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CODE OF PRACTICE REVIEW

PMCPA | Prescription Medicines Code of Practice Authority

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

PUBLIC REPRIMAND FOR ASTELLAS UK

Astellas Pharmaceuticals Limited has been publicly reprimanded by the Code of Practice Appeal Board for failing to provide accurate information to the Code of Practice Panel and the Appeal Board (Case AUTH/2984/10/17).

On appeal from the complainant, a hospital doctor, the Appeal Board overturned the Panel's rulings and ruled breaches of the Code as it considered that a payment of £50,000 to a hospital in 2010 by Astellas UK in relation to the assessment of a hospital treatment protocol was inappropriately linked to the use of a medicine. The medicine in question was Advagraf (tacrolimus) which was indicated to prevent rejection following kidney or liver transplantation.

Those carrying out the re-audits of Astellas in April 2018 in relation to three separate cases Cases AUTH/2780/7/15, AUTH/2883/10/16 and AUTH/2939/2/17, followed up the Appeal Board's concerns at the appeal in Case AUTH/2984/10/17 that Astellas had provided limited documentation, about Astellas UK's submission about the nature and depth of its investigation and that Astellas had not provided detailed accounts from two critical members of staff who were involved in all of the matters at issue and still employed by the company.

At the request of those carrying out the re-audits, a timeline showing key dates and decisions related to the payment in question was provided by an individual via the company's normal process for supplying requested documentation. The timeline had not been previously disclosed as part of Astellas UK's response to the PMCPA. The Panel reconvened and after further comment from Astellas it decided that, taking all the circumstances into account, including Astellas UK's acknowledgement that it had failed to follow its processes for investigating complaints, it decided to report Astellas UK to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure.

In the Appeal Board's view, notwithstanding the historical nature of the matters at issue, adopting basic principles of good governance and compliance practice, common sense and a positive cultural approach to transparency and disclosure should have facilitated more accurate responses and complete disclosure. That such an approach, apparently and on the evidence before the Appeal Board, was not consciously adopted at the outset was, in the Appeal Board's view, and given Astellas' recent compliance history, both inexplicable and inexcusable.

The Appeal Board was deeply concerned about the lack of rigour which Astellas had applied in conducting its investigation.

The Appeal Board considered that this case raised very serious matters including the historic issues relating to patient safety which were not the subject of the complaint and had not been considered or ruled upon as a discrete issue but arose as a coincidental matter during the consideration of the case. In addition, given the level of scrutiny the company was already under in relation to compliance, the Appeal Board was very concerned about the issues as set out above. Consequently, taking all the circumstances into account, the Appeal Board decided that in accordance with Paragraph 12.1 of the Constitution and Procedure, Astellas UK should be reported to the ABPI Board.

The ABPI Board considered the reputation of the industry to be of utmost importance, and therefore carefully considered all of the information before it. The ABPI Board concluded that although Astellas had made mistakes, in its view there was no malintent from the company to conceal. The ABPI Board noted the company's submission that measures had now been taken to address the issues arising from this case. The ABPI Board noted Astellas UK's submission that at no point were any patient safety issues caused by the conduct of Astellas and that the use of Advagraf within the treatment protocol was in line with the relevant summary of product characteristics. The ABPI Board further noted that patient safety was not the subject of the complaint.

The ABPI Board was already due to see the reports of the PMCPA's 2019 re-audit of Astellas UK as a result of its consideration of re-audits in other cases. The failures identified in this case should be considered as a part of those re-audits. The ABPI Board would look closely at the report of the re-audits to ensure that it remained satisfied with the position of the company.

Taking everything into account, the ABPI Board decided that no further action was required.

Full details of Case AUTH/2984/10/17 can be found on page 3.

PUBLIC REPRIMAND FOR SUNOVION

Sunovion Pharmaceuticals Europe Ltd has been publicly reprimanded by the Code of Practice Appeal Board for providing inaccurate and misleading information to the PMCPA (Case AUTH/3027/3/18).

In Case AUTH/3027/3/18, the Panel ruled breaches of the Code following a voluntary admission from Sunovion that it had failed to disclose and document its interactions with patient organisations to which it provided financial support and/or significant indirect/non-financial support. Sunovion accepted the Panel's rulings and provided the requisite undertaking.

CODE OF PRACTICE TRAINING

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

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

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

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

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

HOW TO CONTACT THE AUTHORITY

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Telephone: 020 7747 8880

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

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

Heather Simmonds:	020 7747 1438
Etta Logan:	020 7747 1405
Tannyth Cox:	020 7747 8883
Natalie Hanna:	020 7747 8862

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.

PUBLIC REPRIMAND FOR SUNOVION CONTINUED...

During its consideration of this case, the Panel was concerned to note that the information provided in response to the PMCPA's audit report required in Case AUTH/2935/2/17 was incorrect and further, that only in response to the case preparation manager's request for further comments did Sunovion discover that it had made errors in its initial voluntary admission in Case AUTH/3027/3/18. The Panel noted that self-regulation relied, *inter alia*, upon the provision of complete and accurate information and that Sunovion had already been criticised for not providing accurate information in the case that led to the company being audited, Case AUTH/2935/2/17.

On receipt of the case report for Case AUTH/3027/3/18, as set out in Paragraph 13.4 of the Constitution and Procedure, the Appeal Board considered that this case raised serious issues including about the provision of incomplete and/or inaccurate information and that the imposition of additional sanctions under Paragraph 11.1 should be contemplated.

At its subsequent consideration of the matter, the Appeal Board was concerned that due to poor judgement and/or absence of the necessary process, the company had made a series of errors about its disclosure of payments in its responses to the PMCPA including during the re-audit required in Case AUTH/2935/2/17 in which it had already been criticised for not providing accurate information. Notwithstanding Sunovion's submission that it now had a process in place to ensure such errors did not recur, the Appeal Board noted that self-regulation relied, *inter alia*, upon the provision of complete and accurate information from pharmaceutical companies.

The Appeal Board also decided to require an audit of Sunovion's procedures in relation to the Code to take place at the same time as the re-audit in relation to Case AUTH/2935/2/17 and, on receipt of the report the Appeal Board, would consider whether further sanctions were necessary.

Full details of Case AUTH/3027/3/18 can be found on the PMCPA website (www.pmcpa.org.uk).

CASE AUTH/2984/10/17

HEALTH PROFESSIONAL v ASTELLAS UK

Provision of funding linked to use of Advagraf and failure to provide comprehensive, accurate information

A hospital doctor alleged that Astellas Pharmaceuticals Limited had inappropriately awarded research funding (in region of £250,000) in 2009 in association with the use of Advagraf (tacrolimus) which was indicated for use in kidney and liver transplant patients to prevent rejection. The complainant alleged that the funding was made available to a senior clinician for him/her to study the efficacy of a newly adopted immunosuppressive protocol at the renal transplant unit of a named hospital. According to the complainant, the protocol adopted in 2009 was abandoned by 2012 because of poor outcomes. The protocol was used for patients who received a renal transplant from a living donor and included the use of Advagraf (*de novo*), azathioprine and prednisolone.

The complainant acknowledged that a long time had elapsed since the event, but the details had only come to his/her attention recently. The complainant was concerned that there was a link between the adoption of the protocol and the provision of funding. The complainant also stated that funding, or part thereof, was withdrawn when the outcome was not as expected.

The detailed response from Astellas UK appears below.

The Panel noted that in May 2009 the Astellas Investigator Driven Study Evaluation Committee (IDSEC) had 'approved in principle' a request for £250,000 to fund two studies but wanted a number of questions answered. Each study was to use Advagraf and was due to start in January 2010. Astellas UK submitted that neither study went ahead and no funds were made available by Astellas UK at the time. In 2010 a request for £50,000 for a special purpose fund to support ongoing clinical research from one of the two health professionals who previously asked for the study funding was agreed. According to Astellas UK the payment was made as a medical and educational good and service (MEGS) on 21 December 2010. The relevant Code was the 2008 edition. Following the agreement to donate £50,000, the hospital wrote, confirming that the '… £50,000 grant would permit implementation of a new clinical protocol using Advagraf in *de novo* live related kidney transplantation and to support ongoing clinical research in the area of renal transplantation. The funding would allow the team to employ bank nursing staff/statistical support to extract and analyse fundamental data'. There was no mention in a memorandum of agreement between Astellas UK and the hospital (signed in June 2010) about the clinical protocol but it mentioned that the funding was to support continuing clinical research in the area of transplantation at the hospital to facilitate employment of bank nursing staff statistical support to extract and analyse the data.

Astellas UK had not provided the protocol. The complainant stated it was used from 2009 to 2012 and alleged that following its adoption, Astellas UK agreed to fund a study.

It was not clear when or why Astellas UK decided not to fund the two studies following the request in April 2009. As no payment had been made there was no evidence of inappropriate funding for research in this regard. The Panel therefore ruled no breach of the 2008 Code including Clause 2. The complainant appealed these rulings.

In October 2010 Astellas UK paid £50,000 to the named hospital's special purpose fund. The Panel considered that this payment came within the complainant's general allegation about funding following the adoption of the immunosuppressive protocol. The Panel was concerned about the hospital's description of how the money was to be used which was sent to Astellas UK prior to the payment being made; this was not mentioned in the original request or the signed contract. There was no information before the Panel demonstrating that funding had been withdrawn when the outcome was not as expected as alleged.

The Panel noted with concern the complainant's allegation that the clinical protocol to use Advagraf *de novo* was abandoned by 2012 because of poor outcomes. No copy of the protocol was provided. There were no details about when or how it was agreed. The complainant referred to its adoption in 2009 which was before Astellas UK made the payment of £50,000 in 2010. The Panel noted that in his/her letter of 6 October 2010 a senior person at the hospital with a fundraising role referred to using the £50,000 for implementation of the protocol. The Panel noted that the initial request for the £50,000 funding stated 'As per our recent conversations about clinical research and medical education in the …'. The Panel had no knowledge of the content of these conversations.

Although the Panel was concerned about the circumstances, particularly the impression given, it did not consider that the complainant had shown, on the balance of probabilities, that the funding was inappropriately linked to the use of Astellas UK's product. The Panel therefore ruled on balance no breach of the Code including Clause 2.

On appeal the complainant alleged that the exchange of correspondence between Astellas UK, the requesting health professional and the hospital fundraiser indicated extensive undisclosed

discussions. There was no indication of patient or wider NHS benefit in the request.

The complainant alleged that Astellas UK agreeing to fund two investigator driven clinical studies (IDS) in May-June 2009, had certainly influenced the subsequent adoption of Advagraf in the hospital protocol in September 2009. The change was proposed by the same applicants of the IDS and MEGS.

The Appeal Board noted that the complainant, bore the burden of proof. There was no evidence that funding had been provided for either of the two IDS. The Appeal Board therefore upheld the Panel's ruling of no breach of the 2008 Code including Clause 2 of the 2008 Code. The appeal on these points was unsuccessful.

The Appeal Board noted that according to the complainant in September 2009 the immunosuppressive clinical protocol at the named hospital was changed to Advagraf (*de novo*), azathioprine and prednisolone; the first patient was enrolled in November 2009. The Appeal Board noted, with concern, the complainant's submission that the hospital's clinical protocol was abandoned in 2012 due to high rejection rates, which the complainant submitted had been the subject of internal discussion within the hospital. The Appeal Board noted that the hospital's clinical protocol was the same as that proposed with regard to the second study in the IDSEC application and used Advagraf *de novo*.

The Appeal Board noted Astellas' submission that multiple factors might be involved in the rejection rates and also that there was no evidence to suggest that the provision of the subsequent MEGS to the hospital was linked, directly or indirectly to the hospital changing its immunosuppressant protocol. The Appeal Board considered that since the submission of the application for funding for the studies, there was evidence of ongoing interaction and dialogue between the hospital and certain key individuals at Astellas UK related to provision of funds to the hospital.

The Appeal Board noted the dates of key events.

The Appeal Board also noted the largely illegible document provided by Astellas which appeared to be headed 2009, the format of which appeared to be closely similar to the 2010 memorandum agreement for the £50,000 MEGS payment between Astellas UK and the hospital. It was partially signed. The second signature clause for the health professional bore an indecipherable signature and date. The first signature clause, unsigned, was for a specific Astellas UK member of staff from the medical department. In the Appeal Board's view this document showed that, on the balance of probabilities, at the very least, there was some dialogue between the key individuals at both the hospital and Astellas UK about the provision of funds, via the MEGS route resulting in the partially signed document.

The Appeal Board noted that on 11 May 2010 one of the health professionals who had applied for the study funding to the IDSEC in 2009 wrote to a member of Astellas UK's medical department (first employee) referring to recent conversations about '…clinical research…' to ask for £50,000 for the [special purpose fund] to support ongoing clinical research to facilitate employment of bank nursing staff/statistical support to extract and analyse the necessary data from the hospital's database. The Appeal Board noted that at that time, given Astellas UK's previous and ongoing interactions at the hospital, including the involvement of the first employee, on the balance of probabilities, Astellas UK would have known about the hospital's clinical protocol and the switch to use Advagraf in combination. A memorandum of agreement between Astellas UK and the hospital dated 27 May 2010 was signed by the applicant on 4 June and by Astellas UK on 14 June. The document mentioned that the grant was to support 'your continuing clinical research in the area of transplantation at [named hospital]', and that it was to facilitate employment of bank nursing staff/statistical support to extract and analyse the necessary data from the department's database. There was no mention in the memorandum of agreement about the hospital's clinical protocol. Following the agreement to donate £50,000, a hospital fundraiser wrote on 6 October 2010 confirming that the '… £50,000 grant would be used as part of the ongoing clinical research; it would '… permit implementation of a new clinical protocol using Advagraf in Denovo live related kidney transplantation and to support ongoing clinical research in the area of renal transplantation. The funding shall allow the team to employ bank nursing staff/statistical support to extract and analyse fundamental data'. The first employee responded to the applicant with a letter dated 14 October 2010 headed 'Re: Funding to support your continuing clinical research in the area of transplantation at … [hospital]' and enclosed a cheque for £50,000.

The Appeal Board noted Astellas' submission that the director at the hospital was mistaken that the clinical protocol was new. The Appeal Board was concerned about the description in the letter of how the money was to be used noting that it was received by Astellas UK before the payment was made; 'the implementation of a new clinical protocol' was not mentioned in the original request or the signed agreement. In the Appeal Board's view, the letter from the hospital made it clear that the hospital considered that the payment was linked to its use of Advagraf. The Appeal Board noted that the memorandum of agreement stated that 'You agree to use the Support for the purposes described in this letter only and you will return the Support to the Company if it is not used for these purposes'. Yet despite the reply stating that '… £50,000 grant would permit implementation of a new clinical protocol using Advagraf …' there was no information before the Appeal Board to demonstrate that Astellas UK had taken any action or followed up how the funding was subsequently used.

The Appeal Board noted from Astellas UK at the appeal, that the relevant standard operating procedure at Astellas UK at that time would have allowed the grant on the basis that it was for patient benefit and that it would have been approved by a grants committee, yet there was no record of this. In this regard the Appeal Board noted that the 2008 Code required MEGS to be documented and kept on record. Whilst noting the passage of time the Appeal Board was concerned about other missing core documentation such as records of contacts made by certain Astellas staff with the key health professionals and material submitted to IDSEC. The Appeal Board considered that whilst this had happened several years ago, by the standards required at that time, the documentation was poor. The Appeal Board queried Astellas UK's decision to award the grant given the company's recent interactions with the hospital regarding the IDSEC applications and the clinical switch to using Advagraf and the fact that MEGS were required to be non-promotional and must not constitute an inducement to prescribe, supply, administer, recommend, buy or sell a medicine.

The Appeal Board noted its comments above. The Appeal Board noted the common themes between the second study, the 2009-2012 hospital protocol and that the study funding requested was to help support a renal research fellow and research nurse – which echoed the reference in the MEGS application for support for a nurse/ statistical support to extract and analyse data. The Appeal Board noted the ongoing dialogue about funding outlined above and the failure to keep proper records and that the hospital linked the provision of the funds to Advagraf. The Appeal Board considered that the cumulative effect was that on the balance of probabilities, the payment did not satisfy the requirements for MEGS and was inappropriately linked to the use of Advagraf. The Appeal Board ruled breaches of the Code including a failure to maintain high standards. The Appeal Board considered that the circumstances were such that Astellas UK had brought discredit upon, and reduced confidence in, the industry. A breach of Clause 2 of the 2008 Code was ruled. The appeal on these points was successful.

During the re-audits in April 2018 in relation to other cases concerning Astellas UK and Astellas Europe (Cases AUTH/2780/7/15, AUTH/2883/10/16 and Cases AUTH/2939/2/17 and AUTH/2940/2/17) when those carrying out the re-audits followed up on the Appeal Board's concerns in Case AUTH/2984/10/17, a timeline (dated November 2010) was supplied which included details relevant to Case AUTH/2984/10/17 which had not been supplied previously. On receipt of further information from Astellas UK, the original Panel was reconvened to consider the matter.

The detailed response from Astellas UK is given below and included a report from external counsel which was asked by Astellas to conduct an investigation.

The Panel noted that its concerns were broader than outlined in the scope of the external counsel report requisitioned by Astellas including whether the apparent failure to provide a complete response reflected a cultural approach to compliance and the Code, noting that the failure to provide complete and accurate information had previously been an issue in Case AUTH/2780/7/15.

Numerous documents were requested by the PMCPA and these were supplied by Astellas UK with its response to the detailed questions. The Panel did not understand why these documents were not supplied with the company's responses to the complaint and appeal.

The Panel had a number of very serious concerns about the responses from Astellas and its approach to ensuring that comprehensive details were provided for both the Panel and the Appeal Board.

The Panel was extremely concerned about the company's responses. It appeared that the investigation into the complaint was inadequate. Astellas staff knew there was a timeline but Astellas UK appeared not to attempt to locate the November 2010 timeline nor was it provided in response to the complaint. Further, the Astellas UK timeline which was provided for the appeal was inconsistent with the November 2010 timeline. Astellas had not commented on the accuracy or otherwise of the November 2010 timeline.

The Astellas timeline provided in response to the appeal stated that Astellas closed the study application as not progressed in January 2010 as no revised proposal was submitted by the hospital and the written request for a grant was received on 11 May 2010.

The position regarding the separation of the discussion of the funding of the studies and the provision of a MEGS was not as clearly delineated as implied by the Astellas timeline provided for the appeal. It also appeared that there was more information about the *de novo* study than that supplied by Astellas UK in response to the complaint including that the *de novo* study had been approved by IDSEC on 27 November 2009 and the UK brand team decided not to support this IDS. It was not clear why such a decision was left to a brand team. It also implied that the possible funding of the study was a commercial/marketing decision rather than a medical one. The UK brand team would know about the change of treatment protocol in the hospital and it could be argued that there was no additional benefit to the company in funding the *de novo* study when it considered the matter in November 2009.

The Panel was concerned that Astellas had detailed information about the *de novo* study including the IDSEC submission but these had not been supplied in response to the complaint or appeal. This was inexplicable. It was of further concern that in response to a request for clarification from the PMCPA, Astellas submitted that material not provided previously was found as a result of the external counsel investigation. That was not so in

relation to the *de novo* study. Details were set out in the company's response to the complaint and appeal and yet no source material was provided at that stage.

It was of concern that the request letter from the hospital dated 11 May 2010 provided by Astellas in its response of 7 November 2017 was different to that previously supplied by Astellas as it did not include the wording:

> **'to implement our new clinical protocol using Advagraf in *de novo* live donor kidney transplantation and'**

The letter provided in November 2017 included details of the salary etc for the statistical support. One possible explanation for the differences was that on receiving the letter from the hospital someone at Astellas asked the hospital to amend its request. There was no evidence in that regard. Nonetheless, the original letter from the hospital was highly relevant.

The Panel was extremely concerned to note that Astellas' response of 26 January 2018, in relation to the appeal, specifically stated that there was no reference to using the grant to implement this protocol in the original request or the signed contract for the grant. Astellas also submitted, as part of its response to the appeal, that there was a misunderstanding or misstatement by a hospital fundraiser in the letter of 6 October 2010 who had referred to a 'new' protocol.

The external counsel report stated that discussions around the studies closed in January 2011. This was inconsistent with information provided for the appeal that another member of Astellas UK's medical department (second employee) visited the hospital in January 2010 to confirm in person that the two studies would not go ahead as IDSEC had not received a response. The November 2010 timeline clearly indicated discussions up until October 2010 in relation to the switch study. The external counsel report stated that on 22 December 2010 two named members of the medical department (the second employee and the first employee's line manager) met one of the health professionals to inform him/her that the switch study would not be progressed and to present the MEGS cheque (now made out to the correct payee). The Astellas timeline referred to this cheque as 'grant cheque issued by Astellas' on 21 December 2010.

The Panel was concerned about the impression given by this meeting when the health professionals from the hospital were both informed that the study would not be progressed and presented with the cheque for £50,000. The Panel noted an email from the second employee dated 22 December 2010 to a number of Astellas staff including senior leaders, the first employee and members of the UK brand team to report on the meeting (a copy of the November 2010 timeline was attached to the email). The email mentioned that 'we did of course soften the blow by delivering a £50k cheque today under the MEGS agreement which was for separate work and [the named health professional] seemed grateful for that'. At that meeting the company agreed to cover the cost of an expert who had prepared the study protocol, research ethics preparation and attended project planning meetings. A copy of an invoice for £2,500 was provided. This was the first mention of an additional and relevant payment in relation to the activities at issue, albeit to a third party. It underlined the importance of doing a broad indepth investigation at the outset.

It appeared that Astellas had not made any reasonable effort to look at the issues in the broadest sense to understand the relationship between various Astellas UK staff and the hospital.

The Panel noted the submission from Astellas regarding the timing of events and acknowledged that the time period around an audit/re-audit would be particularly demanding for any pharmaceutical company. Astellas was advised by the PMCPA case preparation manager that a complaint had been received and the response time was extended by the case preparation manager beyond the 10 working days, Astellas did not ask for an extension of time at either stage.

In the Panel's view, there was less overlap with the October 2017 re-audits than that implied by Astellas. The correspondence from the PMCPA referred to the possibility of requesting an extension and indeed the case preparation manager had decided herself to provide one at the outset, in the absence of any such request from Astellas. The Panel considered that stating that Astellas UK was in the middle of a major and important re-audit did not give a fair impression about the demands on the company resulting from the re-audits when responding to the complaint and the complainant's appeal.

The Panel noted that effective self-regulation relied upon the submission of accurate responses to the PMCPA. There was an expectation that companies comprehensively investigated all the circumstances surrounding complaints. Failure to do so and failure to provide an accurate, comprehensive response were serious matters. The PMCPA was extremely concerned about the additional information which only came to light as a result of an interview at the April 2018 re-audits. The Appeal Board had also commented on the limited documentation provided. It appeared that the company either did not recognise the importance and relevance of key information and decided not to follow up key information or decided to ignore this information. It was clear that the investigation team had not obtained all the relevant information from staff. The Panel was concerned about the statement in the external counsel report that information from interviewees did not always appear to have been read in full and incorporated into the responses and that there was a lack of follow-up of potentially relevant issues. Overall, in the Panel's view, the compilation of the response had been reckless; there appeared to be a complete absence of care and attention and due diligence.

The Panel noted Astellas' submission that overall this additional information would not have altered the company's submissions to the Panel and the Appeal Board but that Astellas accepted that there might have been a fuller response.

The Panel was extremely concerned about the inadequate investigation which led to incomplete and misleading responses. The missing information was relevant to rulings. The Panel had previously ruled, on balance, no breach of the Code in relation to the £50,000 MEGS payment. It was extremely concerning that the final outcome of this case would have been different if the complainant, a busy NHS health professional, had not appealed. Effective self-regulation should not rely on the fact that a health professional appealed a ruling to trigger a process which ultimately led to more complete disclosure. Nor should effective self-regulation be reliant upon the coincidental timing of the re-audits which fortuitously gave the opportunity for the PMCPA to follow-up on the Appeal Board's concerns about documentation.

The Panel considered that Astellas UK's behaviour in investigating this matter in October 2017 was unacceptable and was completely inconsistent with the recent and numerous commitments made elsewhere to upholding the highest standards. Astellas Europe and Astellas UK had been audited 5 times since December 2015. It was beyond belief that Astellas UK would not follow its standard operating procedure (SOP) given all the training and emphasis in the company to doing that. In previous cases Astellas had been found seriously wanting in taking appropriate action when responding to the PMCPA. The current suspension of Astellas UK from membership of the ABPI would end on 24 June 2018 and the ABPI Board decided on 5 June there was no need for it to consider expelling Astellas UK from membership. In reviewing the report of the April 2018 re-audits, neither the Appeal Board nor the ABPI Board took into account the matters raised following the appeal in Case AUTH/2984/10/17 as these were still to be considered by the PMCPA. The report of the April 2018 re-audits included a brief summary of the position.

Taking all the circumstances into account, including Astellas UK's acknowledgement that it had failed to follow its processes, the PMCPA decided to report Astellas UK to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure. Given the seriousness of the Panel's concerns and the other cases, the Panel considered that the report to the Appeal Board should be heard at its meeting on 20 June 2018.

The detailed comments from Astellas UK on the report from the Panel appear below.

The Appeal Board noted that Astellas UK was currently suspended from membership of the ABPI until 24 June 2018, having been suspended for the maximum 2 year period. At its meeting on 5 June 2018 in relation to Cases AUTH/2780/7/15, AUTH/2883/10/16 and Cases AUTH/2939/2/17 and AUTH/2940/2/17, the ABPI Board decided, on the evidence before it at that time which included the report of the April 2018 re-audits and a summary framework agreed by the Appeal Board, that there was no need to consider expelling Astellas. In reaching its decision, the ABPI Board noted that Astellas UK was still to respond in relation to the matters raised in Case AUTH/2984/10/17. Further re-audits were required by the Appeal Board to be carried out in March 2019 (Cases AUTH/2780/7/15, AUTH/2883/10/16 and Cases AUTH/2939/2/17 and AUTH/2940/2/17).

The Appeal Board considered the report in Case AUTH/2984/10/17 on 20 June. It noted that the report concerned Astellas UK's recent failure to properly investigate an historic matter including its failure to disclose all relevant documentation to the Panel and Appeal Board, and the company's current approach to compliance. The Appeal Board's role was to consider whether the circumstances warranted the imposition of further sanctions under Paragraphs 11.3 and 12.1 of the Constitution and Procedure.

The Appeal Board noted that Astellas UK had accepted all the rulings of breaches of the Code including Clause 2. The Appeal Board also noted Astellas UK's apology that its responses were not as complete as they should have been. It also noted Astellas UK's view that there were apparent failings in the process of requesting, providing and reviewing information. The company stated it had identified amendments to its processes to address these. The Appeal Board also noted Astellas submissions regarding its responses to the Panel and appeal including Astellas' view that its position in the appeal response would have remained the same in that there was no evidence to indicate that funding was offered or provided as an inducement for the hospital to place Advagraf on its immunosuppressant protocol.

The Appeal Board noted the very detailed consideration of the Panel including its comments on material not previously provided and its view that, overall, the compilation of the company's responses had been reckless; there appeared to be a complete absence of care and attention and due diligence. The Appeal Board also noted that the Astellas representatives referred to aspects of Astellas' investigation as 'too casual', 'cavalier' and stated that the mistakes made were being addressed. The company representatives stated that there was not an institutional failing with respect to compliance in Case AUTH/2984/10/17, a phrase previously used by the PMCPA to describe Astellas' compliance status.

The Appeal Board noted the historical nature of the matters at issue and accepted that retrieving some materials might not have been straightforward. The Appeal Board noted the company's submission in this regard. Nonetheless, the Appeal Board did not consider that the matter at issue in Case AUTH/2984/10/17 was as complex as implied by the company. In the Appeal Board's view, notwithstanding the historical nature of the matters at issue, adopting basic principles of good

governance and compliance practice, common sense and a positive cultural approach to transparency and disclosure should have facilitated more accurate responses and complete disclosure. That such an approach, apparently and on the evidence before the Appeal Board, was not consciously adopted at the outset was, in the Appeal Board's view, and given Astellas' recent compliance history, both inexplicable and inexcusable.

The Appeal Board was deeply concerned about the lack of rigour which Astellas had applied in conducting its investigation.

In the Appeal Board's view, the failures of the investigation team were startling and included an apparent failure, at the outset, to proactively seek information, bearing in mind the broad scope of the case preparation manager's request; primarily, using informal modes of communication (verbal and text messages) to seek critical information; an acknowledged failure to read all information including critical and relevant information provided by staff and an acknowledged failure to properly interrogate material and staff and adopt a policy of full disclosure.

The Appeal Board noted that despite Astellas knowingly deviating from its complaints SOP the company had made no record of this including any written agreed deviations.

