 2012 Edition of the Code and thus the Joint Position 2009 were relevant. This stated that if trial results for an investigational product that had failed in development had significant medical importance study sponsors were encouraged to post the results if possible. The Panel noted AstraZeneca's submission that the study was sponsored, designed and conducted by Forest Laboratories. It had no UK involvement and was conducted in the US. AstraZeneca had reimbursed half the cost of the study in order to use it in the paediatric investigation plan for Zinforo. The Panel noted that AstraZeneca was a UK registered company. It could be argued that this meant the UK Code applied.

The Panel considered that although AstraZeneca was a UK registered company, the circumstances were such that AstraZeneca was not responsible for the disclosure of Forest's study under the ABPI Code. The Panel considered that as there was no UK involvement in study NCT01298843, the matter did not come within the scope of the UK Code and therefore ruled no breach.

Complaint proceedings commenced **14 May 2015**

Case completed **2 July 2015**

CODE OF PRACTICE REVIEW – August 2015

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

AUTH/2747/1/15	**Anonymous health professional v Astellas Pharma Europe**	**Arrangements for a meeting**	**Breaches of Clauses 2, 9.1, 12.1, 18.1 and 20.1** **Required to issue a corrective statement by the Appeal Board**	**No Appeal** **Report from the Panel to the Appeal Board**	**Page 3**
AUTH/2748/2/15	**Bayer v Novartis**	**Promotion of Lucentis**	**Breach Clause 3.2** **Three breaches Clause 7.2** **Two breaches Clause 7.3** **Breach Clause 7.4** **Two breaches Clause 7.9** **Breach Clause 9.1**	**No appeal**	**Page 16**
AUTH/2749/2/15	**Anonymous, non contactable v Chugai**	**Consultancy arrangements and general Code compliance**	**Breach Clause 9.1**	**No appeal**	**Page 34**
AUTH/2750/3/15	Actelion v GlaxoSmithKline	Promotion of Volibris	No Breach	No appeal	Page 43
AUTH/2751/3/15	Anonymous General Practitioner v ViiV Healthcare	Promotion of Triumeq	No breach	Appeal by respondent	Page 46
AUTH/2757/5/15	**Anonymous v Boehringer Ingelheim**	**Congress stand presentation**	**Breaches Clauses 7.2 and 7.8**	**No appeal**	**Page 51**
AUTH/2763/5/15	Paragraph 5.1/ Director v AstraZeneca	Clinical trial disclosure (Caprelsa)	No breach	No appeal	Page 55

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.