The Appeal Board noted the Panel's assessment of the additional information and paperwork including the two different versions of the important letter from the hospital dated 11 May 2010 requesting the MEGS and the emails dated 9 and 10 December 2009 between the first and second employees, that the payment of the MEGS was now clearly linked to the change in the hospital treatment protocol to use Astellas' medicine in a manner consistent with the *de novo* study which had previously been rejected by Astellas' own IDSEC due to patient safety concerns current at that time. The Appeal Board noted that one version of the letter from the health professional at the hospital to Astellas dated 11 May 2010 linked the MEGS payment to the implementation of '… our new clinical protocol using Advagraf in *de novo* live donor kidney transplantation' and was highly relevant and had not been previously disclosed. The Appeal Board noted the company's explanation at the consideration of the report that, on receipt, the first employee asked the health professional to submit an amended version. This amended version of the 11 May 2010 letter had originally been provided to one of the investigators on 31 October 2017 as part of the investigation and disclosed to the PMCPA as part of its response to the complaint. The original 11 May 2010 letter linking the MEGS to the hospital treatment protocol was subsequently provided by the first employee to the investigator but it was unclear whether that attachment to an email dated 3 November 2017 had ever been opened and if so whether its significance had been realised. The Appeal Board considered that the original letter dated 11 May 2010 was highly relevant and provided compelling evidence that at the very least from the hospital's perspective the MEGS was linked to the product.

According to the November 2010 timeline, a newly designed *de novo* study was reviewed and approved by IDSEC on 27 November 2009 although the UK brand team subsequently decided not to support it.

The Appeal Board noted that according to the complainant in Case AUTH/2984/10/17, the hospital treatment protocol was ceased when higher than average rates of rejection were being recorded. Astellas had submitted in that case that multiple factors might be involved in the rejection rates. The Appeal Board noted that the historic patient safety issue was not the subject of the complaint in Case AUTH/2984/10/17 and therefore had not been considered or ruled upon as a discrete issue but rather arose as a coincidental matter during the consideration of that case. The Appeal Board noted its relevant comments above in the Appeal Board ruling. At the consideration of the report the company representatives explained that they had contacted the hospital after the appeal in Case AUTH/2984/10/17 because of the need to be transparent given the seriousness of the information re patient safety which came to light at the appeal. The Appeal Board noted that some of the newly disclosed material was relevant to the historic patient safety issues. The Appeal Board further noted that previous cases had raised patient safety issues (Case AUTH/2883/10/16 and Cases AUTH/2939/2/17 and AUTH/2940/2/17). It was of serious concern that a current investigation into a complaint that revealed an historic patient safety issue was so poor.

The Appeal Board considered that this case warranted the imposition of further sanctions and considered that it would be artificial to consider the proportionality of such sanctions without due regard to previous cases and 5 audits and re-audits over the past 3 years.

The Appeal Board noted that Astellas UK had apologised for its failings in this case and it stated that it was due to undertake measures to ensure that such failings did not reoccur. Nonetheless, the Appeal Board considered that it was fundamental for effective self-regulation for companies to provide accurate information to the Panel and the Appeal Board and for failing to do so it publicly reprimanded Astellas UK in accordance with Paragraph 11.3 of the Constitution and Procedure.

The Appeal Board noted that when it considered the report of the April 2018 re-audits at its meeting on 17 May 2018 it had decided that on the information before it, and noting that Astellas UK was still to respond in relation to the matters raised in Case AUTH/2984/10/17, that sufficient progress had been made by the companies such that the Appeal Board did not consider that it warranted a recommendation for the expulsion of Astellas UK from membership of the ABPI. Whilst noting that the expulsion of a member company was entirely a matter for the ABPI Board, the Appeal Board considered that had this report in Case AUTH/2984/10/17 been before it when it considered

the report of the April 2018 re-audits including the summary framework, it would have considered that insufficient progress had been made on certain parameters and the Appeal Board would have recommended that the ABPI Board expel Astellas from membership of the ABPI. The Appeal Board had previously expressed the view that if a company was expelled from membership from the ABPI for issues relevant to patient safety then the period of expulsion should be for 5 years.

The Appeal Board considered that this case raised very serious matters including the historic issues relating to patient safety. In addition, given the level of scrutiny the companies were already under in relation to compliance, the Appeal Board was very concerned about the issues as set out above. Consequently, taking all the circumstances into account, the Appeal Board decided that in accordance with Paragraph 12.1 of the Constitution and Procedure, Astellas UK should be reported to the ABPI Board. Whilst noting the ABPI Board's role and responsibilities in determining any expulsion, the Appeal Board recommended that Astellas should be expelled from membership of the ABPI for a minimum of 5 years.

The Appeal Board noted that the case raised issues other than the conduct of Astellas. It noted Astellas' statement that following the appeal in March 2018 it had written to the hospital about patient safety issues and considered that the case report, when available, should be provided to the hospital trust at issue as well as the Care Quality Commission, the independent regulator of health and social care in England, with a covering letter. The Appeal Board requested that it be provided with a draft of the covering letters for comment. The Appeal Board noted that the MHRA would receive a copy of the case report in any event.

The detailed comments from Astellas UK on the report from the Appeal Board appears below. The company submitted extensive comments including criticism of the Appeal Board's approach and consideration particularly that there was a lack of due process and unfair and prejudicial treatment of Astellas UK.

The ABPI Board noted the report from the Appeal Board and Astellas UK's comments.

When the ABPI Board had last considered matters relating to Astellas in June 2018 (Cases AUTH/2780/7/15, AUTH/2883/10/16 and Cases AUTH/2939/2/17 and AUTH/2940/2/17), it had been clear that the company would need to ensure that there was an ongoing commitment to sustained culture change throughout the organisation. Previous audits had shown that the compliance culture was improving, so it was disappointing that the company had been reported to the ABPI Board once more.

The view of the Appeal Board was clear. In addition to the report to the ABPI Board in Case AUTH/2984/10/17 and the recommendation that Astellas UK be expelled from membership of the ABPI for five years, the Appeal Board decided that Astellas UK should be publicly reprimanded. However, the ABPI Board remained clear in its view that compliance was an ongoing journey that required continual self-adjustment and improvement. The ABPI Board had confidence that a named senior leader at Astellas UK would be able to lead the company forward on this journey.

The ABPI Board considered the reputation of the industry to be of utmost importance, and therefore carefully considered all of the information before it. The ABPI Board concluded that although Astellas had made mistakes, in its view there was no malintent from the company to conceal. The ABPI Board noted the company's submission that measures had now been taken to address the issues arising from this case. The ABPI Board noted Astellas UK's submission that at no point were any patient safety issues caused by the conduct of Astellas and that the use of Advagraf within the protocol was in line with the SPC for the time the hospital protocol was in force. The ABPI Board further noted that patient safety was not the subject of the complaint.

The ABPI Board was already due to see the reports of the PMCPA's 2019 re-audits of Astellas UK and Astellas Europe as a result of its consideration of re-audits in other cases. The failures identified in this case should be considered as a part of those re-audits. The Board would look closely at the report of the re-audits to ensure that it remained satisfied with the position of the companies.

Taking everything into account, the ABPI Board decided that no further action should be taken in relation to this report from the Appeal Board.

A hospital doctor alleged that Astellas Pharmaceuticals Limited had inappropriately awarded research funding in 2009 in association with the use of Advagraf (tacrolimus) which was indicated for use in kidney and liver transplant patients to prevent rejection.

COMPLAINT

The complainant was seriously concerned about funding for research which was made available by Astellas UK. The complainant alleged that the funding was made available following the adoption of a new immunosuppressive protocol at the renal transplant unit of the named hospital. The immunosuppressive protocol was adopted in 2009 and abandoned by 2012 because of poor outcomes. The protocol was used for patients who received a renal transplant from a living donor and included the use of Advagraf (*de novo*), azathioprine and prednisolone. The complainant stated that he/she currently did not have the formal document which established the protocol, but it might be available if needed.

The complainant stated that a large sum of money (in the region of £250,000) was apparently made available to a senior clinician for conducting a study on the efficacy of the above protocol.

In the complainant's view, this needed to be clarified and fully investigated as if it was true, there might be evidence of inappropriate funding for research and a breach of the Code.

The complainant asked, in particular, if any funding was made available following the adoption of the new immunosuppressive protocol and had this allegedly proposed, or agreed, study followed the normal process in line with trust policy, Good Research Practice and the Code?

The complainant acknowledged that a long time had elapsed since the event, but the details had come to his/her attention only recently. The complainant hoped that an investigation might prove that such events had never happened and that the appropriate actions were followed at the time.

In a subsequent telephone call the complainant stated that his/her concerns included that there was a link between the adoption of the protocol and the provision of funding referenced in the complaint. The complainant also stated that funding, or part thereof, was withdrawn when the outcome was not as expected.

When writing to Astellas UK, the Authority asked it to consider the requirements of Clauses 2, 9.1 and 19.2 of the Code.

RESPONSE

Astellas UK stated that it took all allegations of non-compliance with any regulations, including the Code very seriously, and had conducted a comprehensive investigation in which it had checked all existing records of Astellas UK support of research in the UK and reviewed payments made to the hospital. It appeared that in May 2009 Astellas UK received a request for research funding for two studies. The request was made in April 2009 by two senior health professionals from the hospital. The amount requested to fund both studies was £250,000 and the titles and scientific rational of the proposed studies were:

- Randomised prospective open label trial to investigate the safety and efficacy of switching stable renal transplant recipients from Ciclosporin to Advagraf.
    - The rationale was that a once daily medicine which was less nephrotoxic and better tolerated than Ciclosporin would significantly improve chronic renal allograft failure and an investigator driven study was proposed to evaluate Advagraf in their patient population.
- Primary immunosuppression with Advagraf in Asian and Afro-Caribbean kidney allograft recipients.
    - The study aimed to address the increased incidence of post renal transplant diabetes mellitus (PTDM) in tacrolimus treated patients particularly in African-Americans. PTDM after renal transplantation was associated with adverse outcome on patient and graft survival. They wanted to demonstrate that treating this patient group with Advagraf and rapid steroid withdrawal was effective in minimising the incidence of PTDM.

Astellas UK stated that as background to the immunosuppression landscape at the time, ciclosporin, a calcineurin inhibitor, had played a major role in the advancement of transplant medicine since its inception into clinical use in the late 1970s. While it improved rates of acute rejection and early graft survival, data on long-term survival of renal allografts was less convincing and there were issues with long-term toxicity. When the request to support two clinical studies was made, it was not unreasonable that the proposed investigators were looking to evaluate the transfers of stable patients from ciclosporin to tacrolimus. There was no evidence that there was an inducement for them to do so.

The request was submitted to the Astellas review committee, the Investigator Driven Study Evaluation Committee (IDSEC) in May 2009 and approved in principle with a number of outstanding questions. The responses to the committee's questions were considered by IDSEC on 30 June 2009. However, despite 'approval in principle' by IDSEC, it appeared that no agreement was signed, neither study went ahead and no funds were made available by Astellas UK.

There was no evidence to suggest that the funding requested for these studies was intended to be, or considered, an inducement to include Advagraf on the immunosuppression protocol for the hospital. Rather, it appeared to be a request to support legitimate research to assess whether tacrolimus could improve chronic renal allograft failure and/or minimise the incidence of PTDM.

Astellas UK reviewed all payments made to the hospital by both Astellas UK and Astellas Pharma Europe since 2009 and had identified only one payment. This was categorised in the finance system as a payment in relation to a medical and educational good or service (MEGS) and appeared to be in response to a letter of request received in May 2010 from one of the health professionals who had requested funding for research as detailed above. The request was for £50,000 for a special purpose fund to support ongoing clinical research in the area of renal transplantation and permit the implementation of a new clinical protocol using Advagraf as *de novo* immunosuppression in live related kidney transplantation. The funding was intended to facilitate the employment of bank nursing staff/statistical support to extract and analyse the necessary data from the department's database. The payment was made on 21 December 2010 to the trust.

Astellas UK submitted that there was no evidence that this grant was provided with the expectation that the hospital would include Advagraf on its immunosuppressant protocol, or that it was in any other way an inducement to prescribe Advagraf. Astellas UK thus denied that this grant was provided contrary to the requirements of what was now Clause 19.2 of the Code.

In relation to the complainant's statement that 'The immunosuppressant protocol was adopted in 2009 and abandoned by 2012 because of poor outcomes', Astellas UK assumed that this referred to the hospital's transplantation guidance protocol rather than a study protocol. As noted previously, no study protocol was ever agreed with Astellas UK for the two studies. Astellas UK had no documentation of, or input into, the trust's internal protocols on immunosuppression.

As detailed above, a single payment of £50,000 for a MEGS was made in December 2010 to support ongoing clinical research in the area of renal transplantation. No study funding was ever approved or paid by Astellas UK to the hospital for the two proposed studies and there was no evidence that the application for study support was intended to be, or considered, an inducement to include Advagraf on the hospital's immunosuppression protocol.

There appeared to have been no clinical study approved or agreed with Astellas UK therefore there was no ethics committee approval applied for and no 'Good Research Practice' (or rather GCP; Good Clinical Practice in relation to clinical trials) documented or required.

Given the above, Astellas UK stated that it did not consider that there was any evidence that any of the above detailed activities or funding was an inducement to prescribe Advagraf and thus there had been no breach of what was now Clause 19.2. There had thus been no failure by Astellas UK to maintain high standards and there had been no activity that would either reduce confidence in, or bring into disrepute, the pharmaceutical industry; therefore there was no breach of either Clause 9.1 or 2.

PANEL RULING

The Panel noted that the original request for £250,000 to sponsor two studies was considered by Astellas UK in 2009. A payment of £50,000 was made according to Astellas UK on 21 December 2010. The relevant Code was the 2008 edition. Clauses 18.4 (which cross referred to Clause 18.1) and 18.5 of the 2008 Code were the relevant clauses for the provision of medical and educational goods and services. Clauses 19.1 (which cross referred to Clause 18.1) and 19.2 in the 2016 Code included an additional requirement that details of the payments needed to be disclosed. Clauses 2 and 9.1 were the same in the 2008 and 2016 Codes. There were differences in Clause 2 of the supplementary information between the 2008 and 2016 Codes. The Panel therefore considered this case in relation to the 2008 edition of the Code.

The Panel noted that in May 2009 the Astellas Investigator Driven Study Evaluation Committee (IDSEC) had 'approved in principle' a request for £250,000 to fund two studies but wanted answers to a number of questions. The request was made in April 2009 by two health professionals from the hospital. Each study was to use Advagraf and was due to start in January 2010. Neither study went ahead and no funds were made available by Astellas UK at the time. In 2010 a request from one of the health professionals for £50,000 for the special purpose fund to support ongoing clinical research was agreed and payment was made according to Astellas UK on 21 December 2010. The Panel noted Astellas UK provided a copy of a cheque which appeared to be dated 10 October 2010 which was sent with a letter dated 14 October 2010 from a member of Astellas UK's medical department. Following the agreement to donate £50,000, a senior person at the hospital with a fundraising role wrote on 6 October 2010, received by Astellas UK on 11 October 2010, confirming that the '… £50,000 grant would permit implementation of a new clinical protocol using Advagraf in *de novo* live related kidney transplantation and to support ongoing clinical research in the area of renal transplantation. The funding would allow the team to employ bank nursing staff/statistical support to extract and analyse fundamental data'. There was no mention in a memorandum of agreement between Astellas UK and the hospital (signed in June 2010) about the clinical protocol. The memorandum of agreement mentioned that the £50,000 was to support continuing clinical research in the area of transplantation at the hospital to facilitate employment of bank nursing staff/statistical support to extract and analyse the data from the department's database.

The Panel noted that Astellas UK had not provided the protocol. The company stated it had no documentation of or input to the trust's protocols in immunosuppression. The complainant stated it was used from 2009 to 2012 and alleged that following its adoption, Astellas UK agreed to fund a study.

It was not clear when or why Astellas UK decided not to fund the two studies following the request in April 2009. As no payment had been made there was no evidence of inappropriate funding for research in this regard. The Panel therefore ruled no breach of Clause 18.5 of the 2008 Code. In this regard the Panel also ruled no breach of Clauses 9.1 and 2 of the 2008 Code.

On 12 October 2010 Astellas UK paid £50,000 to the special purpose fund at the trust. The requesting health professional confirmed receipt which was received by Astellas UK on 8 November 2010. The Panel considered that this payment came within the complainant's general allegation about funding following the adoption of the immunosuppressive protocol. The Panel was concerned about the hospital fundraiser's description of how the money was to be used which was sent to Astellas UK prior to the payment being made; this was not mentioned in the original request or the signed contract. There was no information before the Panel demonstrating that funding had been withdrawn when the outcome was not as expected as alleged.

The Panel noted with concern the complainant's allegation that the clinical protocol to use Advagraf *de novo* was abandoned by 2012 because of poor outcomes. No copy of the protocol was provided. There were no details about when or how it was agreed. The complainant referred to its adoption in 2009 which was before Astellas UK

made the payment of £50,000 in 2010. The Panel noted that in his/her letter of 6 October 2010 the hospital fundraiser referred to using the £50,000 for implementation of the protocol. The Panel noted that the initial request for the £50,000 funding stated 'As per our recent conversations about clinical research and medical education in the [department] …'. The Panel had no knowledge of the content of these conversations.

Although the Panel was concerned about the circumstances, particularly the impression given, the Panel did not consider that the complainant had shown, on the balance of probabilities, that the funding was inappropriately linked to the use of Astellas UK's product. The Panel therefore ruled on balance no breach of Clause 18.5 and subsequently no breach of Clauses 9.1 and 2 of the 2008 Code.

APPEAL FROM THE COMPLAINANT

The complainant stated that the information provided by Astellas UK had generated more concerns regarding the events that led to the adoption of Advagraf in the immunosuppressive protocol at the hospital. The complainant presented some considerations based on the information provided and specific queries for the attention of the Appeal Board.

The complainant stated that for the investigator driven clinical study (IDS) for a switch from cyclosporine to Advagraf in stable renal transplant recipients, the objective, number of patients required, recruitment and follow-up period were clearly stated. The definition of 'stable' patients was unclear. The complainant queried if an early switch was considered at 3 to 6 months or after one year?

The complainant alleged that for the IDS for primary immunosuppression with Advagraf in Asian and Afro-Caribbean patients there was no information on this study in the application forms provided. It appeared that Astellas UK had explained a valid rationale for this study. The primary endpoint was not stated nor if the study was intended for a kidney transplant from a deceased donor or a living donor. It was not clear how many patients were required for this study. According to the information provided in the application form, the length of the study would be the same as the 'switch' study; with a similar, 12 months recruitment and 12 months follow-up. It was not clear how patient recruitment for this study would work. The full immunosuppressive regime proposed in the study; specifically, what anti-metabolite was considered (mycophenolate mofetil (MMF) or azathioprine) to be implemented in the protocol together with early steroids withdrawal was not mentioned. It was not stated which control group was considered; specifically, if they were patients on cyclosporine or tacrolimus twice a day-based regimen.

The complainant noted that the immunosuppressive protocol in use at the hospital for renal transplantation at the time of application for the IDS was daclizumab, cyclosporine, MMF, steroids as stated in the application form for IDS.

The complainant alleged that according to the information provided, there was a rather tight timeline between the 'approval in principle' (June 2009) and the expected ethical approval (November 2009), considering that Advagraf was not on the hospital formulary and not part of the immunosuppressive protocol for renal transplantation at the hospital.

The complainant noted that no evidence was provided regarding withdrawal of support to the studies.

The complainant noted that the document provided with Astellas UK's response described as '… written agreement between Astellas and the [hospital] …' was not clearly legible. It appeared to be dated 1 December 2009 (following the adoption of the protocol with Advagraf at the hospital). The format and reference of the document seemed to be the same as the document used in May 2010 'Support of ongoing clinical research at the [hospital] in the area of Clinical Transplantation'. It seemed to refer to undisclosed discussion between Astellas UK and the health professional. The nature of the support agreed by Astellas UK appeared to be £50,000. It bore the name of a specific Astellas UK employee. The complainant alleged that the exchange of correspondence between Astellas UK, the requesting health professional and director at the hospital indicated extensive undisclosed discussions. There was no indication of patient or wider NHS benefit in the request. The director at the hospital indicated that '… The £50,000 grant would permit implementation of a new clinical protocol using Advagraf in Denovo live related kidney transplantation …'. There was no evidence that adequate and clear information was provided to health professionals in the service.

The complainant would be grateful if the Appeal Board requested that Astellas UK provided more detailed information regarding the study on *de novo* use of Advagraf in Afro-Caribbean and Asian patients; specifically the number of patients, the study design and the type of donor.

The complainant would be grateful if Astellas UK was asked to provide further information on the final outcome of the two IDS 'Approved in Principle'; specifically, evidence of withdrawal of support from Astellas UK.

Regarding the MEGS the complainant would be grateful if the Appeal Board requested more detailed information regarding the document that was not clearly legible; specifically:

- The application of funding for MEGS prior to December 2009.
- Evidence of the extensive discussions occurred between Astellas UK and the applicants of the IDS between June 2009 and December 2009.
- Ideally Astellas UK could provide a more easily readable copy.

The complainant would be grateful if the Appeal Board requested that Astellas UK provided detailed

information regarding the MEGS requested by the health professional and subsequently paid in October 2010; specifically:

- What patient benefit was identified?
- What was the wider NHS benefit?
- What clear information was provided to health professionals involved in the management of renal transplant patient?
- What clinical studies in the area of clinical transplantation were supported with the £50,000 grant?

The complainant alleged that the sequence of events constructed from the documentation provided raised more concerns that the role of Astellas UK directly or indirectly induced a change of the immunosuppressive protocol for renal transplant patients. Agreeing to fund two IDS in May-June 2009, had certainly influenced the subsequent adoption of Advagraf in the protocol of the hospital in September 2009. The change was proposed by the same applicants of the IDS and MEGS. It was of crucial importance to understand the actual number of patients required for the IDS B (*de novo* Advagraf in Afro-Caribbean and Asian patients) that Astellas UK had agreed to fund. When the funding application was made, the workload of the unit would only have allowed a limited number of patients to be enrolled in any form of prospective study without changing the protocol. Astellas UK gave a reasonable account of the de-novo study despite there being no information related to this study in any of the documents provided; therefore, it was conceivable that the study synopsis was currently available to Astellas UK and could be shared with the Appeal Board.

The complainant alleged that the 'unfortunate', not clearly readable, document generated major concerns. Careful and tedious reading, together with cross-checking the document provided by Astellas UK, revealed important facts. A meticulous reader would notice: it was dated December 2009, it indicated undisclosed previous discussions and Astellas UK agreed to provide support of £50,000.

The complainant alleged that the fact that an application for MEGS before December 2009 was not provided, indicated that Astellas UK had recognised the change of protocol and it intended to reward the applicants/investigators. It also indicated continued support to the investigators for undisclosed, ongoing research at the hospital under a different funding channel. The continued support was also apparent by the fact that there was no evidence of withdrawal of support for the studies; also that the agreement to pay £50,000 represented the first of possible subsequent payments that could have taken place according to the progress of the study or number of patients on Advagraf. Generally, a withdrawal of financial support for a clinical study was clearly documented and conveyed to the applicants. It might be conceivable that the studies went ahead, but not as intended, but could not be published because of negative outcomes or non significant findings. The MEGS of £50,000, clearly documented in May 2010, failed to identify clear patient and wider NHS benefit and referred to ongoing research in clinical transplantation. Such research was, however, not and its absence might be easily demonstrated by running a simple search. The reference to implementation of the protocol in the letter from the director at the hospital was very disturbing, as it might reflect an undisclosed agreement between Astellas UK and the applicants of the IDS and MEGS. There was no adequate information provided to health professionals in the unit related to IDS and more importantly to MEGS funding. Undoubtedly, the availability of such disclosure as indicated by Clause 18.5 would have allowed close ethical scrutiny of the new protocol proposal and subsequent implementation. The adoption of the protocol with Advagraf, azathioprine and early steroid withdrawal had led to a disastrous rate of biopsy proven acute rejection in standard risk recipients of a renal transplant from a living donor. The complainant provided an extract from the immunosuppression audit (4 slides). Many patients had suffered prolonged admission, had lost their transplants generously donated by a family member, had, following the acute rejection, developed high levels of sensitisation becoming unsuitable for further transplantation or in some cases died suffering further complications generated by the management of acute rejection.

In conclusion, the complainant considered that having reviewed all the documentation, further clarity was needed so that an external observer might have no doubts that there were no links or interdependence between the funding application for IDS; the change of immunosuppressive protocol at the hospital and subsequent payment of MEGS.

The complainant considered that the evidence provided by Astellas UK corroborated the information that had generated his/her concerns, confirming that these events could account for dubious funding of research, aimed to introduce the prescription of Advagraf in a centre that used different immunosuppressants; as a consequence of these events, it might constitute a breach of Clauses 18.5, 9.1 or 2 of the Code.

RESPONSE FROM ASTELLAS UK

Astellas UK stated that its reference to the studies being 'approved in principle' meant that the broad concept of the study could be supported and that a full protocol would need to be submitted for formal consideration. Additionally, Astellas UK provided a timeline outlining the chain of events regarding the matter at issue to provide further clarity.

Astellas UK submitted that it appeared that the complainant was still concerned that there might be a link between its provision of financial support and the hospital placing Advagraf (tacrolimus) on to its immunosuppressant protocol for renal transplant patients. The complainant also alleged that Astellas UK had withheld information that it received in relation to two proposed IDS.

Astellas UK refuted all allegations and considered that there was no evidence to suggest any

inducement from Astellas UK for the hospital to place Advagraf on to its immunosuppressant protocol.

Astellas UK submitted that in relation to the hospital's request for financial support for two IDSs, the proposed investigators had not submitted a formal study protocol. The Astellas UK review committee approved the study in principle only, based on an outline study proposal. Further details and subsequently a revised proposal were requested but not provided (email trail provided). As far as Astellas UK was aware, the two studies did not go ahead. No agreement covering an IDS was signed between Astellas UK and the hospital in relation to the proposed studies and no funds or other support was made available by Astellas UK.

In relation to the MEGS grant of £50,000 provided to the hospital, Astellas UK noted both the Panel's and complainant's concern about the wording in the letter from the hospital fundraiser (dated 6 October 2010) in which he/she referred to the funds as being used to implement a 'new' clinical protocol. Astellas UK submitted that the reference to a 'new' protocol must have been a misunderstanding or misstatement. A new immunosuppressant protocol was agreed by the hospital in September 2009 and first implemented on 1 November 2009. Therefore, in October 2010, the hospital fundraiser was not referring to a 'new' protocol as it had been in place for almost a year. The funding would 'allow the team to employ bank nursing staff/statistical support to extract and analyze fundamental data'; this seemed more fitting for a protocol that had been in place for some time and was in keeping with a typical patient outcomes audit conducted by the NHS. Further, there was no reference to using the grant to implement this protocol in the original request or the signed contract for the grant. Astellas UK concluded that there was no link between it providing a grant and the hospital placing Advagraf on its immunosuppressant protocol.

Astellas UK noted that the complainant raised what appeared to be clinical governance issues at the hospital in 2012. Such serious governance issues should have been addressed by the medical director of the hospital trust when they were originally detected. Astellas UK did not consider that it, the Panel or the Appeal Board could address this matter.

Astellas UK noted the complainant's comments and questions; however the company never received a formal study protocol from the proposed investigators and so it was unable to comment on the specifics the complainant requested. The Astellas review committee approved the study in principle only, based on an outline study proposal and requested further details and a revised proposal (email trail provided) but these were not provided and so as far as Astellas UK knew, the study or studies did not go ahead. No agreement was signed between Astellas UK and the hospital in relation to the proposed IDS and no funds or other support was made available by Astellas UK to the hospital. Astellas UK was unable to provide documentation to evidence the withdrawal of support that was never provided.

Astellas UK submitted that as stated above it had no record of, or input into, the hospital's internal immunosuppression protocols.

Astellas UK submitted that the date provided in the outline proposal for the ethical approval of the proposed IDS was an 'expected' date. As noted above, no formal protocol was submitted to Astellas UK by the proposed investigators which could have been used for ethics approval. As far as Astellas UK was aware, the proposed studies did not go ahead.

Astellas UK submitted that the hard to read enclosure dated 2009 was a draft contract which was never executed. The agreement, dated 27 May 2010, was the final contract which was executed in relation to the grant provided. Reference to previous discussions was a standard contractual recital contained within the Astellas UK contract template. It was also recognised practice for a company to enter in discussion prior to formalizing arrangements in any contract.

Astellas UK could find no reference to any 'discussions' in the letter from the hospital fundraiser. In relation to correspondence between Astellas UK and the health professional, referring to 'discussions', as explained above, it was recognised practice for a company to enter in to discussion prior to formalising arrangements in a legally binding contract.

Astellas UK considered the following to be items which provided benefit to patients and/or the NHS in relation to the grant supplied to the hospital, as detailed in its letter of request, 11 May 2010:

- Supporting ongoing clinical research in the area of renal transplantation
- Staff costs to extract and analyse patient database.

Astellas UK submitted that the Code did not definitively require companies to communicate the provision of a grant to the wider department/relevant parties (this was still only a recommendation).

Astellas UK submitted that the second IDS was proposed by the hospital. As noted above, no formal study protocol was ever submitted and the Astellas UK review committee approved the study in principle only based on an outline study proposal and requested further details and a revised proposal which were not provided.

As far as Astellas UK knew, the studies did not go ahead. No agreement was signed between Astellas UK and the hospital in relation to the proposed IDS and no funds or other support was made available by Astellas UK to the hospital. It was not possible to withdraw support which was not provided. Astellas UK had no further information on this study.

Astellas UK submitted that no clinical studies were supported by the grant/funding it provided to the hospital. The MEGS contract dated 27 May 2010, provided £50,000 to facilitate employment of bank nursing staff/statistical support to extract and

analyse the necessary data from the department's database.

Astellas UK submitted that there was no evidence that its 'agreement in principle' to support the two proposed IDS influenced the adoption by the hospital of Advagraf on to its immunosuppressant protocol for renal transplant patients. The IDSEC approved the study in principle only, in May 2009, based on an outline study proposal. As demonstrated in the detailed (Astellas) timeline provided, when the new protocol was agreed (September 2009) Astellas still had some outstanding questions on the proposed studies and requested further details and a revised proposal which were not subsequently provided and the application had not progressed since June 2009. As noted above, as far as the company was aware, the studies did not go ahead; no agreement signed between Astellas UK and the hospital in relation to the proposed studies and no funds or other support were made available by Astellas UK.

Astellas UK submitted that there was no evidence to suggest that its provision of the grant to the hospital was linked, directly or indirectly, to the hospital changing its immunosuppressant protocol for renal transplant patients.

Astellas UK submitted that its timeline describing the chronological order of events demonstrated that the new clinical protocol was agreed in September 2009. The hospital requested the grant 8 months later ie May 2010; the agreement for the provision of this grant was signed by both parties in June 2010 and the payment was cleared in February 2011. The grant payment was not made to individuals. The cheque was made payable to the disease specialist fund. Astellas UK had reviewed all payments made by it to the hospital and had identified only one relevant payment which was the £50,000 MEGS as described above.

As far as the company knew, this study did not go ahead; there was no agreement signed between Astellas UK and the hospital in relation to the proposed study and no funds or other support were made available by Astellas UK. It was not possible to withdraw support that was never provided. Astellas UK submitted that as noted above, there seemed to be a misunderstanding or misstatement by the hospital fundraiser who referred to a 'new' clinical protocol, yet it appeared the protocol was approved in September 2009 and implemented in November 2009 (as indicated by the complainant.) Therefore, in October 2010 when the letter was written the 'new' protocol to which he/she referred had been in place for almost a year. He/she went on to state that the funding would support 'the team to employ bank nursing staff/statistical support to extract and analyse fundamental data'; this seemed more fitting for a protocol that had been in place for some time and was in keeping with a typical patient outcomes audit. Astellas UK submitted that the incomplete slides provided by the complainant in his/her appeal suggested an audit of clinical outcomes at the hospital. The information provided was incomplete, but showed a high rate of acute rejection; no conclusions were drawn or were apparent from these slides and there were no details provided of any actions taken to address causality. Multiple factors might be involved in these outcomes. The complainant should raise this clinical governance issue with the medical director of the hospital trust; given the seriousness of the matter, it should have been addressed when the issues were originally detected in 2012.

In conclusion, having reviewed and addressed all of the points raised in the complainant's appeal, Astellas UK did not consider that there was any evidence to indicate that it had offered or provided funding as an inducement for the hospital to place Advagraf on its immunosuppressive protocol. Astellas UK thus refuted breaches of Clauses 18.5, 9.1 and 2.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant stated that the information provided by Astellas UK had again generated more concerns as, in his/her opinion, the appeal was not addressed satisfactorily.

Astellas UK had not provided:

- Evidence that appropriate information was provided to the medical and nursing staff of the transplant unit of the hospital regarding the £50,000 MEGS paid in October 2010.
- Evidence of adherence to internal protocol for approval of IDS and MEGS.
- Evidence of withdrawal of support to IDS.
- Evidence of an application for MEGS done by the clinicians of the hospital before the 'draft agreement' for MEGS dated December 2009.

The complainant alleged that some of Astellas UK's statements were highly contradictory and, in some instances clearly incorrect.

APPEAL BOARD RULING

The Appeal Board considered this case in relation to the 2008 edition of the Code.

The Appeal Board noted the submissions from the complainant and Astellas UK including the complainant's submission that he/she had unsuccessfully raised his/her concerns with other regulators and he/she was grateful that the PMCPA had listened and taken action. The complainant referred to a number of issues including that it was unusual to have different treatment protocols for transplants from living and deceased donors. The complainant referred to increases in rejection rates. The complainant had not known that Astellas UK had given £50,000 as a MEGS in 2010 until he/she was notified of the Panel's rulings. The Appeal Board also noted Astellas' concerns about patient safety which the company raised with the PMCPA following receipt of the complainant's appeal. Astellas UK stated at the appeal that it had sought reassurance from the PMCPA that the patient safety issues were raised with the hospital and that the PMCPA had indicated that the complainant had informed the hospital of his/her concerns at the relevant time.

In addition to the complainant's submission that he/she had raised concerns with the hospital, the hospital protocol was discontinued, therefore the PMCPA advised Astellas UK there was no need to raise the complainant's concerns with the hospital immediately. Astellas stated it would disclose it after the appeal.

The complainant stated that, at the time, Astellas was fully aware of the outcomes of the hospital clinical protocol and the reasons for its discontinuation in 2012.

The Appeal Board noted that the broad nature of the appeal raised non-Code matters, including clinical governance in the hospital. The Appeal Board noted that it was only concerned with acts and omissions on the part of Astellas which fell within the scope of the Code.

The Appeal Board noted that the activities in question took place between 2009 and 2012 and that when considering the requirements of the 2008 edition of the Code it had to take into account the standards at that time. In particular the Appeal Board considered that what might currently be considered standard practice in relation to governance including record keeping might have been considered best practice when the matters at issue arose. The Appeal Board also noted that Clause 18.5 of the 2008 Code required MEGS, *inter alia*, to be documented and kept on record by the company.

The Appeal Board also considered that it ought to bear in mind that certain terminology used in the industry such as 'MEGS' might not be commonly used or understood within the NHS. Similarly, it noted that the word 'protocol' was used in relation to both the proposed clinical studies and to the departmental clinical guidance used at the hospital.

The Appeal Board noted that limited documentation had been provided by Astellas UK. It noted Astellas UK's submission about the nature and depth of its investigation. The matter was further complicated by the events having occurred some years ago and a number of staff were no longer with Astellas. Nonetheless, the Appeal Board queried why detailed accounts were not provided from two critical members of staff, who had some involvement in all of the matters at issue and were still employed by Astellas.

The Appeal Board noted from the company representatives that the Astellas IDSEC operated at a regional level. The Appeal Board noted that in May 2009 the Astellas IDSEC had approved 'in principle' a request first made in April 2009 by two health professionals from the hospital for £230,000 to fund two studies. The first an IDS to assess efficacy and safety of switching stable renal transplant recipients from ciclosporin to Advagraf. The second study assessed primary immunosuppression with Advagraf in Asian and Afro-Caribbean kidney allograft recipients. The IDSEC application form and some comments were provided in relation to the first study. No IDSEC documentation was provided in relation to the second. It was unclear how Astellas UK could be confident about the details of that second study, including its approval in principle, given the absence of such documentation.

The IDSEC approved the first study in principle and raised a number questions on 5 May 2009 that needed to be addressed before things could progress. Astellas also stated that the second study was approved in principle. The responses to these queries were considered by the IDSEC on 30 June 2009. Further queries raised by the IDSEC were not documented, however emails of 18 August between an Astellas UK employee and the applicants for the study funding (provided in response to the appeal), referred to a meeting between themselves and the same Astellas UK employee in August 2009 regarding the IDSEC applications. One of the three emails of 18 August referred to the updates being addressed at the upcoming IDSEC. An email from the health professionals at the hospital to the first employee referred to both studies and commented on amendments which appeared to relate to further queries raised by the IDSEC in relation to both studies. The email referred to the proposed Advagraf/azathioprine with steroid withdrawal in the second (acute) study and the investigators' views that this should remain as it was in the current departmental protocol for live transplants. The suggested MMF/Advagraf protocol might not be approved; moreover, medicine costs would escalate and given the current financial climate, that protocol was unaffordable. After responding to queries about the second (acute) study the email stated '…this is a novel, exciting, cost effective protocol that will translate into better adherence to immunosuppression by patients by being a truly once daily regime'. No documentation for the August 2009 IDSEC meeting was before the Appeal Board. The Appeal Board noted Astellas UK's submission that despite these interactions there was no evidence that either study went ahead. The Appeal Board noted the submission from the company representatives at the appeal that a member of Astellas UK's medical department (second employee) had visited the hospital in January 2010 to confirm in person that the funding for the two studies would not go ahead as IDSEC had not had a response to its latest requests, and that there was no other record of this interaction. It appeared that this had not previously been disclosed although the company representatives stated that an entry for January 2010 on its timeline, submitted as part of the appeal, that 'Astellas UK closes study application as not progressed as no revised proposal submitted by [named hospital]' was based on a verbal account. The Appeal Board considered that it was odd that there was no written confirmation that the company would not fund the studies. The Appeal Board noted that the Astellas timeline entry did not refer to a hospital visit, nor did it make it clear that it was based on a verbal account.

The Appeal Board noted that the complainant bore the burden of proof. There was no evidence that funding had been provided for either of the two studies. The Appeal Board therefore upheld the Panel's ruling of no breach of Clause 18.5 of the 2008 Code. In this regard the Appeal Board also upheld

the Panel's rulings of no breach of Clauses 9.1 and 2 of the 2008 Code. The appeal on these points was unsuccessful.

The Appeal Board noted that, according to the complainant, the immunosuppressive clinical protocol at the hospital was changed in September 2009 to Advagraf (*de novo*), azathioprine and prednisolone; the first patient was enrolled in November 2009. The Appeal Board noted, with concern, the complainant's submission that the hospital's clinical protocol was abandoned in 2012 due to high rejection rates, which the complainant submitted had been discussed within the hospital. The Appeal Board noted that the hospital's clinical protocol was the same as that proposed with regard to the second study in the IDSEC application and used Advagraf *de novo*.

The Appeal Board noted Astellas' submission that multiple factors might be involved in the rejection rates. The Appeal Board noted Astellas UK's submission that there was no evidence to suggest that the provision of the subsequent MEGS to the hospital was linked, directly or indirectly, to the hospital changing its immunosuppressant protocol. The Appeal Board considered that since the submission of the application for funding for the studies, there was evidence of ongoing interaction and dialogue between the hospital and key individuals at Astellas UK related to provision of the funds to the hospital.

The Appeal Board noted the dates of key events outlined above.

The Appeal Board also noted the largely illegible document which appeared to be headed 2009 and provided by Astellas UK, the format of which appeared to be closely similar to the 2010 memorandum agreement for the £50,000 MEGS payment between Astellas UK and the hospital subsequently provided. The company representatives confirmed that the largely illegible document was provided from its employee's archive. The Appeal Board did not accept that this was a template as suggested by Astellas at the appeal as it was partially signed. The second signature clause for the health professional bore an indecipherable signature and date. The first signature clause, unsigned, was for a named member of staff from the Astellas UK medical department. In the Appeal Board's view, this document showed that, on the balance of probabilities, at the very least there was some dialogue between the key individuals at both the hospital and Astellas UK about the provision of funds, via the MEGS route resulting in the partially signed document.

The Appeal Board noted that, on 11 May 2010 one of the health professionals who had applied for the study funding to the IDSEC in 2009, subsequently wrote to the Astellas UK employee noted above and referred to recent conversations about '… clinical research…' and asked for £50,000 for the [special purpose fund], to support ongoing clinical research to facilitate employment of bank nursing staff/statistical support to extract and analyse the necessary data from the hospital's database. The Appeal Board noted that at that time, given Astellas UK's previous and ongoing interactions at the hospital, including the involvement of the same first employee, on the balance of probabilities, Astellas UK would have known about the hospital's clinical protocol and the switch to use Advagraf in combination. A memorandum of agreement between Astellas UK and the hospital, dated 27 May 2010, was signed by the applicant on 4 June and by Astellas UK on 14 June. The document mentioned that the grant was to support 'your continuing clinical research in the area of transplantation at [the hospital]', and that it was to facilitate employment of bank nursing staff/statistical support to extract and analyse the necessary data from the department's database at the hospital. There was no mention in the memorandum of agreement about the hospital's clinical protocol. Following the agreement to donate £50,000, a hospital fundraiser wrote on 6 October 2010 confirming that the '… £50,000 grant would be used as part of the ongoing clinical research; it would '… permit implementation of a new clinical protocol using Advagraf in Denovo live related kidney transplantation and to support ongoing clinical research in the area of renal transplantation. The funding shall allow the team to employ bank nursing staff/statistical support to extract and analyse fundamental data'. The Astellas UK employee responded to the applicant with a letter dated 14 October 2010 headed 'Re: Funding to support your continuing clinical research in the area of transplantation at [the hospital]' and enclosed a cheque for £50,000. Payment was made according to Astellas UK on 21 December 2010.

The Appeal Board noted Astellas' submission that the hospital fundraiser was mistaken that the clinical protocol was new. The Appeal Board was concerned about the director at the hospital's description in his/her letter of how the money was to be used noting that it was received by Astellas UK before the payment was made; 'the implementation of a new clinical protocol' was not mentioned in the original request or the signed agreement. In the Appeal Board's view, the letter from the director at the hospital made it clear that the hospital considered that the payment was linked to its use of Advagraf. The Appeal Board noted that the memorandum of agreement stated that 'You agree to use the Support for the purposes described in this letter only and you will return the Support to the Company if it is not used for these purposes'. Yet despite the reply stating that '… £50,000 grant would permit implementation of a new clinical protocol using Advagraf …' there was no information before the Appeal Board to demonstrate that Astellas UK had taken any action or followed up how the funding was subsequently used.

The Appeal Board noted from the representatives from Astellas UK at the appeal, that the relevant standard operating procedure at Astellas UK at that time would have allowed the grant on the basis that it was for patient benefit and that it would have been approved by a grants committee, yet there was no record of this. In this regard the Appeal Board noted that Clause 18.5 of the 2008 Code required that

MEGS were documented and kept on record. Whilst noting the passage of time the Appeal Board was concerned about other missing core documentation such as records of employee's contacts with the key health professionals and material submitted to IDSEC given the employee did not attend these meetings. The Appeal Board considered that whilst this had happened several years ago, by the standards required at that time, the documentation was poor. The Appeal Board queried Astellas UK's decision to award the grant given the company's recent interactions with the hospital regarding the IDSEC applications and the clinical switch to using Advagraf and the fact that MEGS were required to be non-promotional and must not constitute an inducement to prescribe, supply, administer, recommend, buy or sell a medicine.

The Appeal Board noted its comments above. The Appeal Board noted the common themes between the second study, the 2009-2012 hospital protocol and that the study funding requested was to help support a renal research fellow and research nurse – which echoed the reference in the MEGS application for support for a nurse/statistical support to extract and analyse data. The Appeal Board noted the ongoing dialogue about funding outlined above and the failure to keep, as required by Clause 18.5, proper records and that the hospital linked the provision of the funds to Advagraf. The Appeal Board considered that the cumulative effect was that, on the balance of probabilities, the payment did not satisfy the requirements of Clause 18.5 and was inappropriately linked to the use of Advagraf. The Appeal Board ruled a breach of Clause 18.5 and consequently a breach of Clause 9.1 as high standards had not been maintained. The Appeal Board considered that the circumstances were such that Astellas UK had brought discredit upon, and reduced confidence in, the industry. A breach of Clause 2 of the 2008 Code was ruled. The appeal on these points was successful.

Following its consideration of the appeal, the Appeal Board noted that Astellas UK was currently suspended from membership of the ABPI as a result of a number of other cases and actions. The Appeal Board was very concerned about the serious failings in this case but considered that given the timing of events in question which occurred before the cases which led to the suspension, and the ongoing activities including re-audits of both companies in April 2018, that further action in the case was not needed.

CODE OF PRACTICE PANEL FURTHER CONSIDERATION

Those carrying out the re-audits of Astellas in April 2018 in Cases AUTH/2780/7/15, AUTH/2883/10/16 and Cases AUTH/2939/2/17 and AUTH/2940/2/17 followed up the Appeal Board's concerns as set out in the ruling above with Astellas. These being that the limited documentation provided by Astellas UK, Astellas UK's submission about the nature and depth of its investigation and that detailed accounts of the two critical members of staff, who had some involvement in all of the matters at issue and were still employed by Astellas, had not been provided.

At the request of those carrying out the re-audits, a timeline was provided by an individual via the company's normal process for supplying requested documentation. The impression was given at the re-audits that the company had access to his/her laptop.

The timeline was dated 24 November 2010 and headed 'Overview of Investigator Led Studies', used the terms 'Switch IDS' to refer to the first study and '*de novo* IDS' to refer to the second study. The first entry was 30 June 2008 where there was a meeting with one of the hospital doctors, [named], to discuss his/her study. The draft protocol was received on 29 July 2008. There was no date on the November 2010 timeline for when Astellas declined the switch study because of cost. The submission of the second *de novo* study was recorded between 29 July 2008 and 25 March 2009 on the November 2010 timeline. The switch study was approved, in principle, by IDSEC on 5 May 2009. The *de novo* study basic approach was viewed positively. The November 2010 timeline recorded the IDSEC comments on both studies. The first employee met various health professionals and discussed the two studies including on 23 June 2009. On 18 August the first employee fed back to the UK transplant brand team and IDSEC on the discussions with the investigators. On 27 August 2009 IDSEC reviewed the proposals again. It would not approve the *de novo* study (second study), IDSEC was happy with the switch study but would not approve it as the funding (£250,000) was to cover both studies. The resubmitted *de novo* study was reviewed by IDSEC in October 2009. On 17 and 18 November the first employee discussed splitting the funding for the two studies so that the switch study could at least start (£200,000 for the switch study and £50,000 for the de novo study). On 24 November IDSEC issued an IDS Code for the switch study and on 27 November 2009 IDSEC reviewed and approved the *de novo* study. This was not supported by the UK SRC and the Astellas UK brand team decided not to support this IDS. The first mention of the MEGS was in December 2009. The draft IDS research agreement for the switch study and a copy of the MEGS agreement were emailed to the health professional at the hospital on the same day, 17 December 2009. The first employee followed up on 7 January 2010 to ask if one of the health professionals at the hospital had reviewed the draft agreements and again on 21 January 2010. This was followed up with telephone calls in April and May. The November 2010 timeline stated that the first employee received the updated switch study IDS protocol and the incomplete MEGS forms for their audit on 11 May 2010. The first employee followed up in September and October 2010 regarding the switch study. A draft protocol was sent to Astellas on 15 October 2010. The last record on the November 2010 timeline was 19 October 2010 which was an email sent to the hospital setting out the company's comments and questions on what was referred to as the 'draft protocol'.

FURTHER INFORMATION FROM ASTELLAS, MAY 2018

Astellas Europe provided two letters, one being the summary of the investigation by external counsel which was instructed by Astellas' legal department to look at whether Astellas UK followed the company

policy and whether the Astellas UK investigation was reasonable and proportionate. The investigation also looked at the process for creating Astellas UK's response to the PMCPA and how the timeline dated 24 November 2010 came into existence and why it was not disclosed as part of Astellas UK's response to the PMCPA.

The second response provided Astellas' explanation as to how the information would have impacted on Astellas' response to the complaint, both to the Panel and for the appeal.

The investigation concluded that company policy was not followed while investigating the complaint and that the investigation was deficient under the circumstances. Astellas stated that it took these issues very seriously and was considering (in consultation with external counsel) the appropriate actions to ensure that this situation did not occur again.

The report stated that discussions around the studies closed in January 2011. The written request for funding for a MEGS was received in May 2010. Discussions had been ongoing since the year before, at least from December 2009.

Although Astellas UK did not refer to the standard operating procedure (SOP) for conducting an investigation many of the basic steps required by the SOP were followed, however, several important requirements were missed. The report was said to include some examples of the deficiencies in investigatory steps.

There appeared to have been an excessive reliance on the fact that finance had confirmed that no payments had been made by Astellas to the hospital in relation to IDSs. The confirmation from finance came relatively early in the investigations process, and it appeared that this led one of the Astellas staff investigating to believe that the main aspect of the investigation had been completed and there was, therefore, no need to pursue other avenues of investigation in full. This person did not attempt to piece together the story of the MEGS funding and any potential relationship to the hospital's protocol, and did not contact a member of staff in a timely manner. The investigating member of staff stated at interview 'for me, financial data was most crucial, I was so confident that no study was done; we only volunteered MEGS because we happened to see it in the financial data and so offered it by way of full disclosure'. It was clear that he/she did not appreciate that whilst the complaint might have originally inquired only about IDSs and its link to the hospital protocol, it was likely that Astellas UK would also have to answer for other types of funding which might be seen to have influenced the hospital's protocol. The PMCPA (case preparation manager) asked for comprehensive details about any monies supplied or made available to the hospital/ specific clinician in relation to a study/other research in relation to the protocol. The complainant later specifically raised the MEGS in the appeal.

There was a failure to interview key individuals who were integral to the relationship between UK and the hospital with respect to the applications for funding. Of those interviewees who were contacted, one was contacted late and information provided by interviewees did not appear to have been read in full and incorporated into the responses.

There was a lack of follow-up with respect to issues which were raised and could have potentially been relevant.

No notes of interviews were taken or of any document requests made. The process for gathering documents was not methodical or reasonably and proportionately diligent, and as a result only a very limited number of documents were reviewed. The responses were not checked by the two key people involved in the matter at issue.

The Astellas UK team decided not to offer interviewees the opportunity to check the draft and when questioned explained that it was not typical at Astellas for those named in a complaint to be involved beyond being interviewed; all information needed had already been gathered from the interviewees, and as a result of heightened sensitivity within Astellas UK in relation to Code matters and the PMCPA audit, they thought it sensible to keep interactions about the complaint to the minimum number of individuals at Astellas UK that it was reasonable to speak to in investigating the complaint.

The investigation discovered that the November 2010 timeline was created by the first employee who had a relevant role in relation to the applications for funding. When the IDSs did not progress, this employee's line manager asked for a timeline so that in the event that they were asked any questions by the commercial or sales team, they could demonstrate that they had done everything they could do from their end to enable the research to progress. The investigation summary stated that the first employee did not disclose the timeline when corresponding in relation to the complaint, and it might be reasonable for the relevant investigator to have expected the timeline to be provided when he/she became aware of the complaint and was searching for related contracts. There was no evidence of a deliberate attempt to conceal. The investigation summary stated that another employee also possessed the document but did not disclose it, this appeared to be a genuine but careless error in circumstances where he/she was given very little time to respond before the filing of the first response. The lack of follow-up, having been notified in passing by the second employee of the existence of the timeline, appeared to be more reflective of the investigative style and lack of investigations experience (which led in turn to over-reliance on information received from Astellas UK finance that no payment had been made in relation to the IDSs) rather than a deliberate attempt to conceal.

The investigation report set out several mitigating factors that should be taken into account in relation to Astellas UK's conduct of its internal investigation into the complaint:

a) The lack of experience of staff with key roles in the investigation and the perception that this was a complex case. Indeed, the inter-relationship between Study 1, Study 2, the MEGS and the hospital protocol was complex and potentially confusing to those without a thorough understanding of the medication prescribed to transplant patients.
b) Astellas UK was in the middle of a major and important PMCPA re-audit when the complaint was received, which meant that the Astellas UK team, already operating under the short timelines applicable under the Code, was not able to dedicate as much time to putting together the responses as they might have liked. Other resources in Astellas UK might have been, understandably, less responsive during the re-audit. When sharing the complaint with named Astellas staff they were informed that '… we will not share this with anyone in APL in advance of the audit, to keep the focus on the audit …'.
c) The PMCPA re-audit also meant that there was a heightened sensitivity within Astellas UK in relation to Code matters, which, in turn, led to the Astellas UK investigations team not reaching out to all relevant people who could have provided information.
d) One of the investigators who said he/she was aware of the SOP, did not appear to signpost other members of the Astellas UK team to it and the need to follow it.
e) Headcount records at Astellas UK might have been incomplete, which might have been why the names of those who were involved in the matters being complained of and remained at Astellas UK were not provided.
f) It might have been reasonable for the employee to provide the November 2010 timeline in any event when he/she became aware of the complaint and was searching for related contracts. Had the November 2010 timeline been disclosed prior to the filing of the first response (or indeed the response to the appeal), this would have led to different lines of enquiry and a fuller response to the complaint.

A list of interviewees for the investigation, a list of documents provided to the external counsel by Astellas and its chronology of key events were provided.

Astellas also provided a letter setting out its views regarding whether and how the additional information uncovered by the external counsel investigation including the November 2010 timeline provided to the PMCPA at the re-audit, would have impacted the Astellas response to the initial complaint in this case and the subsequent appeal (see below).

Astellas stated that three pertinent emails (copies provided) were uncovered as part of the recent investigation.

The three emails provided related to the timing of applications/discussions about the IDSs, MEGS and the new hospital protocol that were not discovered by the Astellas UK team. Firstly, an email from the first Astellas UK employee to the second employee on 9 December 2009, referred to a conversation that day with a named health professional wanting to implement his/her clinic protocol of Advagraf and azathoprine. The email referred to moving '… the MEGS agreement forwards asap along with the IDS agreement for switch (Ciclosporin to Advagraf) study'. Secondly, the response the following day, 'This is [his/her] preferred protocol and it is not for us to dictate the relative merits of this v Advagraf and MMF'. Thirdly, the 21 January 2010 email from the first employee to a number of colleagues including the second employee who referred to a meeting on 22 January 2010 with two named health professionals to discuss the ciclosporin switch study and Astellas' commitment to 'their ongoing research. They started their first living donor Tx recipient on Advagraf and Azathioprine on Tuesday and are pleased with the results so far. They are calling this … once daily regime and expect to start all new patients onto this regime over the next 12 months …'.

Astellas stated that as concluded in the investigation, had the November 2010 timeline and emails provided been disclosed prior to the filing of the first response (or indeed the response to the appeal), this would have led to different lines of enquiry and a fuller response to the complaint. However, whilst there might have been a fuller response, the overall tenet of the initial response and the position in the appeal response would have remained the same, as outlined below.

Astellas' comments on its previous response to the Panel

Astellas stated that whilst the additional information provided further detail as to the events relating to the investigator sponsored research (ISR) applications (the main focus of the initial complaint) and the MEGS application made to Astellas by the hospital, Astellas did not consider that it provided any evidence that the immunosuppressant protocol was agreed at the hospital in anticipation of Astellas funding either ISR or providing a grant to the hospital, nor did it provide evidence that Astellas agreed to fund such activities in return for the protocol change. Thus, Astellas' overall response to the initial complaint would have remained the same; this being that:

- There was no evidence to suggest that the funding requested for the ISRs was intended to be, or considered, an inducement to include Advagraf on the immunosuppressant protocol at the hospital; and
- There was no evidence that the grant was provided with the expectation or, or reward for, the hospital including Advagraf on its immunosuppressant protocol.

Astellas' comments on its previous response to the appeal

Astellas stated that the additional information would have changed its approach to the appeal, but not its position in relation to whether there

was any evidence to indicate an inappropriate link between the consideration of the ISR application, the provision of the grant and the decision by the hospital to include Advagraf on to its immunosuppressant protocol.

One approach in the appeal response was to demonstrate that there was a clear separation in time between the ISR discussions being closed out, the decision by the hospital to change its protocol and the application to Astellas by the hospital for a grant. The additional information demonstrated an overlap in time between the ISR discussions (which appeared to have continued in to late 2010) and the discussions about the grant application (which appeared to have begun in approximately December 2009); thus the additional information would have changed the timeline presented by Astellas at the appeal hearing.

There appeared to have been at least two occasions where the ISRs, grant and protocol were discussed in the same meeting between the hospital and the Astellas employee but this was not unexpected given the employee's role, and there was no indication in these emails that any support was being offered in return for a protocol change.

Even given the additional information noted above, the Astellas position in the appeal response would have remained the same, in that there was no evidence to indicate that funding was offered or provided by Astellas, as an inducement for the hospital to place Advagraf on its immunosuppressant protocol.

PMCPA CONSIDERATION

The PMCPA considered the additional material and requested further information from Astellas UK.

FURTHER RESPONSE FROM ASTELLAS (11 JUNE 2018)

In response Astellas stated that the previous document was a summary of factual findings of the external counsel's investigation separate from its full report, which had not been disclosed due to its privileged nature.

The scope of the external counsel's investigation was:

a) to investigate whether or not Astellas UK followed company policy in the conduct of an internal investigation which took place following the complaint;
b) notwithstanding whether or not company policy was followed in this regard, to investigate whether or not the internal investigation conducted by Astellas UK was reasonable and proportionate;
c) to investigate who was involved in producing Astellas UK's responses and what process was followed in creating the responses; and
d) to investigate how the November 2010 timeline came into existence, and why it was not disclosed to the PMCPA as part of the responses. ((a) to (d) being referred to as the '[external counsel] Scope').

Astellas responded to the PMCPA questions as set out below. The company provided some additional context relevant to all of the responses below in that Case AUTH/2984/10/17 related to a complex factual scenario which took place many years ago now. Not only did the time delay mean that the recollections of those involved was not clear, it also meant that access to records was not straightforward.

In addition, the case evolved from when it was first lodged in October 2017, with the complainant revealing more information as the case progressed.

Finally, Astellas submitted that it was important to note that the team at Astellas UK was under exceptional pressure at the relevant time as a result of the re-audit in October 2017, as well as a very tight timescale within which to respond to a complex, historical case.

Astellas confirmed that SOP-1177 APL Management of Complaints was current and effective. It was currently being redrafted as a regional SOP, combining SOP-1244 and SOP-1177, and including learnings from this matter. Astellas confirmed that SOP-1425/1.0 was current when provided at the April 2018 re-audits. Subsequently a new version, SOP-1425/2.0 was trained out at Astellas UK in April 2018, and became effective on 1 May 2018.

In their investigation of the case, the team requested information from three sources: first, to individuals to provide their documents; secondly, they instructed the Astellas UK Finance team to extract all financial records relevant to the hospital; and lastly all relevant contracts were requested from the company archive.

The team was provided with documentation by the two employees and at the same time gathered documentation from archives. Hardcopy archives were searched (for example, the MEGS agreement sent to the PMCPA on 8 November 2017 was found in the hardcopy archives) and Finance was able to verify that no payment had been made to the hospital in relation to the IDSs.

The dates used to search for emails for the individuals listed were chosen in light of the external counsel's investigation scope. For these reasons, the first employee's inbox from the date of joining the company was searched. Given the external counsel scope, and the dates of the mailbox searches for the first employee, it was decided that the dates for the second employee (12 April 2012 – 23 May 2018) were appropriate and proportionate. The majority of documents sent to and from the first employee during 2009 – 2011 were copied to the second employee so there was no need to extract the same documents from the second employee's mailbox. In addition to the documents which featured in the first employee's inbox, the second employee provided the external counsel with key documents. The external counsel believed that it was able to sufficiently understand and explain communications between Astellas UK and the hospital in connection with the studies, MEGS and the new hospital protocol through the documents and emails reviewed, and the interviews.

Others who became involved after receipt of the complaint on 16 October 2017 had searches of emails on the period of the October 2017 investigation forward.

The roles of the team were provided.

The first employee was interviewed by one of the investigators who also contacted the second employee by email and text message not by telephone. In any case, the second employee confirmed by email and text message that no funding had been provided to the hospital for IDSs and that he/she could not recall the MEGS agreement so suggested speaking to the first employee. The second employee provided some documentation in the same email correspondence. The view was taken that all the knowledge had been provided and an interview by phone was not necessary (or practical).

The investigator did not contact the line manager to assist with the second response primarily because the investigations team were confident they had the sufficient information to provide a detailed response.

All three members of the team took their responsibilities in relation to the investigation very seriously. They were all directly involved in Astellas' Compliance Excellence Program and were aware of the importance of collaborating fully and openly with the PMCPA.

Astellas submitted that the context in which the investigation took place was also important to bear in mind: the team at Astellas UK were under exceptional pressure at the relevant time as a result of the re-audit in October 2017, as well as a very tight timescale within which to respond to a complex, historical case. The case related to a complex factual scenario which took place many years ago now. In addition, the case evolved over time from when it was first lodged in October 2017, with the complainant revealing more information as the case progressed.

In their investigation the team made requests for information from three sources: first, there was a request to individuals to provide their documents; secondly, they instructed the Astellas UK Finance team to extract all financial records relevant to the hospital; and lastly all relevant contracts were requested from the company archive.

External counsel concluded that a lack of Code investigations experience and the incompleteness of the original complaint led to the team not reading in full and incorporating into the responses the information provided by interviewees. One of the investigators understood the complaint to be querying IDS funding and initially narrowed the investigation on to this topic, and was reassured by Finance in the first few days of the investigation that no funding had been provided for IDSs (and, indeed, by the fact that the amounts referred to in the Finance records tallied with the number in the complaint letter). It was important to note, however, the finance investigation discovered the MEGS funding which was disclosed as part of the response. Information received in relation to the MEGS was not interrogated as thoroughly as an experienced Code investigator might have done.

In addition, due to the passage of time, obtaining records was particularly difficult.

Astellas submitted there was no evidence, (and this was supported by external counsel's findings), that there was any deliberate attempt by the team to omit relevant information provided by interviewees. There was no documentary evidence that any discussions were had by the team around selected disclosure of information provided by interviewees or of any other information gathered, and this was confirmed by each member of the investigations team at interview with external counsel. The process followed by the team was simple: One gathered the information another incorporated it into the responses (and the other reviewed the ABPI Code).

There was not a policy at Astellas of taking interview notes as good practice in Code complaint investigations, and the SOP did not require notes of interviews to be taken. Consequently, the team did not believe this to be necessary or proportionate, especially in light of the fact that the two employees provided their recollections in writing by email, with supporting documentation attached. No discussions were had during which a conscious decision was made not to take interview notes.

In October 2017, Astellas was subject to re-audits by the PMCPA, and it was of the highest priority to the companies to fulfil the commitments made to the PMCPA and embed compliance in its culture. In addition, Astellas UK had been subject to suspension from the ABPI for 18 months, and so all matters relating to the Code were – quite naturally – of great importance and sensitivity in the companies. Management was very mindful of their employees' lack of confidence at that time and fears of making further mistakes. It therefore felt it was appropriate to inform only those individuals of the case whom it was reasonable for them to contact in relation to the investigation of the complaint.

Details of the roles and experience of the investigators were provided. The roles included analysing the Code in effect at the relevant time (2009/2010) and penning the initial drafts of both responses working with the information provided. At the time the complaint was received, all members of the team were already under intense pressure in preparing for the imminent audit, and as soon as the audit was complete they had to focus on responding to the complaint in a short timeframe.

Astellas provided the documents referred to in the external counsel response and requested by the PMCPA.

Where an item was provided previously in connection with the case, Astellas submitted it became aware of such an item at that time. Where an item was not provided previously in connection with Case AUTH/2984/10/17, it was an item found as a result of the external counsel investigation, which was when Astellas became aware of it.

An email from one of the health professionals at the hospital to the first Astellas UK employee on 4 January 2011 stated that the offer for funding the IDS has been withdrawn: 'Your team came to speak to me about switch study and it was informed to me that your company has decided not to support this. I fully understand…'. The health professional was referring to the meeting with the second employee and the first employee's line manager on 22 December 2010, during which they delivered the message that Astellas UK was no longer able to provide funding with respect to study 1.

Astellas confirmed that all emails reviewed by the external counsel relating to the timings of applications/discussions about the IDSs, MEGS and new hospital protocol had now been provided to the PMCPA.

In response to a question that some examples in the deficiencies in investigatory steps were given in the external counsel report and what were the other examples of deficiencies and why were they not included?, Astellas stated that 'some examples' should be more accurately rewritten as 'the categories of examples'. The document was a summary of the factual findings and therefore the deficiencies in investigatory steps were summarised into the seven categories listed. All deficiencies found fitted into one of these categories: none had been excluded.

In relation to the role of the chief executive of Astellas UK, Astellas stated this had three key elements: (i) ensuring that the investigation team was set up to deliver a response within the correct timelines, (ii) reviewing and approving the responses to the PMCPA, and (iii) considering all relevant matters beyond the Code, such as any patient safety implications of the case.

Panel consideration of additional information (12 June 2018)

The Panel noted that the consideration of the merits in Case AUTH/2984/10/17 was complete. Its role was not to reassess the merits of that case but to consider the additional information provided both at the April 2018 re-audit and subsequently by Astellas. This would include whether a report to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure in relation to Astellas' investigation of, and responses to, the complaint and appeal in Case AUTH/2984/10/17 and its conduct in relation to the Code was warranted. Such consideration might involve an assessment of the relevance of new information including whether in the view of the Panel it ought to have been disclosed.

The Panel noted the scope of the external counsel report requisitioned by Astellas. The Panel noted that its concerns were broader than outlined in that report including whether the apparent failure to provide a complete response reflected a cultural approach to compliance and the Code, noting that the failure to provide complete and accurate information had previously been an issue in Case AUTH/2780/7/15.

Numerous documents were requested by the PMCPA and these were supplied by Astellas UK with its response to the detailed questions. The Panel did not understand why these documents were not supplied with the company's responses to the complaint and appeal.

The Panel had a number of very serious concerns about the responses from Astellas and its approach to ensuring that comprehensive details were provided for both the Panel and the Appeal Board.

The Panel noted the emails provided by Astellas UK in its letter of 31 May 2018. The first email was dated 9 December 2009 and referred to the health professional at the hospital wanting to implement his/her clinical protocol of Advagraf and azathioprine. The first employee would 'move the MEGS agreement forward asap along with the IDS research agreement for the switch (Ciclosporin to Advagraf) study'. This email was sent to the second employee and other staff. The second email (dated 10 December 2009), the response referred to it being the health professional's preferred protocol and it was not for the company 'to dictate the relative merits of this v Advagraf and MMF'. The third email dated 21 January 2010 from the first employee referred to a meeting on 20 January with the hospital to discuss the ciclosporin switch study and Astellas' commitment to 'their ongoing research'. This email included:

> 'They started their first living donor Tx recipient on Advagraf and Azathioprine on Tuesday and are pleased with results so far. They are calling this the […], once daily regime and expect to start all new patients onto this regime over the next 12 months with a view to writing up the results for publication.
>
> The switch study IDS research agreement is being reviewed by their R&D department and they are in the process of advertising for the Research Registrar to run the trial. They have not yet submitted to ethics/MHRA, which is disappointing; however they agreed they will start this process immediately so that when the new Research Registrar is in post the project will be ready to start, in early April. They said they are also in the process of identifying potential patients for the study …'.

This email was sent to a number of members of staff, including at least one currently working at Astellas UK. The staff appeared to be commercial staff and a response from the marketing manager asked the first employee to share the great update with the 'team at the next Brand team meeting'.

The Panel was extremely concerned about the company's responses. It appeared that the investigation into the complaint was inadequate. Astellas staff knew there was a timeline but Astellas UK appeared not to attempt to locate the November 2010 timeline nor was it provided in response to the complaint. Further, the Astellas UK timeline which was provided for the appeal was inconsistent with the November 2010 timeline. Astellas had not

commented on the accuracy or otherwise of the November 2010 timeline.

The Astellas timeline provided in response to the appeal stated that Astellas closed the study application as not progressed in January 2010 as no revised proposal was submitted by the hospital and the written request for a grant was received on 11 May 2010.

The Astellas timeline did not refer to the first employee sending the MEGS agreement to the hospital in December 2009. There was an overlap between the discussions about the studies and the discussion about the MEGS. The email from the first employee to the second employee of 9 December 2009 referred to the health professional's clinic protocol, the MEGS agreement and the switch study. This was not mentioned in the November 2010 timeline. However, the November 2010 timeline stated that both the switch study and the MEGS were referred to in a number of the first employee's emails (the first one being 17 December 2009). It was extremely unlikely that the first time MEGS were mentioned was in December 2009. The position regarding the separation of the discussion of the funding of the studies and the provision of a MEGS was not as clearly delineated as implied by the Astellas timeline provided for the appeal. It also appeared that there was more information about the *de novo* study than that supplied by Astellas UK in response to the complaint including that the *de novo* study had been approved by IDSEC on 27 November 2009 and the UK brand team decided not to support this IDS. It was not clear why such a decision was left to a brand team. It also implied that the possible funding of the study was a commercial/marketing decision rather than a medical one. The UK brand team would know about the change of treatment protocol in the hospital and it could be argued that there was no additional benefit to the company in funding the *de novo* study when it considered the matter in November 2009.

The Panel noted from the additional information that the discussions about the switch study started in June 2008 prior to the request to Astellas in April 2009. The protocol for the *de novo* study was provided in March 2009. The hospital treatment protocol was agreed in September 2009, it commenced on 1 November 2009 and the first patient was treated in January 2010. This was soon after the first employee had emailed the MEGS agreement form.

An email from the first employee to the Chair of IDSEC, dated 22 April 2009 included the protocol synopsis for both studies as well as the application forms for both studies. The application forms for the *de novo* study (dated 16 April 2009, 5 May 2009 and 30 November 2009) gave the investigator's name. These forms were highlighted by Astellas. Astellas had not been told the name of the complainant but having attended the appeal on 22 March the company would be aware of his/her identity. The November 2010 timeline referred to two email requests for meetings in June and July 2009. The November 2010 timeline referred to the submission of the *de novo* study by the two health professionals. The date was unclear but appeared to be between 29 July 2008 and March 2009. The Panel noted this information but its role was to consider the matter in relation to the conduct of Astellas.

The Panel was concerned that Astellas had detailed information about the *de novo* study including the IDSEC submission but these had not been supplied in response to the complaint or appeal. This was inexplicable. It was of further concern that in response to a request for clarification from the PMCPA, Astellas submitted that material not provided previously was found as a result of the external counsel investigation. That was not so in relation to the *de novo* study. Details were set out in the company's response to the complaint and appeal and yet no source material was provided at that stage.

The first employee had sent the health professional an email dated 17 December 2009 referring to a telephone discussion about MEGS and requesting a letter on NHS headed paper '…from you requesting could 'Astellas consider providing £50,000 to support your ongoing clinical research at the [named hospital] in the area of Renal Transplant'. The email also stated that it would be helpful to include further details as to the purpose of the funding such as staff salaries, study expenses etc'. On 11 May 2010 the hospital sent the study protocol as requested, the letter requesting £50,000, the MEGS paperwork and the 'live donor IS protocol'. The letter gave the details for the payee and included:

> '… we would appreciate if Astellas would consider an Educational Grant of £50,000 (fifty thousand pounds) to the department **to implement our new clinical protocol using Advagraf in *de novo* live donor kidney transplantation and** to support ongoing clinical research in the area of renal transplantation. This funding would facilitate employment of bank nursing staff/statistical support to extract and analyse the necessary data from our comprehensive database' (emphasis added).

Astellas response to the complaint, 7 November 2017, used similar language to describe the request:

> 'the request was for £50,000 for the Renal Disease Special Purpose Fund to support ongoing clinical research in the area of renal transplantation and permit the implementation of a new clinical protocol using Advagraf as *de novo* immunosuppression in live related kidney transplantation'

It was of concern that the request letter from the hospital dated 11 May 2010 provided by Astellas in its response of 7 November 2017 was different and did not include the wording in bold above:

> 'to implement our new clinical protocol using Advagraf in *de novo* live donor kidney transplantation and'

The letter provided in November 2017 included details of the salary etc for the statistical support. One possible explanation for the differences was that

on receiving the letter from the hospital someone at Astellas asked the hospital to amend its request. There was no evidence in that regard. Nonetheless, the Panel considered that the original letter from the hospital was highly relevant.

The Panel was extremely concerned to note that Astellas' response of 26 January 2018, in relation to the appeal, specifically stated that there was no reference to using the grant to implement this protocol in the original request or the signed contract for the grant. Astellas also submitted, as part of its appeal, that there was a misunderstanding or misstatement by a director at the hospital in the letter of 6 October 2010 who had referred to a 'new' protocol.

The external counsel report stated that discussions around the studies closed in January 2011. This was inconsistent with information provided in writing for the appeal which was clarified by the Astellas representatives at the appeal who explained that a member of Astellas UK's medical department (second employee) visited the hospital in January 2010 to confirm in person that the two studies would not go ahead as IDSEC had not received a response. The November 2010 timeline clearly indicated discussions up until October 2010 in relation to the switch study. The external counsel report stated that on 22 December 2010 two named members of the medical department (the second employee and the first employee's line manager) met one of the health professionals to inform him/her that the switch study would not be progressed and to present the MEGS cheque (now made out to the correct payee). The Astellas timeline referred to this cheque as 'grant cheque issued by Astellas' on 21 December 2010.

The Panel was concerned about the impression given by this meeting when the health professionals from the hospital were both informed that the study would not be progressed and presented with the cheque for £50,000. The Panel noted an email from the second employee dated 22 December 2010 to a number of Astellas staff including senior leaders, the first employee and members of the UK brand team to report on the meeting (a copy of the November 2010 timeline was attached to the email). The email mentioned that 'we did of course soften the blow by delivering a £50k cheque today under the MEGS agreement which was for separate work and [ ] seemed grateful for that'. At that meeting the company agreed to cover the cost of an expert who had prepared the study protocol, research ethics preparation and attended project planning meetings. A copy of an invoice for £2,500 was provided. This was the first mention of an additional and relevant payment in relation to the activities at issue, albeit to a third party. It underlined the importance of doing a broad indepth investigation at the outset.

It appeared that the heightened sensitivity referred to in the external counsel report did not extend to ensuring that the company followed its SOP. It was inexplicable that such a poor investigation was conducted at a time of heightened sensitivity. Members of the investigation team named in the external counsel report had different roles and experiences as would be expected. However, when combined, their skill sets, including their heritage at Astellas, compliance and PMCPA experience, should have enabled them to both recognize the importance of, and to conduct, a proper investigation to ensure the provision of comprehensive information. It appeared that Astellas had not made any reasonable effort to look at the issues in the broadest sense to understand the relationship between various Astellas UK staff and the hospital.

The Panel noted that the external counsel report stated that the investigations team did not refer to the SOP for conducting an investigation following a complaint. It stated twice that one of the investigators, who was aware of the SOP, did not indicate to other members of the investigations team that the SOP should be referred to or signpost it. There was a very strong inference that the other two members of the investigations team were not aware of the SOP and that it was the responsibility of the other to bring it to their attention. The Panel noted that the external counsel report was based, *inter alia*, on interviews with staff. In the Panel's view, this inference was not credible given that both had been trained on the relevant SOP. Irrespective of whether these two individuals had been trained it was incomprehensible given their seniority and knowledge of compliance issues at Astellas why they did not proactively identify whether there was a relevant SOP and follow it.

The Panel noted Astellas' submission in response to the PMCPA's question about the dates used to search for emails, in particular that those chosen for the second employee post-dated the activities at issue. In the Panel's view, Astellas' explanation was poor; that the search dates for the first employee's emails covered the activities in question and the majority of documents to and from the first employee copied in the second employee. A cursory examination of the first employee's emails showed that not all were copied to the second employee. It was clear that the second employee had attended the hospital independently of the first employee. It was shocking that the emails for the relevant time period for a critical senior medical individual with a relevant role had not been searched and, more so, that this decision had been made by Astellas after it was aware of the Appeal Board's concerns about limited documentation, and the discovery of the November 2010 timeline. It was not known whether the mail box contained relevant information but it was the company's failure to investigate the material that was key.

In response to a request to Astellas about which relevant senior staff were notified about the complaint by the investigations team, as set out in the external counsel report, it transpired that such staff were notified by a senior leader from Astellas UK and a senior leader from Astellas Europe rather than the investigations team. It appeared that the external counsel report was also incorrect in this regard.

The Panel noted the submission from Astellas regarding the timing of events and acknowledged

that the time period around an audit/re-audit would be particularly demanding for any pharmaceutical company. Astellas was advised by the PMCPA case preparation manager on 16 October 2017 that a complaint had been received and it would be sent to the company shortly. It was sent later that day with the response time extended by the case preparation manager beyond the 10 working days, ie from 31 October to 7 November 2017. The re-audits (the fourth audits/re-audits of the companies) were held on 18 and 19 October 2017. Thus, the company would be preparing its response to the complaint immediately after the October 2017 re-audits. The company had been given an extension to allow for the re-audits and any activity after the re-audits. The report of the October 2017 re-audits was provided to the company on 7 November 2017 with the response to the report due by 15 November 2017. Astellas was notified that the complainant was appealing on 3 January 2018 and the reasons were provided to the company on 19 January 2018. The appeal was heard on 22 March 2018. Astellas did not ask for an extension of time at either stage.

In the Panel's view, there was less overlap with the October 2017 re-audits than that implied by Astellas. The correspondence from the PMCPA referred to the possibility of requesting an extension and indeed the case preparation manager had decided herself to provide one at the outset, in the absence of any such request from Astellas. The Panel considered that stating that Astellas UK was in the middle of a major and important re-audit did not give a fair impression about the demands on the company resulting from the re-audits when responding to the complaint and the complainant's appeal.

The Panel noted its previous ruling, which was upheld by the Appeal Board on appeal, that there was no evidence that funding had been provided for either of the two studies and thus no breach of Clauses 18.5, 9.1 and 2 of the 2008 Code was ruled by the Appeal Board. The Panel considered that the new information was directly relevant to this decision. It appeared from the new information that Astellas was considering supporting both studies over the time period the hospital would be developing, finalising and implementing its new treatment protocol. Astellas had paid for some expert support to assist development of the study protocol and research ethics approval. The Panel noted Astellas' submission that it had not funded either study but the Panel noted the impression that might have been given by the senior Astellas UK staff visiting the health professionals to confirm that the study would not proceed and at the same visit handing over a cheque for £50,000 even if that cheque was for a MEGS. This was particularly so given the sum of £50,000 was equivalent to the funding sought for the *de novo* study in November 2009 according to the November 2010 timeline. The Panel also noted that based on the material available at the appeal, the Appeal Board's ruling referred to the cumulative effect of the common themes between the second study, the funding requested to help support a renal research fellow and research nurse which echoed the MEGS application and the ongoing dialogue about the funding, the failure to keep proper records and that the hospital linked the provision of funds to Advagraf. The Appeal Board considered that the cumulative effect was that, on the balance of probabilities, the payment did not satisfy the requirements of Clause 18.5 and was inappropriately linked to the use of Advagraf. The Appeal Board ruled breaches of Clauses 18.5, 9.1 and 2.

The Panel noted that effective self-regulation relied upon the submission of accurate responses to the PMCPA. There was an expectation that companies comprehensively investigated all the circumstances surrounding complaints. Failure to do so and failure to provide an accurate, comprehensive response were serious matters. The PMCPA was extremely concerned about the additional information which only came to light as a result of an interview at the April 2018 re-audits. The Appeal Board had also commented on the limited documentation provided. It appeared that the company either did not recognise the importance and relevance of key information and decided not to follow up key information or decided to ignore this information. It was clear that the investigation team had not obtained all the relevant information from staff. The Panel was concerned about the statement in the external counsel report that information from interviewees did not always appear to have been read in full and incorporated into the responses and that there was a lack of follow-up of potentially relevant issues. Overall, in the Panel's view, the compilation of the response had been reckless; there appeared to be a complete absence of care and attention and due diligence.

The Panel noted Astellas' submission that overall this additional information would not have altered the company's submissions to the Panel and the Appeal Board but that Astellas accepted that there might have been a fuller response.

The Panel was extremely concerned about the inadequate investigation which led to incomplete and misleading responses. The missing information was relevant to rulings. The Panel had previously ruled, on balance, no breach of the Code in relation to the £50,000 MEGS payment. It was extremely concerning that the final outcome of this case would have been different if the complainant, a busy NHS health professional, had not appealed. Effective self-regulation should not rely on the fact that a health professional appealed a ruling to trigger a process which ultimately led to more complete disclosure. Nor should effective self-regulation be reliant upon the coincidental timing of the re-audits which fortuitously gave the opportunity for the PMCPA to follow-up on the Appeal Board's concerns about documentation.

The Panel considered that Astellas UK's behaviour in investigating this matter in October 2017 was unacceptable and was completely inconsistent with the recent and numerous commitments made elsewhere to upholding the highest standards. Astellas Europe and Astellas UK had been audited 5 times since December 2015. It was beyond belief that Astellas UK would not follow its SOP given all

the training and emphasis in the company to doing that. In previous cases Astellas had been found seriously wanting in taking appropriate action when responding to the PMCPA. The current suspension of Astellas UK from membership of the ABPI would end on 24 June 2018 and the ABPI Board decided on 5 June there was no need for it to consider expelling Astellas UK from membership. In reviewing the report of the April 2018 re-audits, neither the Appeal Board nor the ABPI Board took into account the matters raised following the appeal in Case AUTH/2984/10/17 as these were still to be considered by the PMCPA. The report of the April 2018 re-audits included a brief summary of the position.

Taking all the circumstances into account, including Astellas UK's acknowledgement that it had failed to follow its processes, the PMCPA decided to report Astellas UK to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure. Given the seriousness of the Panel's concerns and the other cases, the Panel considered that the report to the Appeal Board should be heard at its meeting on 20 June 2018.

COMMENTS FROM ASTELLAS UK ON THE REPORT FROM THE PANEL (20 JUNE 2018)

Prior to the consideration of the report to the Appeal Board, Astellas UK provided the following statement.

Culture and Intent

The Astellas position in relation to its response to this case was that any deficiencies in the internal investigation of the investigations team in this case were not indicative, in any way, of systemic or cultural issues at Astellas in relation to compliance.

Astellas stated it had worked very hard over the last 3 years to address all of the challenges that it had faced, and, as recognized in the most recent re-audit, the culture of compliance within the organization was continuing to improve – and Astellas was already considering the improvements it would make on the basis of this case.

Astellas strongly denied that the investigation in to this complaint demonstrated a 'complete absence of care and attention and due diligence' or that there was a material failure to follow the relevant SOP. Factually, this was an extremely complex case, making any investigation challenging. In addition, given the historical nature of the events at issue, which happened almost ten years ago, and the lack of centrally archived legacy documentation, the complaint team was reliant on requesting all information available from key individuals in their personal records. In some instances, those individuals did not provide all information that they could reasonably have been expected to, including provision of the November 2010 timeline that was discovered during the April 2018 re-audit.

There was no deliberate withholding of information.

Process

Astellas submitted that the investigations team, as well as the wider organization, was very aware of the importance of having in place clear and comprehensive processes, as well as the need to follow these processes.

Astellas received the external counsel report at the same time that the PMCPA did and had now reviewed it in detail. There were a number of reasons why Astellas disagreed with the report's conclusion that there was a failure to follow the relevant SOP (although Astellas noted the conclusion that many of the basic steps were in fact followed). There were no allegations made in the complaint or appeal in relation to the conduct of individuals so there was no justification for involving human resources (HR). For the same reason, the complaints team had no right to forensically review the email in-box for any individuals. The SOP referred to reviewing emails, not searching individuals email in-boxes. There were good reasons as to why the complaints team did not meet within 2 working days of receipt of the complaint, given that the complaint was received on the first day of the October 2017 re-audit and the Case Preparation Manager had granted an extension for the response. It was a request by senior management at Astellas that the complaint was not circulated as widely as the SOP required, given that the organization was focusing on the October 2017 re-audit and the actions required as a result of that. It was true and unfortunate that one key document in particular was missed by the complaints team and Astellas was already adapting the process to ensure that such a mistake would not happen in the future. The intent and the actions of the complaints team was focused on building as comprehensive picture as possible of the events surrounding the ISR applications. Indeed, these investigations led to the discovery and voluntary disclosure of the MEGS in question, and any payment made in connection with it.

In conclusion, Astellas stated that this was a complex and historic case, and there were a number of factors that contributed to the response not being as complete as it should have been, for which it apologised. There were apparent failings in the process of requesting, providing and reviewing of information which might reasonably have been expected. Astellas had already identified amends to its process to address this. As an organisation Astellas would continue to be focused on compliance and continuous quality improvement.

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board noted that Astellas UK was currently suspended from membership of the ABPI until 24 June 2018, having been suspended for the maximum 2 year period. At its meeting on 5 June 2018 in relation to Cases AUTH/2780/7/15, AUTH/2883/10/16 and Cases AUTH/2939/2/17 and AUTH/2940/2/17, the ABPI Board decided, on the evidence before it at that time which included the report of the April 2018 re-audits and a summary

framework agreed by the Appeal Board, that there was no need to consider expelling Astellas. In reaching its decision, the ABPI Board noted that Astellas UK was still to respond in relation to the matters raised in Case AUTH/2984/10/17. Further re-audits were required by the Appeal Board to be carried out in March 2019 (Cases AUTH/2780/7/15, AUTH/2883/10/16 and Cases AUTH/2939/2/17 and AUTH/2940/2/17).

The Appeal Board noted that the matter before it was a report which concerned Astellas UK's recent failure to properly investigate an historic matter including its failure to disclose all relevant documentation to the Panel and Appeal Board, and the company's current approach to compliance. The Appeal Board's role was to consider whether the circumstances warranted the imposition of further sanctions under Paragraphs 11.3 and 12.1 of the Constitution and Procedure. As part of its consideration of the report, the Appeal Board would not re-consider the merits of Case AUTH/2984/10/17, although it would comment on the relevance of certain materials that were not previously disclosed.

The Appeal Board noted that Astellas UK had accepted all the rulings of breaches of the Code including Clause 2. The Appeal Board also noted Astellas UK's apology that its responses were not as complete as they should have been. It also noted Astellas UK's view that there were apparent failings in the process of requesting, providing and reviewing information. The company stated it had identified amendments to its processes to address these. The Appeal Board also noted Astellas submissions regarding its responses to the Panel and appeal including Astellas' view that its position in the appeal response would have remained the same in that there was no evidence to indicate that funding was offered or provided as an inducement for the hospital to place Advagraf on its immunosuppressant protocol.

The Appeal Board noted the very detailed consideration of the Panel including its comments on material not previously provided and its view that, overall, the compilation of the company's responses had been reckless; there appeared to be a complete absence of care and attention and due diligence. The Appeal Board also noted that the Astellas representatives referred to aspects of Astellas' investigation as 'too casual', 'cavalier' and stated that the mistakes made were being addressed. The company representatives stated that there was not an institutional failing with respect to compliance in Case AUTH/2984/10/17, a phrase previously used by the PMCPA to describe Astellas' compliance status.

The Appeal Board noted a number of comments made by Astellas UK about the complainant revealing more information as the case progressed (drip-feeding) and queried whether that was so. The Appeal Board did not explore this with Astellas, noting the matter before it concerned, *inter alia*, the disclosure of information by Astellas. The Appeal Board did not consider that it could be reasonably argued that the sequential complaint and appeal from the complainant contributed to the matters which gave rise to this report.

The Appeal Board noted the historical nature of the matters at issue and accepted that retrieving some materials might not have been straightforward. The Appeal Board noted the company's submission in this regard. Nonetheless, the Appeal Board did not consider that the matter at issue in Case AUTH/2984/10/17 was as complex as implied by the company representatives at the consideration of the report. In the Appeal Board's view, notwithstanding the historical nature of the matters at issue, adopting basic principles of good governance and compliance practice, common sense and a positive cultural approach to transparency and disclosure should have facilitated more accurate responses and complete disclosure. That such an approach, apparently and on the evidence before the Appeal Board, was not consciously adopted at the outset was, in the Appeal Board's view, and given Astellas' recent compliance history, both inexplicable and inexcusable.

The Appeal Board noted the summary of the external counsel report. The Appeal Board noted its concerns were broader than matters raised in the summary of the external counsel report. The Appeal Board noted that neither the Panel nor it had sight of the full report as Astellas invoked its right to claim legal privilege in relation to the full report which Astellas was fully entitled to do. However, the Appeal Board noted the company representatives' submission that the full report contained commercially sensitive matters and queried whether a redacted copy could have been provided. In this regard, the Appeal Board noted relevant comments made by company representatives about the investigation that were not part of the summary report. The Appeal Board noted the company representatives stated that the summary report was a good reflection of the investigation.

The Appeal Board was deeply concerned about the lack of rigour which Astellas had applied in conducting its investigation. The Appeal Board was concerned about the investigation team. In the Appeal Board's view, given the company's submission about the lack of investigation expertise of one of the team, it was wholly unclear why he/she had been appointed to lead the investigation, including gathering evidence. The explanation at the appeal on this point was inadequate. Nonetheless, a much more diligent approach and the cumulative experience of the other two members of the investigations team should have, in the Appeal Board's view, prevented the errors that had occurred.

In the Appeal Board's view, the failures of the investigation team were startling and included an apparent failure, at the outset, to proactively seek information, bearing in mind the broad scope of the case preparation manager's request; primarily, using informal modes of communication (verbal and text messages) to seek critical information; an acknowledged failure to read all information including critical and relevant information provided by staff and an acknowledged failure to properly interrogate material and staff and adopt a policy of full disclosure.

The Appeal Board noted from the company representatives at the consideration of the report that, in relation to the November 2010 timeline, there were differing accounts about what the first employee was originally asked verbally to provide; the first employee's recollection that he/she was asked to provide a top line summary was supported by his/her emailed response to that request (31 October 2017). According to the company representatives, the investigator's recollection was that he/she had asked for everything. That there was a discrepancy on this important point was, in part, a consequence of the investigation's failure to put such requests in writing and at the very least to make contemporary notes of any telephone calls. The Appeal Board noted from the Astellas representatives at the report that when questioned why the November 2010 timeline was disclosed at the re-audit and not previously, the first employee had assumed that management had it as he/she believed that someone had accessed his/her computer in his/her absence as certain files had disappeared and then been restored. The company representatives said that the company would not do this but, nonetheless, in the Appeal Board's view, this gave rise to concerns about the company culture. In any event, the failure to discover the existence of the November 2010 timeline at the outset reflected the failings of the investigation including a failure to interview the first employee's line manager, who, along with the second employee, had originally been provided with a copy of the November 2010 timeline (emails of 24 and 25 November 2010).

The Appeal Board noted with concern the company representatives' assertion at the consideration of the report that neither responses were shown or discussed with the second employee prior to their submission to the PMCPA, although the response to the appeal was subsequently shared. None of this documentation was provided to the first employee.

The Appeal Board noted the concerns raised in the Panel's consideration about the dates used to search for emails for the second employee in the summary external counsel report. At the consideration of the report to the Appeal Board the company representatives confirmed that, after the submission of the external counsel summary report, the external counsel had been instructed to look at the second employee's inbox to 'verify' the first employee's inbox. The precise dates for this second search, its extent and outcome were not stated in writing. This was new information. External counsel was confident that given the scope of its investigation it had discovered all it needed from the initial search.

The Appeal Board noted that despite Astellas knowingly deviating from its complaints SOP the company had made no record of this including any written agreed deviations.

The Appeal Board noted the Panel's assessment of the additional information and paperwork including the two different versions of the important letter from the hospital dated 11 May 2010 requesting the MEGS and the emails dated 9 and 10 December 2009 between the first and second employees, that the payment of the MEGS was now clearly linked to the change in the hospital treatment protocol to use Astellas' medicine in a manner consistent with the *de novo* study which had previously been rejected by Astellas' own IDSEC due to patient safety concerns current at that time. The Appeal Board noted that one version of the letter from the health professional to Astellas dated 11 May 2010 linked the MEGS payment to the implementation of '… our new clinical protocol using Advagraf in *de novo* live donor kidney transplantation' and was highly relevant and had not been previously disclosed. The Appeal Board noted the company's explanation at the consideration of the report that, on receipt, the first employee asked the health professional to submit an amended version. This amended version of the 11 May 2010 letter had originally been provided to one of the investigations team on 31 October 2017 as part of the investigation and disclosed to the PMCPA as part of its response to the complaint. The original 11 May 2010 letter linking the MEGS to the hospital treatment protocol was subsequently provided by the first employee to the investigator but it was unclear whether that attachment to an email dated 3 November 2017 had ever been opened and if so whether its significance had been realised. The Appeal Board considered that the original letter dated 11 May 2010 was highly relevant and provided compelling evidence that at the very least from the hospital's perspective the MEGS was linked to the product.

According to the November 2010 timeline, a newly designed *de novo* study was reviewed and approved by IDSEC on 27 November 2009 although the UK brand team subsequently decided not to support it.

The Appeal Board noted that according to the complainant in Case AUTH/2984/10/17, the hospital treatment protocol was ceased when higher than average rates of rejection were being recorded. Astellas had submitted in that case that multiple factors might be involved in the rejection rates. The Appeal Board noted that the historic patient safety issue was not the subject of the complaint in Case AUTH/2984/10/17 and therefore had not been considered or ruled upon as a discrete issue but rather arose as a coincidental matter during the consideration of that case. The Appeal Board noted its relevant comments above in the Appeal Board ruling in Case AUTH/2984/10/17. At the consideration of the report the company representatives explained that they had contacted the hospital after the appeal in Case AUTH/2984/10/17 because of the need to be transparent given the seriousness of the information re patient safety which came to light at the appeal. The Appeal Board noted that some of the newly disclosed material was relevant to the historic patient safety issues. The Appeal Board further noted that previous cases had raised patient safety issues (Case AUTH/2883/10/16 and Cases AUTH/2939/2/17 and AUTH/2940/2/17). It was of serious concern that a current investigation into a complaint that revealed an historic patient safety issue was so poor.

The Appeal Board considered that this case warranted the imposition of further sanctions and considered that it would be artificial to consider the

proportionality of such sanctions without due regard to previous cases and 5 audits and re-audits over the past 3 years.

The Appeal Board noted that Astellas UK had apologised for its failings in this case and it stated that it was due to undertake measures to ensure that such failings did not reoccur. Nonetheless, the Appeal Board considered that it was fundamental for effective self-regulation for companies to provide accurate information to the Panel and the Appeal Board and for failing to do so it publicly reprimanded Astellas UK in accordance with Paragraph 11.3 of the Constitution and Procedure.

The Appeal Board noted that when it considered the report of the April 2018 re-audits at its previous meeting (17 May 2018) it had decided that on the information before it, and noting that Astellas UK was still to respond in relation to the matters raised in Case AUTH/2984/10/17, that sufficient progress had been made by the companies such that the Appeal Board did not consider that it warranted a recommendation for the expulsion of Astellas UK from membership of the ABPI. Whilst noting that the expulsion of a member company was entirely a matter for the ABPI Board, the Appeal Board considered that had this report in Case AUTH/2984/10/17 been before it when it considered the report of the April 2018 re-audits including the summary framework, it would have considered that insufficient progress had been made on certain parameters and the Appeal Board would have recommended that the ABPI Board expel Astellas from membership of the ABPI. The Appeal Board had previously expressed the view that if a company was expelled from membership from the ABPI for issues relevant to patient safety then the period of expulsion should be for 5 years.

The Appeal Board considered that this case raised very serious matters including the historic issues relating to patient safety. In addition, given the level of scrutiny the companies were already under in relation to compliance, the Appeal Board was very concerned about the issues as set out above. Consequently, taking all the circumstances into account, the Appeal Board decided that in accordance with Paragraph 12.1 of the Constitution and Procedure, Astellas UK should be reported to the ABPI Board. Whilst noting the ABPI Board's role and responsibilities in determining any expulsion, the Appeal Board recommended that Astellas should be expelled from membership of the ABPI for a minimum of 5 years.

The Appeal Board noted that the case raised issues other than the conduct of Astellas. It noted Astellas' statement that following the appeal in March 2018 it had written to the hospital about patient safety issues and considered that the case report, when available, should be provided to the hospital trust at issue as well as the Care Quality Commission, the independent regulator of health and social care in England, with a covering letter. The Appeal Board requested that it be provided with a draft of the covering letters for comment. The Appeal Board noted that the MHRA would receive a copy of the case report in any event.

COMMENTS FROM ASTELLAS UK ON THE REPORT FROM THE APPEAL BOARD

Astellas UK provided a detailed response in which it strongly disagreed with the Appeal Board's findings and recommendations to expel Astellas from the ABPI. The findings and recommendations of the Appeal Board were wholly unfair, disproportionate and were based on:

An overzealous and inaccurate linking of a perceived lack of investigative rigour in an isolated case concerning historical events with alleged issues of patient safety for which no evidence existed; no evidence had ever been produced nor were such issues raised at the time of considering Case AUTH/2984/10/17;

Factual inaccuracies, misinterpretations of complex facts or matters on which the Appeal Board had insufficient knowledge or factual bases; and

Significant procedural flaws and unfair and prejudicial treatment.

Astellas UK provided the background to the case.

No Issue of Patient Safety

Astellas submitted that it was entirely incorrect to characterise the matter as a patient safety issue and it was troubling that the Appeal Board artificially linked the perceived lack of investigative rigour to that perceived issue.

Astellas did not accept the Appeal Board's assessment that 'this case raised very serious matters including the historic issues relating to patient safety'. At no point were there any patient safety issues, which were caused by the conduct of Astellas or use of Advagraf. The Appeal Board had not transparently informed Astellas of what those historic patient safety issues were supposed to be. Advagraf was one of the leading products in its field and its use of Advagraf (at the dose range) in combination with other immunosuppressive agents, such as azathioprine and corticosteroids as described in the clinical protocol of the hospital (including clinical use of Advagraf in a *de novo* setting) were expressly permitted by the SPC. Its use was consistent with clinical guidelines set out by the Renal Association and the National Institute for Health and Care Excellence (NICE).

It was therefore incorrect and totally unjustified without any clear evidence to link Astellas' conduct, including the engagement with the hospital in relation to the funding of the retrospective data analysis, in any way to an issue of patient safety. Rather, there was an allegation of a clinical governance issue under the responsibility of the hospital which chose independently to use a particular medicine or medicine regime within a complex transplant setting at the hospital according to its clinical governance framework. It was Astellas which raised these allegations of clinical governance concerns in the first place with the PMCPA and insisted that these issues be raised with the hospital.

This request was denied by the Appeal Board and Astellas unilaterally ensured that the hospital was fully informed after proceedings of the case ended.

Alleged Factual Inaccuracies, Misrepresentation of Complex Facts, or Matters on which the Appeal Board had Insufficient Knowledge or Factual Bases

Astellas stated its investigations had been significantly mischaracterised. Astellas did not accept the Appeal Board's conclusion that the internal investigation lacked rigour, that it was 'reckless' or there was a 'complete absence of care and attention and due diligence'. Astellas had acknowledged that with the benefit of hindsight the internal investigation could have been performed differently. While there were errors in the internal investigation for which Astellas took responsibility, in no way did any of these errors constitute reckless behaviour or a disregard for the established process.

The complaint as an isolated case, was adequately investigated in a manner that was reasonable and proportionate to the issues being investigated. Astellas did not agree that it characterised the investigation as 'too casual' or 'cavalier'. It was language used by Astellas in response to a discrete question. There was no factual basis for the conclusion that the requirements of Clause 18.5 of the Code were not met. It seemed in a large part to rely on an approach to inducement that was misconceived. Aside from a cheque for £2,500 to cover costs incurred by the hospital, Astellas made no payments to fund any proposed IDS at the hospital. Astellas submitted that the £50,000 MEGS was not conditional on Advagraf continuing to be used. There was no evidence that the hospital protocol was changed as a result of Astellas' actions.

The Appeal Board had also drawn unfavourable conclusions about the company culture without a proper basis. As the PMCPA was well aware, Astellas and its affiliates had invested very significant resources in compliance improvement within the organisation at all levels and such improvements were ongoing. Senior management had fully committed to such efforts. The progress had been continually monitored, assessed and validated both internally and externally by specialists in regulatory compliance. The meaningful progress was specifically acknowledged in the re-audits in April 2018.

Alleged Significant Procedural Flaws and Unfair and Prejudicial Treatment

Astellas stated that the PMCPA and the Appeal Board had not followed the procedures set out in the PMCPA Constitution and Procedure and their approach had undermined the fundamental principles of procedural fairness.

Crucially, patient safety was not the focus in either the complaint or the appeal; there was no reference to patient safety in the Panel's consideration of the additional information or in its report of Astellas to the Appeal Board.

The letter notifying Astellas of the outcome made no reference to a number of points which were specifically raised by Astellas' representatives during the Appeal Board consideration on 20 June that demonstrated Astellas' commitment to compliance and transparency. Astellas was concerned and troubled that these points were apparently not taken into account at all by the Appeal Board or, if they were, that inadequate weight was attached to them.

The language used in both the Panel and Appeal Board consideration of the additional information was highly prejudicial and emotive, exaggerated and subjective rather than factual and objective. This could unduly influence a decision-making body to whom the matter had been referred and regulatory authorities who were entitled to undertake separate investigations. Just some examples of this language used included the words, 'reckless', 'inexplicable' and 'inexcusable'.

For the PMCPA to communicate to the MHRA, the Appeal Board's decision and recommendation of expulsion was inappropriate and highly prejudicial and these actions could undermine the fundamental principles of procedural fairness during the process leading up to the hearing before the ABPI Board. Perhaps even more troubling, was that this communication to the MHRA was conducted in an informal and undocumented way with no context or details.

Finally, although the Appeal Board ruling in particular noted that it could not make a decision in isolation and consideration must be taken of five audits and re-audits over the past 3 years, the Appeal Board's decision then went on to attach no weight to the significant progress that had been made by Astellas, as specifically recognised in the latest report for the re-audit in April 2018.

Astellas' Investigation and External Counsel Review

Astellas stated given the exceptional circumstances and the historical complexities of this case, the initial investigation was proportionate and reasonable having regard to the specific allegation made by the complainant, namely that £250,000 had been paid to conduct studies relating to the efficacy of a protocol that included Advagraf. The investigations team conducted a reasonable degree of due diligence ahead of responding to the PMCPA in November 2017, gathering information from a variety of sources and did not materially deviate from its internal process. It was important to note that even if the investigations team had the additional information that derived from the further investigation that took place, Astellas would have reached the same conclusion. Nevertheless, Astellas accepted that the deviations were not conducive to conducting the best investigation possible which appeared to be the standard required by the PMCPA regardless of the circumstances. This was an important lesson learned by Astellas which had therefore further strengthened the company's process for conducting an internal investigation.

The only reason that the external counsel report was not shared with the Appeal Board was because it was a legally privileged document and once waived, the legal privilege would be lost. This was formally acknowledged at the Appeal Board meeting on 20 June. The fact that Astellas provided a summary, could not be interpreted as Astellas not providing reasonable transparency, as was suggested by the Appeal Board.

Conclusion

Astellas stated that for all the reasons given in the detailed comments, the recommendation to expel Astellas from the ABPI was wholly inappropriate, disproportionate and unfair. The recommendation was unsound because: (a) there was no evidence to warrant such a sanction according to the requirements set out in the Constitution and Procedure; (b) the conduct of the PMCPA and Appeal Board had been unfair, prejudicial and procedurally flawed; and (c) it failed, in any way, to recognise Astellas' broader and significant compliance improvement framework that had been reviewed by the PMCPA and specifically recognised and acknowledged in its re-audits of April 2018.

The Astellas response gave detailed comments including on the issues covered in the executive summary above. Comments covered clinical governance (and patient safety) and the Appeal Board ruling. In addition, Astellas commented on alleged mischaracterisations, factual inaccuracies, procedural flaws including about the complainant's identity and apparent interest, the failure to approach the hospital for comment and unfair treatment. The company also provided detailed comments on its internal investigation, the external counsel review and Astellas' compliance framework. The full response was provided to the ABPI Board but is not reproduced here other than the conclusion below:

> Astellas stated that there was no proper factual basis for the recommended sanction to be imposed on Astellas.
>
> Astellas stated that as shown in its submission, the findings and recommendations of the Appeal Board were based on its numerous mischaracterisations, factual inaccuracies and significant procedural flaws and unfair and prejudicial treatment.
>
> At no point were there any patient safety issues which were caused by the conduct of Astellas, or use of its product Advagraf. Rather, it appeared that there was an allegation of clinical governance concerns, which was the responsibility of the hospital. Astellas stated that it was Astellas who raised these governance issues with the PMCPA and insisted that these issues be raised with the hospital.
>
> There had been a lack of due process and unfair and prejudicial treatment of Astellas. The language used by the Panel and the Appeal Board was highly concerning, and statements made by Astellas had been taken out of context. Further, the PMCPA had already communicated (in an informal and undocumented manner) the recommendation to expel Astellas from the ABPI to the MHRA well in advance of any consideration of the matter by the ABPI Board.
> The Appeal Board had drawn unfavourable conclusions about the company culture without proper basis. Astellas and its affiliates had invested significant resources in compliance improvement within the organisation at all levels and the progress had been continually monitored, assessed and validated both internally and externally by specialists in regulatory compliance, and was specifically acknowledged in the re-audits conducted by the PMCPA in April 2018 and subsequently by the Appeal Board.
>
> Astellas stated that the initial investigation, whilst there were areas for improvement, followed the broad investigatory steps set out in the SOP and was proportionate given the nature and content of the complaint namely:
>
> - the complaint was passed on to Astellas' Ethics and Compliance (E&C) team and relevant senior people were notified about the complaint;
> - an investigations team was established promptly, and was allocated responsibilities and timelines with respect to the investigation;
> - the investigations team sought input from relevant employees, searched archives, trawled financial records and IDSEC files such that the external counsel review found that no information was withheld deliberately;
> - further the external counsel review concluded that even with additional improvements to investigation process, including the more detailed version of event as described in the November 2010 timeline, the substantive conclusions would have remained the same;
> - a response to the PMCPA was sent in a timely manner; and
> - finally, as noted previously, it was Astellas that proactively disclosed the existence of the MEGS to the PMCPA.
>
> The Appeal Board's recommendation had failed to attach any weight to the meaningful and continued improvement that Astellas had demonstrably made which had been acknowledged by the PMCPA, Appeal Board and the ABPI Board.
>
> In this context, it was disproportionate to recommend expulsion on the basis of errors in the investigation process in an isolated case, where there was clearly no element of patient safety for which Astellas could be responsible and the Astellas product in question was used within the terms of the SPC in a protocol which was independently adopted by the hospital.
>
> For all the reasons given above, the recommendation made by the Appeal Board was unfair and based on incorrect facts and unsound analysis.

PMCPA response

The PMCPA responded in detail to Astellas' submission refuting all the allegations including those of unfair treatment and stressing that the processes followed were transparent and Astellas was treated fairly. All the points raised by Astellas at the time of the Panel's and Appeal Board's considerations were taken into account. The procedure and process for this report was the same as for all the previous reports. The PMCPA limited its response to matters of fact and noted the differences of view. The PMCPA provided detailed comment including that the Appeal Board noted that the historic patient safety issue was not the subject of the complaint in Case AUTH/2984/10/17 and therefore had not been considered or ruled upon as a discrete issue but rather arose as a coincidental matter during the consideration of that case. The PMCPA also provided detailed comment on the clinical governance issue referred to by Astellas and that the PMCPA was satisfied that relevant details which came to light as part of the appeal in the case had been provided to the hospital at the time. The hospital protocol ran from 2009-2012. At the time of the appeal, March 2018, the complainant stated that there was no current patient risk. The Director of the PMCPA's view was that as the MHRA was informed as to when the updated case reports in Cases AUTH/2780/7/15, AUTH/2883/10/16 and Cases AUTH/2939/2/17 and AUTH/2940/2/17 would be published, it was important to update the MHRA as to the status of Case AUTH/2984/10/17. All the updated case reports included some details about Case AUTH/2984/10/17. This brief confidential update was not premature and did not undermine the fundamental principle of procedural fairness during the process. It was a statement of fact that in Case AUTH/2984/10/17 the Appeal Board decided to report Astellas UK to the ABPI Board with a recommendation that the company be expelled from membership of the ABPI. The MHRA asked to be informed on the progress of the ongoing matter. A copy of the PMCPA response was provided to the ABPI Board.

Astellas' further responses

Astellas responded and included some amendments to its initial response. It did not respond to the PMCPA's detailed comments. A copy was provided to the ABPI Board.

Astellas' response referred to certain interactions with the complainant as well as commenting on the complainant's current job. Details were provided to the complainant who disagreed with Astellas' assessment of various matters. Astellas was given the details and informed that although the comments were important and relevant to the matter in general, they were not directly relevant to the subject of the report from the Appeal Board to the ABPI Board. Astellas requested that the complainant's response was provided to the ABPI Board. The ABPI Board was not provided with the complainant's response.

Astellas' verbal submission at the ABPI Board meeting

In addition to the detailed documents Astellas UK referred to its disappointment at being reported to the ABPI Board which it submitted was counterintuitive given the efforts made by the company and its achievements. The changes in senior leadership, culture, compliance framework, and improvements shown in the pulse survey referred to at the ABPI Board meeting in June 2018 were mentioned.

Astellas UK focussed on six points stressing the importance of each issue, the concerns Astellas had in relation to that issue. The six points were listed in the summary document provided by Astellas to the ABPI Board at the meeting as:

- safety issues
- approach to what was inappropriate funding
- credibility of the complainant
- failure to seek third party observations
- Astellas' approach to compliance, and
- lack of proportionality in the criticism of the quality of the investigation which included the significant number of mitigating factors.

Astellas concluded that the Appeal Board recommendation was sufficiently flawed such that the ABPI Board should not expel Astellas from membership of the ABPI.

ABPI BOARD CONSIDERATION OF THE REPORT FROM THE APPEAL BOARD

The ABPI Board noted the report from the Appeal Board and Astellas UK's comments.

When the ABPI Board had last considered matters relating to Astellas in June 2018 (Cases AUTH/2780/7/15, AUTH/2883/10/16 and Cases AUTH/2939/2/17 and AUTH/2940/2/17), it had been clear that the company would need to ensure that there was an ongoing commitment to sustained culture change throughout the organisation. Previous audits had shown that the compliance culture was improving, so it was disappointing that the company had been reported to the ABPI Board once more.

The view of the Appeal Board was clear. In addition to the report to the ABPI Board in Case AUTH/2984/10/17 and the recommendation that Astellas UK be expelled from membership of the ABPI for five years, the Appeal Board decided that Astellas UK should be publicly reprimanded.

However, the ABPI Board remained clear in its view that compliance was an ongoing journey that required continual self-adjustment and improvement. The ABPI Board had confidence that a named senior leader at Astellas UK would be able to lead the company forward on this journey.

The ABPI Board considered the reputation of the industry to be of utmost importance, and therefore carefully considered all of the information before it. The ABPI Board concluded that although Astellas had made mistakes, in its view there was no malintent from the company to conceal. The ABPI Board noted the company's submission that measures had now been taken to address the issues arising from this case. The ABPI Board noted Astellas UK's submission that at no point were any patient safety issues caused by the conduct of Astellas and that the use of Advagraf within the protocol was in line with the SPC for the time the hospital protocol was in force. The ABPI Board further noted that patient safety was not the subject of the complaint.

The ABPI Board was already due to see the reports of the PMCPA's 2019 re-audits of Astellas UK and Astellas Europe as a result of its consideration of re-audits in other cases. The failures identified in this case should be considered as a part of those re-audits. The ABPI Board would look closely at the report of the re-audits to ensure that it remained satisfied with the position of the companies.

Taking everything into account, the ABPI Board decided that no further action should be taken in relation to this report from the Appeal Board.

Complaint received	**13 October 2017**
Undertaking received	**16 April 2018**
Panel reconvened	**12 June 2018**
Appeal Board Consideration	**22 March 2018, 20 June 2018**
ABPI Board Consideration	**4 September 2018**

CASE AUTH/2987/10/17

ANONYMOUS CONTACTABLE V SHIRE

Alleged promotion prior to the grant of a marketing authorisation

A contactable complainant who wished to remain anonymous complained about Shire and its communication with payers, key opinion leaders (KOLs) and other stakeholders. It appeared that the complainant was an ex-employee of Shire.

The complainant identified three matters (a market research survey, a review by the National Institute of Health and Care Excellence (NICE) and visits by medical science liaison staff (MSLs)).

The detailed response from Shire is given below.

The complainant alleged that an agency communicated to external KOLs and payers on behalf of Shire regarding a market research study exploring a study linked to managed entry agreement types. The email was not approved and highlighted Shire and the medicine's name teduglutide (Revestive).

According to the complainant, Shire failed to take action when this issue was raised by the agency and the response was not to do anything to avoid escalation of the matter (lack of transparency).

The Panel noted that it appeared that both the UK company and Shire International had a role in the market research in question, although the response was not entirely consistent on this point. The extent of each affiliates' responsibilities were not clear. Nonetheless, the Panel noted that the email in question was sent to UK recipients and that aspect of its use came within the scope of the Code. The UK company was responsible for the acts and omissions of its overseas affiliate that came within the scope of the Code. The Panel also noted that although the communication was sent by a third party agency it was an established principle that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel noted that the email in question sent by the third party UK based agency to ten UK health professionals invited them to participate in market research to test the managed entry agreement (MEA) design for Revestive and stated that the agency was working with Shire Pharmaceuticals to design a complex patient access scheme (PAS) to improve cost effectiveness and facilitate patient access to its new product for short bowel syndrome (SBS) – Revestive (teduglutide). Teduglutide was described as the first approved treatment in Europe for this debilitating disease and that it offered an important new treatment option to patients who were reliant on parenteral nutrition.

The Panel noted the broad definition of promotion and considered that the email in question was promotional and noted Shire's admission that the promotional nature of the email would not have been clear to the recipients. Its promotional nature was therefore disguised. The Panel therefore ruled a breach of the Code as acknowledged by Shire.

The email was sent without Shire UK's consent or knowledge. The email was described as unauthorised. In an email dated 16 February an international Shire employee stated that the agency was commissioned from his/her budget and that the third party agency was briefed on the CMLR process and he/she was surprised that this had happened. It was unclear whether the CMLR process included examination of materials and thus the Panel was unable to comment on whether the agency was appropriately briefed. An email dated 16 February sent by a UK employee stated that as it was not a UK only project and was 'signed by international' 'we needed to know more about the contracting, briefing of the agency on the SOPs and other procedure'. It thus appeared that there were internal governance concerns about activities taking place in the UK which were commissioned, at least in part internationally. Such activities had to comply with the Code and the company's internal processes should facilitate this. The Panel noted its comments and ruling above and considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel noted that Shire had provided evidence to show that the matter was escalated within Shire and actions were taken to investigate the matter. Shire provided material demonstrating the action taken to stop any further communication by the market research agency without full review and approval by UK signatories.

The Panel noted that the complainant bore the burden of proof. The Panel considered that bearing in mind all the evidence before it the complainant had not established that Shire had asked its employees not to address the issue and to avoid escalation or that Shire failed to take action when the issue was raised as alleged. No breach of the Code was ruled in this regard.

Noting its comments and rulings above the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

The complainant further alleged that Shire communicated with the NHS during the process of a review of teduglutide by the National Institute for Health and Care Excellence (NICE). The company sent both medical and market access (commercial team) to discuss pricing and product reimbursement before the product was approved by the Committee

for Medicinal Products for Human Use (CHMP) ie off-licence discussion. The complainant alleged that Shire had also tried to circumvent the NICE process because it believed it was not going to be successful in a health technology appraisal (HTA) by initiating discussions with the clinical reference groups (CRGs) directly and not the National Health Service (England) (NHSE) committee. The complainant noted that the CRGs were mainly clinicians who could prescribe. The complainant subsequently stated that the medicine at issue was Natpar and that he/she had emails on communication with the NHSE to try to influence the clinicians to vote to exclude Natpar (parathyroid hormone) (product for Hypo-parathyroid) out of the NICE process. He/she stated that there were also emails communicating with the NHSE CRG directly as well as commercial discussion with medical on those items.

The complainant alleged that the market access team, with medical, attended meetings to discuss the pricing for a product that was not licensed and access options were made.

Negotiation with NHS directly was very minimal. Shire did not inform NICE of the communication on purpose to pass the process as they knew they would not pass NICE CE (cost effectiveness) limit.

The Panel noted that the complainant's original complaint referred to Teduglutide but he/she later confirmed that Natpar was the product at issue. The Panel therefore considered the complainant's allegation with regard to Natpar.

The Panel noted the broad role of the CRGs as described by Shire, namely to advise NHSE on the best ways that specialised services should be commissioned and paid for. The Panel noted that given the CRG's role and the broad definition of promotion in the Code there was a possibility that interactions with a CRG, especially those initiated by a company, might be considered promotional. The Panel noted that the status of each such interaction should be considered on its individual merits.

Shire had not argued that any of its interactions constituted advance budgetary information but did refer to certain interactions being with health professionals making policy decisions on budgets.

The Panel noted Shire's submission that Natpar was licensed in the UK on 26 April 2017.

In relation to the interactions between a named CRG clinician and Shire in December 2016 and a telephone call in January 2017 these appeared to be in response to the health professional's original unsolicited request and supplementary unsolicited request in December. The Panel did not have the original email communications but based on the company's account there was no evidence that the company's interactions went beyond the information requested by the clinician or was otherwise promotional in nature or went beyond the scope of the original requests. The Panel noted that the complainant bore the burden of proof and had not established that the interactions were promotional. On the evidence before it the Panel considered that, on the balance of probabilities, Shire could take the benefit of the exemption to the definition of promotion in relation to unsolicited requests and did not consider that the interactions listed above promoted Natpar prior to the grant of its licence. No breach of the Code was ruled. This ruling was not appealed.

In relation to the interaction with another named member of the Specialised Endocrine CRG in January the Panel noted that the original request from the health professional was described by Shire as unsolicited. There was no evidence that the response went beyond the original request. The Panel noted that the complainant bore the burden of proof and had not established that the interactions were promotional. On the evidence before it the Panel considered that, on the balance of probabilities, Shire could take the benefit of the exemption to the definition of promotion in relation to unsolicited enquiries and did not consider that the interactions listed above promoted Natpar prior to the grant of its licence. No breach of the Code was ruled. This ruling was not appealed.

The Panel considered that the face-to-face meeting in January 2017 with the named CRG clinician above was different to the interactions described above as it had been initiated by Shire. It could thus not take the benefit of the exemption to the definition of promotion in relation to unsolicited enquiries. Part of the meeting appeared to explore the possibility of the named CRG clinician from becoming a key opinion leader and referred to participation in advisory boards, clinical trials and registries and other global medical activities. In the Panel's view such interactions were legitimate but had to comply with the Code. The Panel noted that the meeting was also attended by a member of the Shire market access team to answer questions about policy as the named CRG clinician had previously wanted to propose a policy about Natpar to the CRG. Whilst noting Shire's submission that the member of the market access team had a non promotional role, the Panel considered that certain aspects of the individual's job description might be considered promotional. Noting the general comments above about the broad definition of promotion and the CRG's role, the Panel considered, on the balance of probabilities, that the meeting was promotional, it had been initiated by Shire in anticipation of, *inter alia*, discussions about Natpar and the CRG policy prior to the grant of Natpar's licence. Shire had apparently arranged for the attendance of the market access team member who, in part, had a promotional role. On balance, a breach of the Code was ruled. Noting the arrangements for the meeting, the Panel considered that, on balance, high standards had not been maintained. A breach of the Code was ruled. These rulings were appealed by Shire.

The Panel noted the complainant's concern that Shire tried to circumvent the NICE process because it believed it was not going to be successful in a health technology appraisal (HTA) by initiating discussions with the CRGs directly and not the

National Health Service (England) (NHSE) committee and that Shire had tried to influence the CRG clinicians to vote to exclude Natpar from the NICE process.

In relation to the discussion with NICE in February 2017 regarding access issues for rare diseases and the proposed Natpar submission, clinical trial data and advice on a phase IV study, the Panel noted that information supplied to national public organisations such as NICE was exempt from the definition of promotion in the Code providing the information was factual, accurate and not misleading. Shire had not sought to take the benefit of this exemption. It was not clear to the Panel on the limited information before it whether the exemption applied to the interaction in question. The Panel did not know who had initiated the discussion. The complainant bore the burden of proof and had not established that the interaction was promotional and the Panel thus ruled no breach of the Code. This ruling was not appealed.

In relation to the subsequent telephone conversation between the two named CRG clinicians above and Shire's market access team member and a medical manager in February, the Panel noted that, according to Shire, NICE had suggested that Shire got agreement from NHSE perhaps through the CRG on certain matters. The Panel noted that the original conversation with NICE had included discussion about the phase IV study. This was reflected in a conversation in early February which was summarised in a subsequent email. It appeared that NICE had agreed with Shire's approach that the NICE assessment be delayed/suspended pending phase IV study results and suggested that agreement be obtained from NHSE perhaps through the CRG, although NICE was unsure about the level of decision making required for this in NHSE. The complainant appeared to object in principle to these discussions. In the Panel's view, such discussions were legitimate so long as they complied with the Code. The interaction with the CRG in February had apparently taken place at the suggestion of NICE and the suggestion had arisen during the course of what, on the evidence before it, the Panel had considered to be a non promotional conversation. In the Panel's view the complainant had not established that this aspect of the discussions (in relation to delaying/suspending the NICE assessment) with the CRG was promotional as alleged. No breach of the Code was ruled. This ruling was not appealed.

The Panel noted that the discussion in February had also occurred in relation to Shire's proposal of a managed entry agreement, and according to the email this matter had also been referred to earlier. No details of the managed entry scheme were provided. The Panel considered that managed access schemes were acceptable in principle under the Code but that they should be carried out in conformity with its requirements. The Panel noted the broad definition of promotion in the Code and the advisory role of the CRG in relation to commissioning and funding as set out above. The Panel considered that it was difficult to see this aspect of the discussion as anything other than promotional. As Natpar did not have the benefit of its licence at the relevant time a breach of the Code was ruled. The Panel considered that high standards had not been maintained and ruled a breach of the Code. These rulings were appealed by Shire.

In relation to the meeting that occurred with the Department of Health in March there was insufficient information before the Panel in relation to the status of the discussions. The complainant bore the burden of proof and the Panel considered that it had not been established that these meetings were promotional or otherwise in breach of the Code. No breach of the Code was ruled. This ruling was not appealed.

The Panel noted that independently of the interactions above Shire had updated four members of the CRG about Natpar's price. An email referred to their request to be updated with information about rhPTH (1-84) which was described as unlicensed and referred to their role on the CRG in making policy decisions on budgets. Shire submitted that two of these individuals had made a verbal request to be updated on pricing at an advisory board. The Panel noted that the other two members of the CRG had previously been involved in the discussions at issue above. The Panel noted that the complainant bore the burden of proof and had not established that any of the interactions were promotional as alleged. No breach of the Code was ruled. This ruling was not appealed.

The Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of Clause 2 was ruled. This ruling was not appealed.

The Appeal Board noted that Natpar was indicated in the treatment of a rare disease (adults with chronic hypoparathyroidism) and so the number of accessible clinicians in the therapy area would be small. In the rare disease arena it was likely that many of the health professionals involved would be prescribers as well as policy makers and so, with regard to activities related to Natpar, it would be difficult for Shire to avoid having to interact with those who, of necessity, wore 'two hats'. In discussions and the like with such people, the Appeal Board considered that companies should be extremely careful to correctly characterise their activities as either promotional or non-promotional; it was otherwise too easy for the boundaries to become blurred. The Appeal Board noted the broad definition of promotion. Participants in a meeting should be given clear sign posts as to its promotional status. Companies should be careful not to compromise the independence of prescribers who were also policy makers. The Appeal Board accepted that rare diseases presented some difficulties and it was often hard for companies to ensure they had the right conversations with the right people. Nonetheless, compliance must be achieved. The Appeal noted that although the number of patients affected by rare diseases was

small, the cost of their treatment was significant to the NHS. The Appeal Board noted that Natpar's licence was granted in April 2017 ie shortly after the activities subject to the complaint.

The Appeal Board noted that it had the benefit of more information than that which had been submitted to the Panel. The Appeal Board noted the context for the meeting in January 2017. The Appeal Board noted that the attending clinician was both a prescriber and policy maker, it nonetheless did not consider that, on the balance of probabilities, Natpar had been promoted at the meeting prior to the grant of its marketing authorisation. No breach of the Code was ruled. In that regard the appeal on this point was successful.

The Appeal Board was concerned, however, about the lack of a detailed record of the meeting. The Appeal Board considered that given the difficulties discussed above about working in the area of rare diseases, the rigour with which Shire had documented the meeting was poor and in that regard it considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

With regard to the telephone call which took place in February 2017, and subsequent email, the Appeal Board noted that there appeared to be no precise definition of what a managed entry agreement was. Shire submitted that although the email, the record of the call, referred to a managed entry agreement it also referred to such as being 'in line with the criteria for in year service developments'. The Appeal Board noted the company's definition of managed entry agreement and in year service development and considered that the difference between the two activities was not sufficiently clear; at the very least there appeared to be a degree of overlap and both might potentially involve data collection. The Appeal Board noted that the call record referred to a previous conversation with NICE in which in year service developments were discussed and which implied that an in-year service development for a small cohort of patients was already supported by the CRG. The need for an in-year service development arose because it was thought unlikely that the current Natpar data set would be sufficient for a positive recommendation from NICE. Shire thus wanted to delay the NICE submission and so the CRG would need to prepare for an alternative mechanism of access post licence. Shire's representatives explained that this would involve collecting data in a high risk population and that this activity was initially proposed by the CRG. The Appeal Board considered that, given the circumstances and the context in which the call had occurred, Natpar had not been promoted prior to the grant of its marketing authorisation. No breach of the Code was ruled. The call had been well documented and in that regard the Appeal Board considered that high standards had been maintained. No breach of the Code was ruled. The appeal on both points was successful.

The complainant further alleged that Shire's internal strategy had MSLs target numbers of visits to physicians and linked this to their key performance indicators (KPIs) despite the fact that an MSL role should be reactive and not proactive, particularly when it came to many products not yet licensed. The complainant stated that this might have changed after the internal team complained however, it was a strategy that showed a lack of respect for ethics and code of conduct.

The complainant alleged that the MSL issue was linked to targets for medical team to meet with KOLs, it was linked to their evaluation and possible bonuses, which was against the ethics of the industry and the role of MSLs to be reactive and not proactive.

The Panel noted that the complainant bore the burden of proof and that the complainant had provided no evidence to establish, on the balance of probabilities, that proactive promotional discussions about unlicensed medicines had occurred. No breach of the Code was ruled.

The Panel noted the MSL Performance Goals and Objectives. The Panel noted that the MSL role varied across the industry but the relevant part of the Authority's guidance applied to those that had a non promotional role. The Panel noted the MSL key performance indicators and Shire's submission that the quantative measure for health professional interactions was an aspirational measure. The Panel considered that applying an aspirational KPI in relation to the number of visits to KOLs (rather than the percentage of visit requests completed or similar), which was linked to an MSL's remuneration, was inappropriate and might encourage behaviour that was inconsistent with the Code. High standards had not been maintained in this regard and a breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure. No breach of Clause 2 was ruled.

A contactable complainant who wished to remain anonymous complained about Shire Pharmaceuticals Limited and its communication with payers, key opinion leaders (KOLs) and other stakeholders. It appeared that the complainant was an ex-employee of Shire.

The complainant identified three matters (a market research survey, a review by the National Institute of Health and Care Excellence (NICE) and visits by medical science liaison staff (MSLs)). The complainant added three further emails to his/her initial complaint in further correspondence.

In writing to Shire, attention was drawn to the requirements of Clauses 2, 3, 9.1, 12.2 and 18.1 of the Code as well as the supplementary information to Clause 3.1, Advance Notification of New Products or Product Changes which May Significantly Affect Expenditure.

Shire stated that it was unclear whether the complainant was a Shire employee, ex-employee or another type of complainant.

1 Market Research Survey

COMPLAINT

The complainant alleged that Shire communicated through an agency to external KOLs and payers around doing a market research study exploring a study linked to managed entry agreement types. However, the agency communicated with the external stakeholders without approving the email internally, the email highlighted the company and the medicine's generic name.

In a second email to the Authority, the complainant stated that the email to the KOLs/payers could be investigated as part of the communication. The complainant did not have any emails but stated that the agency could be questioned as part of the investigation. The complainant stated he/she was then asked not to do anything, to let it go instead of addressing it.

In a third email, the complainant stated he/she did not have emails, but if the PMCPA investigated the agency, and the emails on the possible break of the Code, the PMCPA would have the trail if it asked for it, and would see how Shire asked the team not to do anything about it and not to address it to avoid the escalation.

In a fourth email, the complainant stated that the market research agency used for Revestive (teduglutide), a product for short bowel syndrome, communicated the brand name and the company to the participants, an email was sent to external participants without being approved internally through Zinc process. Shire failed to take action when this issue was raised by the agency and the response was not to do anything to avoid escalation of the matter (lack of transparency).

RESPONSE

Shire stated that it did not understand the details and wording of the original complaint above. Shire was not aware of any market research carried out exploring a study and managed entry agreements. It was difficult at first to know where to start looking and investigate due to the unspecific nature and lack of details in the allegation, however with the further information provided in the complainant's fourth email Shire looked to see if it had conducted any market research using a market research agency, with regard to Revestive and managed entry agreements. There were a number of challenges encountered, namely:

- Shire was still not entirely certain as to which market research activity the complainant referred to as the details in the allegation were not specific.
- Shire considered that the market research which might be at issue was initiated at the beginning of 2016 by Baxalta International. Baxalta was acquired by Shire from Baxter Healthcare in June 2016 and many of the systems and records either no longer existed or were difficult to access particularly as Shire was not certain exactly where to look or know what it was looking for
- Many of those who worked at Baxalta/Shire when this market research was conducted were no longer with the organisation (Shire UK had had more than 85% staff turnover due to company acquisition, restructuring and office relocation).

Shire provided an email trail from a market research agency; it understood that this market research was commissioned by Shire International based in Switzerland and assumed that this was the activity to which the complainant referred. It appeared that the market research agency sent a communication to ten UK health professionals without the knowledge or consent of Shire UK (copy provided).

Shire submitted that contrary to the complainant's allegations, this matter was escalated to European compliance. As evidenced in the email trail provided, actions were taken to investigate this matter and identify what had happened and how. There was no evidence that Shire's response was not to do anything to avoid escalation as alleged. The precise nature of the actions and outcome of what happened with this issue, however, were uncertain as neither of the UK employees involved still worked for Shire and so it was not possible to follow up with them. Further, this was the only email trail Shire had been able to find relating to this matter.

Also, contrary to the allegation that Shire failed to take any action when this matter was raised, Shire provided copies of a discussion guide and associated slides that went through UK review and approval after the unauthorised communication by the agency to UK health professionals had initially been flagged. This demonstrated that Shire stopped any further communication by the market research agency without full review and approval by UK signatories.

Shire noted that Revestive was licensed in the UK in August 2012 whereas the Revestive market research was conducted in the UK, and the market research agency communicated with the ten UK health professionals, in February 2016. Shire UK recognised that although the communication was sent to UK health professionals by a third party market research agency instructed by Shire International, this came within the scope of the UK Code and Shire UK was responsible for the actions of that third party. Shire also recognised that the initial communication sent to the ten UK health professionals by the market research agency promoted Revestive although this would not have been clear to the recipients, therefore Shire acknowledged that there had been a breach of Clause 12.2 of the Code.

Despite there being a breach of Clause 12.2 in relation to this specific part of the allegations, Shire did not accept that high standards had not been maintained and/or that Shire had bought discredit to or reduced confidence in the industry because:

- The communication (copy provided) was sent to a limited number of UK health professionals by a third party market research agency without the knowledge and/or authority of Shire UK – Shire UK had been badly let down by the third party

- On discovering that this had happened, contrary to the complainant's allegations, Shire UK took immediate action, escalated the matter to the European head of compliance and reviewed and approved a subsequent non-promotional communication (copy provided) to be sent to UK health professionals as part of this market research activity
- Clause 12.2 stated that market research activities must not be disguised promotion and must be conducted with a primarily scientific or educational purpose. Shire UK submitted that the market research activity itself met the criteria of Clause 12.2 – it was just the initial communication sent to the limited number of UK health professionals without the knowledge and/or authority of Shire UK that did not.

Shire therefore submitted that high standards had been maintained; it had not brought discredit upon and/or reduced confidence in the industry and therefore there was no breach of Clauses 9.1 and 2.

PANEL RULING

The Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The Panel also noted that the complainant was responsible for describing those matters which he/she considered were potentially in breach of the Code. In this regard the Panel noted Shire's submission that it did not understand the wording and details of certain parts of the complaint.

The Panel noted that it appeared that both the UK company and Shire International had a role in the market research in question, although the response was not entirely consistent on this point. According to the response the agency which produced and disseminated the email in question was instructed by Shire International. An internal email dated February 2016 described the activity as 'not a UK only project', noting that the contracts with the agency were completed through Shire International. A further email also dated February 2016 described the market research as a market access project with 'a UK pilot managed by UK NST'. The extent of each affiliates' responsibilities were not clear. Nonetheless, the Panel noted that the email in question was sent to UK recipients and that aspect of its use came within the scope of the Code. The UK company was responsible for the acts and omissions of its overseas affiliate that came within the scope of the Code. The Panel also noted that although the communication was sent by a third party agency it was an established principle that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel noted that the email in question sent by the third party UK based agency to ten UK health professionals invited them to participate in market research to test the managed entry agreement (MEA) design for Revestive and stated that the agency was working with Shire Pharmaceuticals to design a complex patient access scheme (PAS) to improve cost effectiveness and facilitate patient access to its new product for short bowel syndrome (SBS) – Revestive (teduglutide). Teduglutide was described as the first approved treatment in Europe for this debilitating disease and that it offered an important new treatment option to patients who were reliant on parenteral nutrition.

The Panel noted the broad definition of promotion and considered that the email in question was promotional and noted Shire's admission that the promotional nature of the email would not have been clear to the recipients. Its promotional nature was therefore disguised. The Panel therefore ruled a breach of Clause 12.2 as acknowledged by Shire.

The email was sent without Shire UK's consent or knowledge. The email was described as unauthorised. The supplementary information to Clause 12.2 stated that market research should be examined to ensure that it did not contravene the Code. In an email dated 16 February an international Shire employee stated that the agency was commissioned from his/her budget and that the third party agency was briefed on the CMLR process and he/she was surprised that this had happened. It was unclear whether the CMLR process included examination of materials and thus the Panel was unable to comment on whether the agency was appropriately briefed. An email dated 16 February sent by a UK employee stated that as it was not a UK only project and was 'signed by international' 'we needed to know more about the contracting, briefing of the agency on the SOPs and other procedure'. It thus appeared that there were internal governance concerns about activities taking place in the UK which were commissioned, at least in part internationally. Such activities had to comply with the Code and the company's internal processes should facilitate this. The Panel noted its comments and ruling above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that Shire had been asked to respond to Clause 18.1 of the Code. The Panel did not consider that the complaint raised a Clause 18.1 matter and thus ruled no breach of Clause 18.1 on this point.

The Panel noted that Shire had provided evidence to show that the matter was escalated within Shire and actions were taken to investigate the matter. Shire provided a discussion guide and associated slides that were approved in the UK demonstrating the action taken to stop any further communication by the market research agency without full review and approval by UK signatories.

The Panel noted that the complainant bore the burden of proof. The Panel considered that bearing in mind all the evidence before it the complainant had not established that Shire had asked its employees not to address the issue and to avoid escalation or that Shire failed to take action when the issue was raised as alleged. No breach of Clause 9.1 was ruled in this regard.

Noting its comments and rulings above the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

2 NICE Review

COMPLAINT

The complainant alleged that Shire communicated with the NHS during the process of a review of teduglutide by the National Institute for Health and Care Excellence (NICE). The company sent both medical and market access (commercial team) to discuss pricing and product reimbursement before the product was approved by the Committee for Medicinal Products for Human Use (CHMP) ie off-licence discussion. The complainant alleged that Shire had also tried to circumvent the NICE process because it believed it was not going to be successful in a health technology appraisal (HTA) by initiating discussions with the clinical reference groups (CRGs) directly and not the National Health Service (England) (NHSE) committee. The complainant noted that the CRGs were mainly clinicians who could prescribe.

In a second email, the complainant stated that he/she had emails on communication with the NHSE to try to influence the clinicians to vote to exclude Natpar (parathyroid hormone) (product for Hypo-parathyroid) out of the NICE process. He/she stated that there were also emails communicating with the NHSE CRG directly as well as commercial discussion with medical on those items.

In a third email, the complainant stated that the medicine at issue was Natpar, not teduglutide and provided some of the emails from market access and medical in Shire trying to influence prescribers in the CRG to overturn the NICE process discussion to take the product out of the process as Shire did not think it would be successful. The complainant confirmed that the email attachments provided were only for the Panel and not to be sent to Shire. The Panel decided not to take these email attachments into account as Shire had not had an opportunity to respond to the matters raised therein.

The complainant alleged that the market access team, with medical, attended meetings to discuss the pricing for a product that was not licensed.

In a fourth email, the complainant stated that Natpar was the product Shire communicated with CRGs and NHSE around, using a dual contact (market access and medical together). The product was off-licence when communication around pricing, as well as access options were made. Negotiation with NHS directly was very minimal. Shire did not inform NICE of the communication on purpose to pass the process as they knew they would not pass NICE CE limit.

RESPONSE

Shire explained that, at the time of the alleged activity, teduglutide had a marketing authorisation – it was granted in August 2012. Shire was not aware of any pre-licence activity for teduglutide in the UK and therefore could not comment on any activities prior to licence.

Shire noted the subsequent correspondence and information provided by the complainant and submitted that again, due to the wording and unspecific nature of the allegations, it struggled to know exactly how to investigate this matter. It considered that it might be helpful if it summarised Shire's activities in the UK relating to Natpar, CRGs, NHSE, NICE and the communication with these groups around pricing for Natpar which was licensed in the UK on 26 April 2017.

Background – about Clinical Reference Groups (CRGs) role in commissioning

Shire noted that National Health Service England (NHSE) had six programmes of care boards (NPoC). Each NPoC has several CRGs to provide clinical advice and leadership. These groups of clinicians, commissioners, public health experts, patients and carers used their specific knowledge and expertise to advise NHSE on the best ways that specialized services should be provided ie commissioned and payed for.

CRGs led on the development of clinical commissioning policies, service specifications and quality standards. They also provided advice on innovation, horizon scanning, service reviews and guide work to reduce variation and deliver increased value. CRGs, through their Patient and Public Voice (PPV) members, also helped ensure that any changes to the commissioning of specialised services involved patients and the public.

Natpar (recombinant human parathyroid hormone, rhPTH – the product mentioned by the complainant in the second and third correspondence) was a hormone replacement therapy for adults with underactive parathyroid glands, a condition known as 'hypoparathyroidism' and therefore would be within scope of the Specialised Endocrinology CRG to review, assess and advise the NHSE accordingly and as mentioned above.

Shire interactions with of the Specialised Endocrinology CRG related to Natpar

Shire provided a list of the membership of the Specialised Endocrinology CRG – four names which were marked in bold were with whom Shire interacted before the grant of the Natpar marketing authorisation (26 April 2017).

In December 2016, Shire Medical Information received an unsolicited request from a named CRG clinician (and member of the CRG), who was preparing a briefing for the NHS and the Specialised Endocrinology CRG. He/she wanted a point of contact from the Medical Department at Shire who could provide him with guidance on the development of Natpar. This was routed to the UK medical team. A Shire medical manager emailed the named CRG clinician to ask what specific information was required. Following a telephone call, the

named CRG clinician confirmed he/she wanted information to help complete sections of the NHSE Provisional Policy Proposal (PPP) form, specifically with reference to information about Natpar. Upon discussion, there was no urgent timeline for response and the named clinician was happy to wait for a response until after the Christmas break.

There was a further unsolicited request from the named CRG clinician later in December requesting, from Shire's perspective, the likely population size for Natpar for the proposed indication so that he/she could update the CRG with respect to the development of the application of a commissioning policy. This process was started by the CRG completing a PPP form. On 4 January 2017, the Shire medical manager telephoned the named CRG clinician and referred him to Section 17 of the PPP form which stated that if 'there is a planned or published Technology Appraisal, then NHSE cannot proceed to form a policy'. The Shire medical manager also told the clinician that as Natpar was on the work plan for NICE, there was no longer a requirement for the CRG to complete the form with the intent of the CRG developing a commissioning policy.

The clinician emailed on the same day (4 January) and referred to the conversation with the Shire medical manager and noted that at the forthcoming CRG meeting when updating the group about the product he/she would ensure that the current consideration of Natpar by NICE was discussed. Shire would be advised of the outcome of these discussions including whether further information was required'.

On 9 January, there was an unsolicited request from another named member of the CRG to a Shire employee. This request for specific information was passed for response to the Shire medical manager. The named CRG clinician appeared frustrated as Shire's non-promotional market access team member had requested that the CRG Chair send a formal request in writing specifically outlining exactly and specifically what information was required. This was done to remain compliant with the Code as at that point Natpar did not have a marketing authorisation. The clinician responded expressing frustration at the process, noting that material was normally circulated to the CRG a week beforehand and asked whether Shire had contacted a named CRG clinician and requested copies of any correspondence.

The Shire employee sent the following response and a one-page document on 9 January (copy provided):

> 'I understand you have verbally requested the following information:
>
> 1) Proposed indication and expected timeline for licence
> 2) Literature source for pivotal study
> 3) Estimated eligible population in England
> 4) Potential positioning of the product
> 5) NICE review update
> 6) Cost of the product.'

Face-to-face meeting with the initial named CRG clinician (joint meeting with the Shire medical manager and market access)

The Shire employee requested a face-to-face meeting with the named CRG clinician to discuss participation in Shire activities around hypoparathyroidism ie fact finding, participation in advisory boards, clinical trials, registries, symposiums, and being involved in global medical activities. The meeting was also to better understand how hypoparathyroidism was managed in a specific leading centre; the non-promotional meeting took place on 19 January. The meeting was also attended by Shire's market access team member. Shire's market access team member was asked to attend with the Shire medical manager to answer any questions about policy as the named CRG clinician had previously wanted to propose a policy for Natpar to the CRG.

On 2 February, there was a debrief call set up by a senior Shire market access executive about a discussion that Shire had had with NICE on 1 February about access issues for rare diseases. During their discussions, the possibility of delaying the Natpar submission to NICE was discussed given the nature of the clinical trial data and seeking advice from NICE about the proposed phase IV study (further information was provided in the email below).

On 6 February, a call took place between the two named CRG clinicians, referred to above, the Shire market access team member and the Shire medical manager. The purpose of this call was to provide the clinicians with an update on the discussion with NICE, who suggested Shire contact the Specialised Endocrine CRG, which was followed by the following email from the Shire medical manager to the named CRG clinician and the Chair from the CRG on 8 February:

> 'Many thanks for joining the call today following a request to be updated on the progress with NICE. This is the brief synopsis of our discussion, which you have requested I put in writing prior to your discussion. The information below is confidential.
>
> - rhPTH (1-84) - recombinant parathyroid hormone (currently unlicensed) - has recently been included on the NICE work plan for a single technology appraisal (STA).
>
> - Based on the clinical trial and economic evidence currently available, it is very unlikely that NICE will make a positive recommendation through the STA process. Furthermore, Shire engaged with the NICE Scientific Advice Committee in November 2016, to seek advice on the proposed Phase IV study which was being designed to enrich the current dataset in the indicated population. However, changes were suggested by NICE to the inclusion criteria and endpoints within the proposed trial, which Shire are now incorporating into the study, in order to address NICE's requirements.

- Due to challenges with the limited dataset, and with the support from the Endocrine CRG, we would like to propose delaying/suspending the NICE STA until the Phase IV study has been completed, giving a full data package in the indicated population. The results for the study are expected in 2019/20.

- In the interim, we would like to get the support of the CRG with regards to proposing an in-year service development, for the small cohort of patients (approx. 60-80 patients in the UK) who are difficult to control and have high resource utilisation due to recurrent hospitalisations, monitoring and specialist visits.

- As discussed previously, Shire would be willing to discuss a suitable Managed Entry Agreement in line with the criteria for in year service developments, to allow for a predictable budget impact and the collection of data to provide evidence of efficacy and safety in this severe population.

- Last week, Shire met with [NICE] to discuss access issues for rare diseases as well as the approach suggested above, outlining the challenges with the current data package, the scientific advice from NICE on the proposed Phase IV study, the CRG support for an in year service development for a small cohort of patients, and the possibility of delaying/ suspending NICE until Shire has Phase IV results. NICE could see the sense in this approach and suggested to get agreement from NHSE, perhaps through the Endocrine CRG setting out the case and sending to NICE However, [NICE] couldn't confirm the level of decision making in NHSE that would be needed but suggested that the CRG approach may be an appropriate one.

- Based on the information above, would the Endocrine CRG be supportive of this approach for delaying the NICE STA? If in agreement, we will need your help to identify who (if anyone) in NHSE would need to endorse this above the CRG. Furthermore, the case will need to be submitted to NICE before 18 February 2017 asking to delay I suspend their review.'

On 13 February, the Shire market access team member followed up with the Specialised Endocrine CRG with the following:

> 'Would it be possible for you to update me on your progress regarding a potential CRG communication/ letter to NICE as discussed last week. The deadline is the 18th Feb, which is the end of this week. If you are happy to share your progress and decision that would be really helpful.
>
> As the CRG members had wanted to be kept updated with regards to NICE and Natpar, and on the advice of [NICE], Shire provided information to the CRG members to ask if this was an appropriate approach to delay NICE until the data package for Natpar was complete, and to consider a commissioning policy in the interim.'

Department of Health (DoH) meeting (9 March 2017) and pricing discussions with CRG

Shire met with the DoH on 9 March 2017 to discuss the higher price for Natpar compared with the originally marketed Preotact. For the rare disease of hypoparathyrodism Natpar was to be priced much higher than the price of Preotact (the same chemical entity) when licensed and marketed some years earlier and in a different therapy area.

The following email was sent as selected CRG members had requested to be kept updated on pricing of Natpar:

> 'Dear XX
>
> I hope you are very well.
>
> As you have requested to be kept up to date with information relating to rhPTH(1-84)- which is currently unlicensed, and you have a role in the Endocrinology CRG in making policy decisions on budgets, I would like to make an appointment to see you to discuss pricing.
>
> Apologies there is a tight timeline for me to provide this information which will be available from the middle of next week 1st of March to the 9th March.
>
> If you could let me have some slots within that timescale that you are available I will do my best to accommodate.'

A briefing document entitled 'Additional information to provide to [health professionals] who have requested further information about pricing' – was certified on 8 March 2017 to provide a discussion guide for the Shire market access team leader when discussing pricing with health professionals – a copy of the certified briefing document was provided.

In relation to this, meetings were held by the Shire market access team member either as a teleconference (TC) or face-to-face (F2F) with the selected CRG members in March 2017.

Two of the Specialised Endocrinology CRG members that attended meetings, as well as the two named CRG clinicians had previously attended Shire advisory boards on hypoparathyroidism, and had verbally requested to be kept updated on pricing of Natpar.

The marketing authorisation for Natpar was granted on 26 April 2017.

Shire submitted that none of the activities in the UK relating to Natpar, the Specialised Endocrinology CRG NHSE, NICE and its communication with these groups around pricing for Natpar constituted pre-licence promotion because:

- Communication was limited to a small number of individuals who had leadership roles either within NHSE, the Specialised Endocrinology CRG or NICE
- Communication was reactive and/or when these key individuals had requested to be kept updated
- Communication content was limited to pricing and specific details these individuals needed to know in order to plan their budgets in relation to their commissioning roles
- Activity involved medical and other non-promotional employees - the number of Shire employees involved in these activities was also limited.

As a result, Shire submitted that there was no pre-licence promotion of Natpar with the Specialised Endocrinology CRG, NHSE or NICE as alleged and therefore no breaches of Clauses 3, 3.1, 9.1 or 2.

PANEL RULING

The Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant had made detailed allegations but provided little evidence in support. The Panel noted Shire's submission about the wording used by the complainant and the unspecific nature of the allegations.

The Panel noted that the complainant's original complaint referred to Teduglutide but he/she later confirmed that Natpar was the product at issue. The Panel therefore considered the complainant's allegation with regard to Natpar.

The Panel noted the broad definition of promotion at Clause 1.2 of the Code. The Panel noted the broad role of the CRGs as described by Shire, namely to advise NHSE on the best ways that specialised services should be commissioned and paid for. The Panel noted that given the CRG's role and the broad definition of promotion in the Code there was a possibility that interactions with a CRG, especially those initiated by a company, might be considered promotional. The Panel noted that the status of each such interaction should be considered on its individual merits.

The Panel noted that Clause 1.2 provided an exemption to the definition of promotion stating that replies made in response to individual enquiries from members of the health professions or other relevant decision makers or in response to specific communications from them whether of enquiry or comment, were excluded from the definition of promotion, but only if they related solely to the subject matter of the letter or enquiry, were accurate and did not mislead and were not promotional in nature.

The Panel noted that Clause 3.1 stated that a medicine must not be promoted prior to the grant of the marketing authorization that permitted its sale or supply. The supplementary information to Clause 3.1, in recognition of the fact that NHS organisations and others had to plan estimated budgets in advance, allowed a narrow exemption for advance notification of new products or product changes. The supplementary information provided a list of requirements which must be met to ensure that companies provided *bona fide* advance notification. Shire had not argued that any of its interactions constituted advance budgetary information but did refer to certain interactions being with health professionals making policy decisions on budgets.

The Panel noted Shire's submission that Natpar was licensed in the UK on 26 April 2017.

In relation to the interactions between the named CRG clinician and Shire in December 2016 and a telephone call in January 2017 these appeared to be in response to the health professional's original unsolicited request and his supplementary unsolicited request. The Panel did not have the original email communications but based on the company's account there was no evidence that the company's interactions listed above went beyond the information requested by the named CRG clinician or was otherwise promotional in nature or went beyond the scope of the original requests. The Panel noted that the complainant bore the burden of proof and had not established that the interactions were promotional. On the evidence before it the Panel considered that, on the balance of probabilities, Shire could take the benefit of the exemption to the definition of promotion at Clause 1.2 in relation to unsolicited requests and did not consider that the interactions listed above promoted Natpar prior to the grant of its licence. No breach of Clause 3.1 was ruled. This ruling was not appealed.

In relation to the interaction with a second named member of the CRG in January 2017, the Panel noted that the original request from the health professional was described by Shire as unsolicited. There was no evidence that the response went beyond the original request. The Panel noted that the complainant bore the burden of proof and had not established that the interactions were promotional. On the evidence before it the Panel considered that, on the balance of probabilities, Shire could take the benefit of the exemption to the definition of promotion at Clause 1.2 in relation to unsolicited enquiries and did not consider that the interactions listed above promoted Natpar prior to the grant of its licence. No breach of Clause 3.1 was ruled. This ruling was not appealed.

The Panel considered that the face-to-face meeting on 19 January 2017 with the first named CRG clinician above was different to the interactions described above as it had been initiated by Shire. It could thus not take the benefit of the exemption to the definition of promotion set out at Clause 1.2 in relation to unsolicited enquiries. Part of the meeting appeared to explore the possibility of the named CRG clinician becoming a key opinion leader and referred to participation in advisory boards, clinical trials and registries and other global medical activities. In the Panel's view such interactions were legitimate but had to comply with the Code. The Panel noted that the meeting was also attended by a member of the market access

team to answer questions about policy as the named CRG clinician had previously wanted to propose a policy about Natpar to the CRG. Whilst noting Shire's submission that the member of the market access team had a non promotional role, the Panel considered that certain aspects of the individual's job description might be considered promotional. Noting the general comments above about the broad definition of promotion and the CRG's role, the Panel considered, on the balance of probabilities, that the meeting was promotional, it had been initiated by Shire in anticipation of, *inter alia*, discussions about Natpar and the CRG policy prior to the grant of Natpar's licence. Shire had apparently arranged for the attendance of the market access team who, in part, had a promotional role. On balance, a breach of Clause 3.1 was ruled. Noting the arrangements for the meeting, the Panel considered that, on balance, high standards had not been maintained. A breach of Clause 9.1 was ruled. These rulings were appealed by Shire.

The Panel noted the complainant's concern that Shire tried to circumvent the NICE process because it believed it was not going to be successful in a health technology appraisal (HTA) by initiating discussions with the clinical reference groups (CRGs) directly and not the National Health Service (England) (NHSE) committee and that Shire had tried to influence the CRG clinicians to vote to exclude Natpar from the NICE process.

In relation to the discussion with NICE on 1 February to discuss access issues for rare diseases and the proposed Natpar submission, clinical trial data and advice on a phase IV study, the Panel noted that an exemption to the definition of promotion stated that information supplied to national public organisations such as NICE was exempt from the Code providing the information was factual, accurate and not misleading. Shire had not sought to take the benefit of this exemption. It was not clear to the Panel on the limited information before it whether the exemption applied to the interaction in question. The Panel did not know who had initiated the discussion. The complainant bore the burden of proof and had not established that the interaction was promotional and the Panel thus ruled no breach of Clause 3.1 of the Code. This ruling was not appealed.

In relation to the subsequent telephone conversation between the two named CRG clinicians, Shire's market access team member and its medical manager on 6 February, the Panel noted that, according to Shire, NICE had suggested that Shire get agreement from NHSE perhaps through the Endocrine CRG on certain matters. The Panel noted that the original conversation with NICE had included discussion about the phase IV study. This was reflected in the conversation on 6 February which was summarised in a subsequent email dated 8 February. It appeared that NICE had agreed with Shire's approach that the NICE assessment be delayed/suspended pending phase IV study results and suggested that agreement be obtained from NHSE perhaps through the Endocrine CRG, although NICE was unsure about the level of decision making required for this in NHSE. In the Panel's view, the complainant appeared to object in principle to these discussions. In the Panel's view, such discussions were legitimate so long as they complied with the Code. The interaction with the CRG on 6 February had apparently taken place at the suggestion of NICE and the suggestion had arisen during the course of what, on the evidence before it, the Panel had considered to be a non promotional conversation. In the Panel's view the complainant had not established that this aspect of the discussions (in relation to delaying/suspending the NICE assessment) with the CRG was promotional as alleged. No breach of Clause 3.1 was ruled. This ruling was not appealed.

The Panel noted that on 6 February discussion had also occurred in relation to Shire's proposal of a managed entry agreement, and according to the email dated 8 February this matter had also been referred to prior to 6 February. No details of the managed entry scheme were provided. The Panel considered that managed access schemes were acceptable in principle under the Code but that they should be carried out in conformity with its requirements. The Panel noted the broad definition of promotion in the Code and the advisory role of the CRG in relation to commissioning and funding as set out above. The Panel considered that it was difficult to see this aspect of the discussion as anything other than promotional. As Natpar did not have the benefit of its licence at the relevant time a breach of Clause 3.1 was ruled. Noting the content of the discussion and its ruling of a breach of Clause 3.1, the Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1. These rulings were appealed by Shire.

In relation to the meeting that occurred with the Department of Health on 9 March there was insufficient information before the Panel in relation to the status of the discussions. The complainant bore the burden of proof and the Panel considered that it had not been established that these meetings were promotional or otherwise in breach of the Code. No breach of Clause 3.1 was ruled. This ruling was not appealed.

The Panel noted that independently of the interactions above Shire had updated four members of the CRG about Natpar's price in March 2017. An email to all 4 CRG members referred to their request to be updated with information about rhPTH (1-84) which was described as unlicensed and referred to their role on the CRG in making policy decisions on budgets. Shire submitted that two of these individuals had made a verbal request to be updated on pricing at an advisory board. The Panel noted that the other two members of the CRG had previously been involved in the discussions at issue above. The Panel noted that the complainant bore the burden of proof and had not established that any of these interactions in March were promotional as alleged. No breach of Clause 3.1 was ruled. This ruling was not appealed.

The Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of Clause 2 was ruled. This ruling was not appealed.

During the consideration of this matter the Panel noted the job description of the market access role and noting the broad definition of promotion queried where all aspects of this role were truly non-promotional in nature. The Panel asked that Shire be advised of its concerns.

APPEAL BY SHIRE

Shire noted that the complainant was anonymous and contactable and appeared to be an ex-employee (although this latter point had not been confirmed). The complaint provided little detail and/or evidence and appeared confusing and contradictory in places. The PMCPA contacted the complainant on several occasions to gain more information and clarifications.

Shire, however, appealed the Panel rulings in respect of the NICE Review (two points) a face-to-face meeting which took place on 19 January and allegations relating to managed entry agreements. Shire addressed each part separately.

Face-to-Face meeting on 19 January 2017

Shire noted that the Panel ruled a breach of Clause 3.1 and 9.1 in relation to a face-to-face meeting that took place on 19 January 2017 with the named CRG clinician.

Shire noted that NHSE had six programmes of care boards (NPoC) and each NPoC had several clinical reference groups (CRGs) to provide clinical advice and leadership. The CRGs were made up of clinicians, commissioners, public health experts, patients and carers, used their expertise to advise NHSE on the most appropriate provision of specialised services. They also led on the development of clinical commissioning policies, service specifications and quality standards.

The Specialised Endocrinology CRG was reviewing and advising the NHSE in relation to Natpar (recombinant human parathyroid hormone, rhPTH).

Shire had been in contact with some members of the Specialised Endocrinology CRG prior to the grant of the marketing authorisation for Natpar. This had been set out in detail in the original response to the complaint and the Panel found that there had been no breach of the Code in respect of those communications. In order to understand the context of the meeting with the named CRG clinician on 19 January 2017 Shire submitted that it was necessary to look at the timeline of some of those communications:

13 December 2016 Shire medical information received an unsolicited request from the named CRG clinician who was preparing a briefing for the NHS and the Specialised Endocrinology CRG. He wanted a point of contact within Shire to provide him with guidance on the development of Natpar. This request was routed to the named CRG clinician.

14 December 2016 The request was routed to the UK medical team.

15 December 2016 The named CRG clinician was contacted by Shire's medical manager asking what specific information was sought. The clinician wanted help and support completing the NHSE Provisional Policy Form (PPP), specifically with reference to information about Natpar. Further clarity was sought about the PPP form, and level of detail required.

Additionally, in the same call, Shire's medical manager checked whether the named CRG clinician would be willing to meet face-to-face to discuss medical activities that he/she could take part in. The intention of the meeting was not to talk about Natpar at all and was a non-promotional medical affairs meeting. There was to be no product discussions at this meeting. The purpose of this meeting was to ascertain the clinician's willingness to take part in Shire medical activities around hypoparathyroidism, for example, advisory boards, phase 4 studies and registries, and also to learn about how hypoparathyroidism was managed at a UK leading centre the clinician suggested late January. The Shire medical manager had previously contacted the clinician to seek his willingness to take part in a Shire Delphi Panel, but the clinician had not responded to this email.

16 December 2016 Email from the Shire medical manager to the named CRG clinician thanking him/her for call on 15 December and seeking additional clarity about the literature search required for the PPP form.

The Shire medical manager sent a text message to the named CRG clinician to ask if the F2F meeting could take place on 19 January. There was no response to this text message.

19 December 2016 The Shire medical manager sent a text message to the named CRG clinician the CRG to ask if they could speak to confirm the F2F meeting. A call was arranged, and on that telephone call, the clinician wanted additional information about

	Natpar to brief the CRG on 10 January. The clinician was asked to document this in an email so the medical team member could respond specifically to that enquiry. The named CRG clinician by email set out the subject matter of his/her enquiry, namely the likely population size for the indication so that the CRG could be updated about the development of an application to NHSE for consideration of development of a commissioning policy. The Shire medical manager sent a text message to pencil in the date for the F2F meeting on 19 January.
4 January 2017	The Shire medical manager telephoned the named CRG clinician and referred him/her to section 17 of the PPP which stated that if 'there is a planned or published Technology Appraisal, the NHSE cannot proceed to form a policy'. The Shire medical manager told the named CRG clinician that as Natpar was on the work plan for NICE, there was no longer a requirement for the Specialised Endocrinology CRG to complete the form with the intent of the CRG developing a commissioning policy.
4 January 2017	The named clinician responded by email and referred to the conversation with the Shire medical manager and noted that at the forthcoming CRG meeting when updating the group about the product he/she would ensure that the current consideration of Natpar by NICE was discussed. Shire would be advised of the outcome of these discussions including whether further information was required.
9 January 2017	An unsolicited request from another named CRG clinician to a Shire market access team member by email. The request was passed to the Shire medical manager and not responded to by Shire's market access team member as all the non-promotional activities were being led on and managed by the Shire medical team and the person with the medical/scientific expertise to be able to address the questions and requests. The CRG clinician appeared frustrated that Shire market access team member had requested a formal written request. This was in order to understand the specific nature of the request.
9 January 2017	The clinician responded by email expressing frustration at the process noting that material was normally circulated to the CRG a week beforehand and asked whether Shire had contacted a named CRG clinician and requested copies of any correspondence.
9 January 2017	The Shire medical manager responded to the CRG clinician by listing what he/she understood to be the 6 items which were the subject of the verbal request. A one page document setting out the information the CRG clinician requested headed 'Please note that rhPTH (1-84) is currently unlicensed in Europe, including the UK' was provided.
10 January 2017	Specialised Endocrinology CRG meeting took place at which Natpar was discussed.

Shire submitted that initially, the meeting on 19 January was only to be attended by the Shire medical manager, as the remit of the meeting had been to understand the named CRG clinician's willingness to take part in Shire medical activities. However, after internal team discussions and the fact that the CRG meeting had taken place, it was decided that Shire market access team member should attend this meeting with the Shire medical manager in a non-promotional capacity. The team had also discussed the level of frustration with the second named CRG clinician with how it appeared that Shire were being bureaucratic, slow and apparently unwilling to share information about Natpar. Given that the CRG meeting had taken place nine days earlier, and that there might be questions and requests at that meeting specifically in relation to specialised commissioning, the internal decision was made for Shire market access team member to attend, as he/she would have the specific expertise to answer/address any questions that might be raised. It would be likely that these questions would be raised at the 19 January meeting, and therefore in a non-promotional capacity and there only to reactively respond to any such specialist questions, Shire's market access team member attended with the Shire medical manager.

The Shire medical manager recorded this meeting on Shire's CRM system and referred to the meeting as an introductory meeting (it was the first time

the Shire medical manager met the named CRG clinician face-to-face). The objective of the meeting was recorded as 'Burden of Illness'. There was no mention of product (Natpar) which was an option to be selected in the CRM system, highlighting that discussions were merely about fact finding and not about Natpar.

The non-promotional element of the meeting was further evidenced in the Shire medical manager's follow up email to members of Shire's global medical team which referred to the clinician's willingness to take part in Shire medical activities.

Following this face-to-face meeting, the named CRG clinician had engaged with Shire to participate in the ongoing Phase IV study and registry.

The non-promotional roles of the medical lead and the market access lead were explained to the named CRG clinician at the beginning of the meeting. Most of the meeting was taken up by the Shire medical manager on the medical side and a short period of time at the end of the meeting was spent by the Shire medical access team member responding to queries from the named CRG clinician about a potential in-year service policy as a result of the Specialised Endocrinology CRG on 10 January 2017.

Shire noted that the Panel found that all interactions between 13 December 2016 and 19 January 2017 were in compliance with the Code.

Shire noted that the Panel ruled that the 'on the balance of probabilities, that the meeting was promotional, it had been initiated by Shire in anticipation of, *inter alia*, discussions about Natpar and the CRG policy prior to the grant of Natpar's licence'.

Shire submitted that from the information provided above it was clear that there were no product discussions at this meeting nor was it intended that there would be such discussions. Accordingly, it was not a promotional meeting.

Shire noted that even though the market access lead had some promotional aspects to his/her role there were also non-promotional aspects to this role and on this occasion, he/she was acting in a non-promotional capacity. Accordingly, Shire submitted that the meeting was non-promotional and therefore not in breach of Clause 3.1 of the Code. In consequence Shire refuted a breach of Clause 9.1 and requested that the Appeal Board did not uphold the Panel's rulings.

Discussion on 6 February 2017 re Managed Entry Agreement

Shire noted that the Panel found that there was a breach of Clauses 3.1 and 9.1 in relation to the discussion on 6 February 2017 and Shire's proposal of a managed entry agreement. Shire submitted that a managed entry agreement was usually a risk share agreement between NHS and the company.

In addition to the timeframe set out above, the Appeal Board needed to be aware of the lead up to the discussion/email correspondence on 6/8 February 2017.

1 February 2017	Shire met with NICE to discuss issues for rare diseases. The Panel had ruled no breach of the Code with regard to this interaction. In addition, Shire submitted that these interactions were exempt under Clause 1.2 as long as they were factual accurate and not misleading which they were. At this meeting there was discussion about the challenges with the Natpar data package and the Phase IV study which resulted in the discussion leading to the possibility of delaying the submission to NICE given the nature of the clinical trial data available. There was also discussion around obtaining CRG support for an in-year service development for a small cohort of patients. NICE agreed with this approach and suggested that Shire obtain the agreement of NHSE perhaps through the Specialised Endocrinology CRG. Shire noted that an in year service development ("IYSD") was a term used by NHSE to refer to policies which were cost saving or cost neutral to the NHS. Where a product might lend itself to such an approach often required companies to be proactive to NHSE in highlighting this potential. An accepted entry route into the assessment process that decided whether the product did qualify for IYSD was via the CRG.
6 February 2017	Shire's medical access team member and the Shire medical manager updated the two named CRG clinicians referred to above as representatives of the Specialised Endocrinology CRG of the above discussions with NICE.
8 February 2017	The Shire medical manager emailed the two named CRG clinicians summarising the call on 6 February 2017. The email stated: 'Many thanks for joining the call today following a request to be updated on the progress with NICE. This is the brief synopsis of our discussion, which you have requested I put in writing

prior to your discussion. The information below is confidential.

- rhPTH (1-84) - recombinant parathyroid hormone (currently unlicensed) - has recently been included on the NICE work plan for a single technology appraisal (STA).

- Based on the clinical trial and economic evidence currently available, it is very unlikely that NICE will make a positive recommendation through the STA process. Furthermore, Shire engaged with the NICE Scientific Advice Committee in November 2016, to seek advice on the proposed Phase IV study which was being designed to enrich the current dataset in the indicated population. However, changes were suggested by NICE to the inclusion criteria and endpoints within the proposed trial, which Shire are now incorporating into the study, in order to address NICE's requirements.

- Due to challenges with the limited dataset, and with the support from the Endocrine CRG, we would like to propose delaying/ suspending the NICE STA until the Phase IV study has been completed, giving a full data package in the indicated population. The results for the study are expected in 2019/20.

- In the interim, we would like to get the support of the CRG with regards to proposing an in-year service development, for the small cohort of patients (approx. 60-80 patients in the UK) who are difficult to control and have high resource utilisation due to recurrent hospitalisations, monitoring and specialist visits.

- As discussed previously, Shire would be willing to discuss a suitable Managed Entry Agreement in line with the criteria for in year service developments, to allow for a predictable budget impact and the collection of data to provide evidence of efficacy and safety in this severe population

- Last week, Shire met with [NICE] to discuss access issues for rare diseases as well as the approach suggested above, outlining the challenges with the current data package, the scientific advice from NICE on the proposed Phase IV study, the CRG support for an in year service development for a small cohort of patients, and the possibility of delaying/suspending NICE until Shire has Phase IV results. NICE could see the sense in this approach and suggested to get agreement from NHSE, perhaps through the Endocrine CRG setting out the case and sending to NICE. However, [NICE] couldn't confirm the level of decision making in NHSE that would be needed but suggested that the CRG approach may be an appropriate one.

- Based on the information above, would the Endocrine CRG be supportive of this approach for delaying the NICE STA? If in agreement, we will need your help to identify who (if anyone) in NHSE would need to endorse this above the CRG. Furthermore, the case will need to be submitted to NICE before 18th February 2017 asking to delay / suspend their review.'

Shire stated that the reference to a 'Managed Entry Agreement' was incorrect in the email of 8 February. The correct reference was made in the subsequent paragraph to 'an in-year service development for a small cohort of patients'. This was what was meant

in these communications on 6/8 February. The idea was that if the NICE route was suspended then the relevant clinicians could make an application to NHSE on a cost neutral basis and NICE had suggested that this was best done through the Specialised Endocrinology CRG at the meeting on 1 February 2017.

There never was a managed entry scheme put in place nor were there any discussions in relation to a managed entry scheme. The discussions with the two named CRG clinicians took place as a result of the suggestion of NICE and the request by the named CRG clinicians to be kept up-to-date on any discussions with NICE and NHSE. The discussion related to in-year service policy only and the issues that had arisen with NICE. There was no promotional aspect to these discussions at any stage.

Shire submitted that although the incorrect use of the term 'Managed Entry Agreement' was used in one part of the email dated 8 February 2017, the intention was set out in the subsequent paragraph whereby Shire was seeking 'CRG support for an in-year service development for a small cohort of patients' and NICE had agreed with this approach and suggested that Shire contact the Specialised Endocrinology CRG.

No details of a managed entry agreement were ever discussed by any of the parties. Shire was merely seeking to understand the correct process by which a potential in year service policy could be developed.

The discussion on 6 February 2017 and subsequent email of 8 February 2017 all related back to the previous CRG commissioning policy discussions in January and the request of the named CRG clinicians to be kept up-to-date. Shire submitted that there was no promotional element to any of these discussions and the Panel was incorrect in finding that 'it was difficult to see this aspect of the discussions as anything other than promotional'.

Accordingly, Shire submitted that the communication was non-promotional and therefore not in breach of Clause 3.1 of the Code. In consequence it also refuted a breach of Clause 9.1 and requested that the Appeal Board did not uphold the Panel's rulings in this regard.

In summary, for all the reasons stated above Shire strongly believed that the two activities were not promotional and therefore no beach of Clause 3.1 had occurred. As a consequence, there was no breach of Clause 9.1. Shire respectfully requested that the Appeal Board did not uphold the Panel's rulings of breaches.

COMMENTS FROM THE COMPLAINANT

There were no comments from the complainant.

APPEAL BOARD RULING

The Appeal Board noted that Natpar was indicated in the treatment of a rare disease (adults with chronic hypoparathyroidism) and so the number of accessible clinicians in the therapy area would be small. In the rare disease arena it was likely that many of the health professionals involved would be prescribers as well as policy makers and so, with regard to activities related to Natpar, it would be difficult for Shire to avoid having to interact with those who, of necessity, wore 'two hats'. In discussions and the like with such people, the Appeal Board considered that companies should be extremely careful to correctly characterise their activities as either promotional or non-promotional; it was otherwise too easy for the boundaries to become blurred. The Appeal Board noted the broad definition of promotion. Participants in a meeting should be given clear sign posts as to its promotional status. Companies should be careful not to compromise the independence of prescribers who were also policy makers. The Appeal Board accepted that rare diseases presented some difficulties and it was often hard for companies to ensure they had the right conversations with the right people. Nonetheless compliance must be achieved. The Appeal noted that although the number of patients affected by rare diseases was small, the cost of their treatment was significant to the NHS. The Appeal Board noted that Natpar's licence was granted in April 2017 ie shortly after the activities subject to the complaint.

The Appeal Board noted that it had the benefit of more information than that which had been submitted to the Panel. The Appeal Board noted the context in which the meeting of 19 January had occurred and Shire's submission that it had originally been set up by Shire medical to discuss the attending clinician's participation in Shire activities around hypothyroidism to include, *inter alia*, advisory boards, clinical trials and registries. The company representatives explained that it was decided nearer the time to include a colleague from market access in order that he/she might be able to answer any questions regarding access that had arisen from a CRG meeting that had taken place some days previously. According to Shire there were no specific discussions about the product and although the market access colleague had some promotional elements to his/her role, he/she was bonussed only on qualitative aspects of his/her role, not on sales. In addition, the second named CRG clinician had, ten days before the meeting, emailed the market access colleague and criticised Shire for being 'unbelievably bureaucratic' when he/she had stated, *inter alia*, that he/she could only send information in response to a written request. It was hoped that the attendance of the market access colleague would avoid any further frustration on the part of the CRG. The Appeal Board noted the role of the named CRG clinician and although it had some reservations about the clinician's potential conflicts of interest given he/she was both a prescriber and policy maker, it nonetheless did not consider that, on the balance of probabilities, Natpar had been promoted at the meeting prior to the grant of its marketing authorisation. No breach of Clause 3.1 was ruled. In that regard the appeal on this point was successful.

The Appeal Board was concerned, however, about the lack of a detailed record of the meeting. The meeting was recorded on a medical CRM log

form which originated from Shire Global and was designed to record top line data only. It did not appear to have a section to record the fact that a colleague had also attended the meeting. It was not recorded on the form logging the 19 January meeting, and completed by medical, that a market access colleague had also attended. The Shire representatives submitted at the appeal that market access personnel did not have access to the CRM system and so the market access colleague who had attended could not create his/her own record of the meeting. The core communication objectives were recorded as 'Burden of Illness' because, according to the Shire representatives, this was the 'best fit' choice from a short drop-down menu. In the Appeal Board's view this did not adequately reflect the discussions which had taken place. There were no minutes recorded of the meeting; a short email giving very brief detail of the meeting only referred to the clinician wanting to be part of the registry and the Phase 4 study. The Appeal Board considered that given the difficulties discussed above about working in the area of rare diseases, the rigour with which Shire had documented the meeting was poor and in that regard it considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

With regard to the telephone call which took place on 6 February 2017, and subsequent email of 8 February, the Appeal Board noted that there appeared to be no precise definition of what a managed entry agreement was. Shire submitted that although the email of 8 February, the record of the call, referred to a managed entry agreement it also referred to such as being 'in line with the criteria for in year service developments'. The Appeal Board noted the company's definition of managed entry agreement and in year service development and considered that the difference between the two activities was not sufficiently clear; at the very least there appeared to be a degree of overlap and both might potentially involve data collection. The Appeal Board noted that the call record referred to a previous conversation with NICE in which in year service developments were discussed and which implied that an in-year service development for a small cohort of patients was already supported by the CRG. The need for an in-year service development arose because it was thought unlikely that the current Natpar data set would be sufficient for a positive recommendation from NICE. Shire thus wanted to delay the NICE submission and so the CRG would need to prepare for an alternative mechanism of access post licence. Shire's representatives explained that this would involve collecting data in a high risk population and that this activity was initially proposed by the CRG. The Appeal Board considered that, given the circumstances and the context in which the call had occurred, Natpar had not been promoted prior to the grant of its marketing authorisation. No breach of Clause 3.1 of the Code was ruled. The call had been well documented and in that regard the Appeal Board considered that high standards had been maintained. No breach of Clause 9.1 was ruled. The appeal on both points was successful.

3 Medical Science Liaison (MSL) visits

COMPLAINT

The complainant alleged that Shire's internal strategy had MSLs target numbers of visits to physicians and linked this to their key performance indicators (KPIs) despite the fact that an MSL role should be reactive and not proactive, particularly when it came to many products not yet licensed, ie no CHMP approvals. The complainant stated that this might have changed after the internal team complained however, it was a strategy that showed a lack of respect for ethics and code of conduct.

In a second email, the complainant stated that for the MSL targets, he/she did not have any specific documents as this was conveyed to him/her through the medical team which was not happy with the commercial implications.

In a third email, the complainant stated that he/she did not have emails for the MSL targets but, if the PMCPA investigated, those documents would be available (if Shire had not disposed of them).

In a fourth email, the complainant alleged that the MSL issue was linked to targets for medical team to meet with KOLs, it was linked to their evaluation and possible bonuses, which was against the ethics of the industry and the role of MSLs to be reactive and not proactive.

RESPONSE

Shire strongly refuted the allegations that it had a lack of respect for ethics and code of conduct and that it performed any activity against the pharmaceutical industry's high standards. Shire took the Code and the company's ethical standards very seriously – it was disappointed that the complainant alleged differently – Shire stood by the position that this was simply not correct. The MSL job description clearly outlined the primary duties for the MSL including the 'compliant communication and education of Shire's marketed and emerging product portfolio to meet the educational and professional needs of Shire's key customers'. In 2016 through to early 2017, there were internal discussions on the most appropriate measures (ie KPIs) for the job performance for MSLs within Shire. The complainant referred to internal discussions with the Shire International medical affairs team before the agreed performance goals and objectives (KPIs) for MSLs in the UK were approved.

Shire submitted that the division of KPIs for the MSL role was broken down into 4 focus areas where the MSL working time was spent: MSL Plan development and implementation; Leadership and self-management; Cross-functional contribution and Process management and implementation. In the focus area MSL time was spent working on the MSL plan development and implementation: specifically in 'develop and continue execution of MSL plan' bullet of the MSL performance goals and objectives (KPIs) it clearly provided guidance that the quantitative measure for health

professional interactions was an aspirational measure. Additionally, the qualitative aspects of interactions with KOLs ('analyse medical insights') were also used as key performance measures for the MSL. Shire strongly believed that the performance measures for MSLs were balanced, ethical and appropriate for a non-promotional role.

The complainant also alleged that the MSLs had undertaken pro-active unlicensed discussions despite not providing any evidence. Shire strongly refuted this allegation and from the MSL job description it could be clearly seen in the 'KOL engagement' responsibility section – 'KOL engagement: through compliant scientific exchange ...' implying that the MSL would only respond to any unlicensed discussion reactively to a request for further information from a health professional. Shire ensured that all MSLs operated in this manner.

Clause 1.7 of the Code stated 'the term "representative" means a representative calling on members for the health professions and other relevant decision makers in relation to the promotion of medicines'. Whilst it was clear that Shire's MSLs called upon on members of the health profession (as per industry standards) it was also clear that, from the MSL job description in terms of primary duties, responsibilities (% of time) and the MSL Key performance measured (as outlined above), the MSL role was neither based upon nor measured through promotion of Shire medicines thereby clearly distinguishing the MSL role from the representative role as per the definition given in Clause 1.7.

In conclusion, Shire strongly refuted the allegations that it had done anything inappropriate, unethical or contrary to the Code in relation to the MSL role within Shire UK. It did not consider that any aspect of the MSL job description and/or KPIs gave any basis for concern nor was in breach of the Code. Shire therefore refuted any allegation of breaches of the Code.

PANEL RULING

As with Points 1 and 2 above, the Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties.

The Panel noted the complainant's allegation that the number of visits to physicians was linked to the MSLs key performance indicators which in turn were linked to bonus payments and inferred that this encouraged proactive discussions of medicines prior to the grant of their licence.

The Panel noted the MSL Performance Goals and Objectives included, *inter alia*, 'HCP interactions: Aspiration for KOL face to face interactions'. They also instructed the MSL of their time to spend on the percentage in the field, aiming to spend less time in internal meetings.

The Panel noted that the complainant bore the burden of proof and that the complainant had provided no evidence to establish, on the balance of probabilities, that proactive promotional discussions about unlicensed medicines had occurred. No breach of Clause 3.1 was ruled.

The Panel noted that guidance about Clause 3 published by the Authority stated that the remuneration of those employed as medical and scientific liaison executives and the like must not be linked to the number of enquiries answered or the number of visits, meetings etc but a bonus scheme linked to the percentage of enquiries or visit requests completed may be acceptable. Remuneration should not be linked to sales in any particular territory or place or to sales of a specific product or products and, in particular, might not include a bonus scheme linked to such sales. Bonus schemes linked to a company's overall national performance, for example sales in the UK, might be acceptable. The Panel noted that the guidance was not part of the Code or its supplementary information but was, nonetheless, relevant.

The Panel noted the MSL Performance Goals and Objectives. The Panel noted that the MSL role varied across the industry but the relevant part of the Authority's guidance applied to those that had a non promotional role. The Panel noted the MSL key performance indicators and Shire's submission that the quantative measure for health professional interactions was an aspirational measure. The Panel considered that applying an aspirational KPI in relation to the number of visits to KOLs (rather than the percentage of visit requests completed or similar), which was linked to an MSL's remuneration, was inappropriate and might encourage behaviour that was inconsistent with the Code. High standards had not been maintained in this regard 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 reserved to indicate particular censure. No breach of Clause 2 was ruled.

Complaint received **25 October 2017**

Case completed **31 July 2018**

CASE AUTH/2997/12/17

ANONYMOUS CONTACTABLE HEALTH PROFESSIONAL v ABBVIE

Promotion of Synagis

A contactable, anonymous complainant who described him/herself as a 'very concerned' health professional complained about the presentation of Synagis (palivizumab) clinical data by an AbbVie representative at a meeting. Synagis was indicated for the prevention of serious lower respiratory tract disease requiring hospitalisation caused by respiratory syncytial virus (RSV) in children at high risk for RSV disease.

The complainant explained that at the meeting a number of health professionals gave presentations and an AbbVie representative talked about congenital heart disease (CHD) and presented specific case studies of patients who had various CHD complications together with reasons why they should be put forward for prophylaxis with Synagis. The case study slides appeared to be added into the presentation outside the medical approval process. A request for a copy of the case studies was refused. In the complainant's view, AbbVie was trying to influence the audience to prescribe Synagis to all CHD patients outside the NHS England (NHSE) Guidelines. The claims on the slides did not refer to any published data or local audits.

The complainant stated that having a representative presenting medical case studies and subsequent outcomes, completely reduced his/her confidence in the pharmaceutical industry and discredited the content of the whole educational event.

The detailed response from AbbVie appears below.

The Panel noted that the representative had delivered a promotional presentation on CHD which was certified as such and included a single case study at the end.

The Panel noted AbbVie's submission that a 'Pathways' document, a set of three scenarios, was used in the meeting. The scenarios were printed and left on tables during the session for discussion and were not formally presented as inferred by the complainant. Each scenario described a patient and then asked five questions about RSV immuno-prophylaxis and the use of Synagis.

The Panel noted that it was not unacceptable for a representative to discuss and present case studies as alleged, provided that the manner in which it was done complied with the Code. The Panel considered that there was no evidence that by allowing the representative to present and/or facilitate a discussion on the three scenarios within the Pathways document the representative or the company had failed to maintain high standards. No breach of the Code was ruled.

The Panel was concerned to note that the meeting organisers did not consider the Pathways document was promotional thus requiring certification. As the document had not been certified, a breach of the Code was ruled as acknowledged by AbbVie. A robust certification procedure underpinned self-regulation and the failure to recognise the promotional nature of the document and therefore that it required certification, meant that AbbVie had failed to maintain high standards and a breach of the Code was ruled.

The Panel noted that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics (SPC). The Panel noted the allegation that in the complainant's view, AbbVie was trying to influence the audience to prescribe Synagis to all CHD patients outside NHSE Guidelines. The Panel noted, however, that the Code did not state that a medicine must only be promoted in a manner that was consistent with NHSE Guidelines although it did require that all information, claims and comparisons must be accurate and must not be misleading either directly or by implication, by distortion, exaggeration or undue emphasis.

The Panel noted AbbVie's submission about the most recently published NHS commissioning arrangements for Synagis and the Joint Committee on Vaccinations and Immunisation (JCVI) recommendations on RSV and Synagis. The Panel noted that an undated, unsigned NHSE commissioning arrangements letter listed children over 2 years old as being not acceptable under the guidance for treatment due to little or no evidence for RSV prophylaxis. The JCVI document on RSV only referred to the use of Synagis in infants under 2 years of age. This was reflected in the presentation in question which referred to NHSE Guidance of November 2016 in relation to co-morbidities associated with CHD. The Panel noted that within a preceeding section 'Burden of RSV in CHD' one slide stated that 'Of 1806 US children aged under 5 years who died with bronchiolitis between 1979 and 1997, 9.9% had CHD'. The Panel was concerned about this statement in a promotional presentation noting Synagis' licensed indication. The Panel noted that other slides made it clear that data related to those aged less than 2 years, babies or small neonates. The Panel noted that the three scenarios in the Pathways document clearly referred to infants born in 2017. The Panel, whilst noting its concern above, did not consider that a general statement about the prevalence of CHD in patients under 5 years with bronchiolitis, within an introductory section about

risk factors for CHD, was misleading or otherwise qualified the subsequent reference to NHSE Guidelines within section 'JCVI Guidelines for CHD'. The Panel noted the narrow allegation and did not consider that the complainant had established that AbbVie was trying to misleadingly influence the audience to prescribe Synagis to all CHD patients outside the NHSE Guidelines as alleged. No breach was ruled.

The Panel noted the complainant's general allegation that the claims on the slides did not refer to published data or local audits conducted including the outcomes of prophylaxis with the said patient cohort. The complainant had not provided any material to support his/her allegations in this regard and it was not clear which claims he/she considered required references to published data or local audits as alleged. It was not for the Panel to make out a complainant's allegation. The Panel thus ruled no breach of the Code.

The Panel noted its comments and rulings above and did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

A contactable, anonymous complainant, who described him/herself as a 'very concerned' health professional, complained about the presentation of clinical data about the use of Synagis (palivizumab) by an AbbVie representative at a meeting held on 15 September 2017 at a named hospital. Synagis was indicated for the prevention of serious lower respiratory tract disease requiring hospitalisation caused by respiratory syncytial virus (RSV) in children at high risk for RSV disease. The title of the meeting was 'Mini Embrace 2017, Empower, Educate & Engage'.

COMPLAINT

The complainant explained that at the hospital meeting, a number of health professionals gave presentations on various topics. Additionally, an AbbVie representative, who the complainant recalled was accompanied by his/her manager, delivered a talk on congenital heart disease (CHD). The complainant stated that the agenda for the meeting (ref AXSYN170496c) was prepared in April 2017.

In addition to the above, the complainant noted that the representative presented slides of specific case studies of patients who had various CHD complications together with reasons why they should be put forward for prophylaxis with Synagis. The complainant stated that he/she was appalled that AbbVie had put forward a representative to discuss and present clinical case studies. The case study slides did not appear to have any preparation codes displayed on them and appeared to be added into the presentation outside the medical approval process.

During the presentation, the complainant requested a copy of the case studies but was told they could not be shared. The complainant stated that in his/her view, AbbVie was trying to influence the audience to prescribe Synagis to all CHD patients outside the NHS England (NHSE) Guidelines. The claims on the slides did not refer to any published data or local audits conducted including the outcomes of prophylaxis with the said patient cohort. The complainant stated that a representative presenting medical case studies and subsequent outcomes completely reduced his/her confidence in the pharmaceutical industry and discredited the content of the whole educational event; he/she would not be attending such meetings in the future.

In writing to AbbVie the Authority asked it to consider the requirements of Clauses 2, 7.2, 7.4, 9.1, 14.1 and 15.2 of the Code.

RESPONSE

AbbVie strongly refuted any suggestion that its alleged actions constituted a breach of Clause 2 (or indeed other clauses referred to by the Authority) and noted that it took its compliance and ethics obligations under the Code very seriously. AbbVie stated that in its view, the conduct of the meeting and the materials were appropriate; there was insufficient evidence to enable the complainant to discharge the burden of proof on the balance of probabilities.

AbbVie stated that the precise focus of the complaint and the specific case studies referred to by the complainant were unclear. Given this uncertainty, it had been hard to respond to the complaint but the company had addressed the pieces that it believed it could relate to below.

AbbVie noted that the complaint was submitted over 3 months after the meeting in question; in its view, a 'very concerned' health professional would have complained shortly after the meeting if he/she had genuine compliance concerns.

AbbVie stated that as part of its investigation, it had extensively interviewed the representative concerned and his/her line manager who also attended the meeting in question. The company did not accept the conduct and behaviours as alleged.

AbbVie provided a copy of the final agenda for the meeting along with the signed attendance sheet. The objective was to hold an educational meeting for health professionals to encourage discussion and best practice sharing before the RSV season started, which was usually between October and March. AbbVie's representatives' briefing material was provided which outlined the role of the representative during these meetings and the importance of compliance with the Code.

Based on its investigation, AbbVie did not consider that the complainant could prove, on the balance of probabilities, that he/she was at the meeting in question. Furthermore, it was AbbVie's view that nothing in the meeting discredited the industry. If the complainant was not at the meeting, then there was no basis for him/her to complain about the representative's conduct, nor to suggest that the meeting could be in breach of Clause 2.

AbbVie stated that there were a number of inaccuracies within the complaint to support its view that the complainant had not been at the meeting:

- The complaint stated the meeting ran from 9:30am-2:45pm. The final agenda, and save-the-date invitation (copies provided), showed that the meeting actually took place between 10am and 3:30pm on 15 September 2017. The draft agenda, which was not circulated to attendees, showed that the meeting was initially due to run between 9:30am and 2:45pm (copy provided).

- The preparation code (AXSYN170496c) cited by the complainant was that of the draft agenda not of the final document (ref AXSYN171184), the 'published agenda' had a preparation code. However, the final agenda had a different reference code. The draft agenda was not circulated to attendees.

- The complainant focussed on a number of presentations and specifically referred to a 'talk on CHD' and some 'specific case studies of patients who had various CHD complications'. These were referred to by the complainant as 'clinical case studies'. AbbVie provided copies of what it believed were the presentations at issue; 'CHD – What is a significant comorbidity?' and a Pathways document. The company submitted that it was most likely that the scenarios in the latter document were the focus of the complaint. This document was not a set of clinical case studies but hypothetical scenarios that were printed out and put on the tables to prompt discussion during the AbbVie facilitated workshop. The complainant's lack of precision about the materials supported the contention that he/she was not at the meeting.

- AbbVie stated that the complainant's statement that he/she requested a copy of the clinical case studies did not accord with its investigation which confirmed that no-one at the meeting requested copies of either 'CHD – What is a significant comorbidity?' or of the Pathways document.

AbbVie referred to Clause 15.2 that, 'Representatives must at all times maintain a high standard of ethical conduct in the discharge of their duties and must comply with all the relevant requirements of the Code'. The points above undermined the credibility of the alleged breach of this clause. If the complainant was not at the meeting, then he/she could not make this allegation and the meeting could not have 'completely reduced' his/her confidence in the pharmaceutical industry and 'discredited the content' of the event.

AbbVie submitted that if the complaint was focussed on the presentation 'CHD – What is a significant comorbidity?', then this was given at the meeting by the representative and there was one case study included at the end of it.

The primary intention of the meeting was to clarify the profiles of babies that fell within the Department of Health's (DoH's) Joint Committee for Vaccination and Immunisation (JCVI) recommendations for infants who would benefit from prophylaxis with Synagis. The case study reinforced a patient profile of a baby falling within the JCVI recommendations rather than making claims about the product. In this case study the baby, who received Synagis, had no RSV illness during the RSV season. As part of the introductory slide to the case study, it quite clearly stated that 'this case study is representative only and individual patient response may vary'. As the case study was for illustrative purposes only, and there were no claims, there was no need for references.

Although the presentation in question was originally planned to be delivered by an external speaker, the final agenda sent to attendees made it known that the representative would present the session on CHD. It was not inappropriate, as alleged, for a representative to present the session. The representative who gave the presentation and facilitated the case study was suitably qualified to do so.

AbbVie stated that the meeting was promotional and the presentation was certified as such. AbbVie provided a copy of the approval certificate, details of the certifier's experience and qualifications and a list of supporting references.

AbbVie stated that, in its view, there had been no breach of the Code as the presentation was balanced, fair, substantiated and certified for use at a promotional meeting. The company referred to its comments above about Clause 15.2.

AbbVie noted that the Pathways document was a set of scenarios used within the patient centred communication element of the meeting which was an AbbVie-facilitated workshop.

These slides were not clinical case studies but on-label scenarios used in a workshop to address the challenges faced in ensuring babies, identified for RSV prophylaxis with Synagis, and who fell under the care of more than one unit during their early care, were appropriately followed-up and brought forward for Synagis injections at the start of the next year's RSV season. This could be challenging as Synagis injections might not be initiated for some months after the baby was discharged from the care of the physician who had identified the need for RSV prophylaxis. AbbVie stated that no claims were made in the text of the three scenarios or subsequent questions and there was no need to refer to published data as the complaint suggested.

AbbVie explained that during the session, attendees were divided by tables, every table had to discuss the scenarios, ask questions and then each health professional would provide feedback. The scenarios were printed and left on tables during the session for discussion and were not formally presented by a speaker. AbbVie submitted that there was no evidence to support the complainant's allegation that the scenarios were used to promote 'Synagis to CHD patients outside the NHSE Guidelines'; AbbVie noted that the Code did not prohibit the promotion of medicines that were not funded by the NHSE.

Notwithstanding this, in the case of each of the three scenarios in the workshop, the decision as to whether Synagis use would be appropriate was left to workshop participants.
The JCVI recommendations on RSV identified three distinct groups of patients for which Synagis was recommended. The JCVI recommendations also allowed Synagis to be considered in a fourth group of babies 'where clinical judgement of other individual patient circumstances strongly suggest that prophylaxis would prevent serious RSV infection in infants who are at particular risk of complications from RSV'. The health professionals attending the workshop would have been fully aware of the content of the JCVI recommendations which were covered in the preceding session.

AbbVie stated that the most recently published NHS Commissioning arrangements for Synagis stated upfront that 'the policy to support the commissioning of palivizumab to reduce the risk of RSV in High Risk Infants for the 2017 vaccination season remains under the remit of Public Health England and the policy guidance is contained in the Green Book (Immunisation against Infectious Diseases) Chapter 27a'. Chapter 27a of the Green Book constituted the JCVI recommendations for RSV which, as stated above, allowed for clinical judgement on whether RSV prophylaxis with Synagis was appropriate. Against this background, it was relevant and appropriate to have the health professionals attend the workshop to discuss and agree whether, in their clinical judgement, prophylaxis with Synagis was appropriate for each clinical scenario. Given that the discussion was led by the health professionals and that no conclusion was drawn by AbbVie employees who facilitated the session, there was no evidence to support the complainant's statement that the scenarios were used to promote 'Synagis to CHD patients outside the NHSE Guidelines'.

AbbVie stated that, in its view, there had been no breach of the Code as the scenarios were for discussion only; no claims or comparisons were made.

AbbVie did, however, recognise that the document was not certified. As explained above, the intention of the document was not to promote Synagis, although it was used in the context of a promotional meeting and so this was a potential breach of Clause 14.1. It appeared that the document was not certified as the AbbVie meeting organisers considered it to be non-promotional. The relevant team members were being re-trained on this aspect of the Code.

In conclusion, AbbVie had serious concerns about the intention behind this complaint. Without prejudice to this, it did not believe there was sufficient evidence to discharge the burden of proof on the balance of probabilities.

PANEL RULING

The Panel noted that AbbVie accepted that the employee in question, who presented at the meeting, an account specialist, was a representative as defined by the Code and that the meeting was promotional in nature. The representative had delivered a presentation entitled 'CHD – What is a significant comorbidity?' (ref AXSYN170496i) which was promotional and was certified as such and included a single case study at the end. The Panel noted the complainant's allegation that beyond this presentation, the representative also presented slides of specific case studies of patients who had various CHD complications and why he/she would put these patients forward for prophylaxis with Synagis.

The Panel noted AbbVie's submission that a Pathways document, a set of three scenarios, was used within the patient centred communication element of the meeting which was an AbbVie facilitated workshop. The Panel noted that according to AbbVie, the scenarios were printed and left on tables during the session for discussion and were not formally presented as inferred by the complainant. Each scenario described a patient and then asked five questions including: 'Should this baby receive RSV immuno-prophylaxis?' 'At each stage discuss and document the possible obstacles in identifying this baby for Synagis.' 'Who are the key individuals in this patient's care that can identify this baby for the Synagis programme – where do you think the responsibility lies?' and 'Explore strategies that ensures this patient is identified for Synagis throughout the patient journey.'

The Panel noted that it was **not necessarily unacceptable** in principle under the Code for a representative to discuss and present case studies as alleged, provided that the manner in which it was done complied with the Code. The Panel noted that the complainant bore the burden of proof and considered that there was no evidence that, by allowing the representative to present and/or facilitate a discussion on the three scenarios within the Pathways document that he/she or the company had failed to maintain high standards on this narrow point. No breach of Clauses 9.1 and 15.2 were ruled.

The Panel noted that the Pathways document was not certified. The Panel noted that the Synagis meetings alignment toolkit for account specialists for the mini embrace meetings referred to pre-approved materials for all sessions other than the patient centred communication session. The Panel noted the content of the Pathways document which, according to AbbVie, was to be used during the patient centred communication session and was concerned that the meeting organisers did not consider the document was promotional thus requiring certification. The Pathways document had not been certified and the Panel therefore ruled a breach of Clause 14.1 as acknowledged by AbbVie. In the Panel's view, a robust certification procedure underpinned self-regulation and the failure to recognise the promotional nature of the Pathways document, and therefore that it required certification, meant that AbbVie had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent

with the particulars listed in its summary of product characteristics (SPC). The Panel noted that according to its SPC, Synagis was indicated for the prevention of serious lower respiratory tract disease requiring hospitalisation caused by RSV in children less than 2 years of age at high risk of RSV disease. The Panel noted the allegation that in the complainant's view, AbbVie was trying to influence the audience to prescribe Synagis to all CHD patients outside NHSE Guidelines. The Panel noted that the Code did not state that a medicine must only be promoted in a manner that was consistent with NHSE Guidance as implied by the complainant. The Code, however, did require that all information, claims and comparisons must be accurate and must not be misleading either directly or by implication, by distortion, exaggeration or undue emphasis.

The Panel noted AbbVie's submission about the most recently published NHS commissioning arrangements for Synagis and the JCVI recommendations on RSV and Synagis. The Panel noted that an undated, unsigned copy of an NHSE commissioning arrangements letter included children over 2 years old in a list of co-morbidities that were not acceptable under the guidance due to little or no evidence for RSV prophylaxis. The DoH's JCVI document on RSV only referred to the use of Synagis in infants under 2 years of age. This was reflected in the presentation in question which referred to NHSE Guidance of November 2016 in relation to co-morbidities associated with CHD. The Panel noted that within a preceeding section 'Burden of RSV in CHD' a slide entitled 'Evidence for risk factors in hsCHD' stated that 'Of 1806 US children aged under 5 years who died with bronchiolitis between 1979 and 1997, 9.9% had CHD'. The Panel was concerned about this statement in a promotional presentation noting Synagis' licensed indication. The Panel noted that other slides made it clear that data related to those aged less than 2 years or babies or small neonates. The Panel noted that the three scenarios in the Pathways document clearly referred to infants born in 2017. The Panel, whilst noting its concern above, did not consider that a general statement about the prevalence of CHD in patients under 5 years with bronchiolitis, within an introductory section about risk factors for CHD, was misleading or otherwise qualified the subsequent reference to NHSE Guidelines within the section 'JCVI Guidelines for CHD'. The Panel noted the narrow allegation and did not consider that the complainant had established that AbbVie was trying to misleadingly influence the audience to prescribe Synagis to all CHD patients outside the NHSE Guidelines as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that the complainant had made a general allegation that the claims on the slides did not refer to any published data or local audits conducted including the outcomes of prophylaxis with the said patient cohort. The complainant, who had the burden of proving his/her complaint on the balance of probabilities, had not provided any material to support his/her allegations in this regard and it was not clear which claims he/she considered required references to published data or local audits as alleged. It was not for the Panel to make out a complainant's allegation. The Panel thus ruled no breach of Clause 7.4.

The Panel noted its comments and rulings above and did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

Complaint received **18 December 2017**

Case completed **17 July 2018**

CASE AUTH/3017/2/18

ANONYMOUS CONTACTABLE v CELGENE

Certification and approval of material for meetings

An anonymous, contactable complainant complained about a number of 'meetings in a box' materials produced by Celgene UK for use by its representatives. The material related to Otezla (apremilast) which was indicated for the treatment of adults with psoriatic arthritis or moderate to severe chronic plaque psoriasis.

The complainant alleged that the materials were not certified and were never approved for use by representatives. The immunology and inflammation (I&I) senior team knew this and sought to repress it rather than be transparent.

The detailed response from Celgene is given below.

The Panel noted that the complainant referred specifically to seven materials. The Panel noted that Celgene listed a further eighteen materials, the Panel noted that the only material that it considered from Celgene's list was the briefing document because although not specifically referred to by the complainant, it related to the training of the materials at issue which was a matter raised by the complainant.

The Panel noted Celgene's submission that all meetings in a box materials were withdrawn on 5 January 2018 because a final signatory did not consider that the wording on the job bag summary made it clear that the materials were intended for use by health professionals as well as for use by representatives.

In the Panel's view it was vital that signatories were given accurate information about the intended use and dissemination of materials. When materials were to be used both by representatives and by health professionals that should be made clear.

The Panel noted Celgene's submission that the wording on the job bag summaries could be construed to mean that the materials were for use only by the representatives to present and that was the information provided to the final signatories when certifying. Therefore in the Panel's view the materials and use by health professionals had not been certified and thus a breach of the Code was ruled. The Panel considered that Celgene had failed to maintain high standards on this point and a breach of the Code was ruled. Conversely and contrary to the complainant's allegation the use of the materials in question by representatives had been certified and no breach of the Code was ruled in that regard.

The Panel noted Celgene's submission that representatives were all extensively trained on the content of the meetings in a box materials as these data were also used in the then current promotional materials, such as detail aids Celgene had not provided a copy of the detail aids and other materials current at the relevant time and did not refer to or provide any relevant briefing on these materials. The Panel queried whether representatives had been properly trained on the specific content of the meetings in a box modules rather than merely being familiar with them. The Panel queried whether familiarity was sufficient and was concerned, given that the meetings started in February 2017, that representatives only received further specific and detailed training on some of the meetings in a box materials in September 2017. Taking all of the circumstances into account the Panel decided on balance that detailed briefing on the clinical content of the meetings in a box modules had not been provided prior to their first use in February 2017 and a breach of the Code was ruled. The Panel considered that failure to brief representatives on the clinical content of the meetings in a box slide decks prior to their first use in February 2017 meant that Celgene had failed to maintain high standards and a breach of the Code was ruled.

The Panel noted that a briefing document for the meetings in question was certified on 6 March 2017, after the first meeting in a box meeting took place on 28 February. The Panel noted that the briefing material in question covered process and did not cover their clinical content. In the Panel's view the briefing material in question on the approval process should have been certified in advance of the first meeting being planned. The Panel noted Celgene's submission that this single briefing document was used prior to certification and a breach of the Code was ruled. The Panel considered that failing to certify the briefing document prior to its first use meant that Celgene had failed to maintain high standards and a breach of the Code was ruled.

The Panel noted that the complainant had provided no evidence in support of his/her allegation that the senior I&I team tried to repress the fact that the team was using uncertified materials and therefore ruled no breach of the Code.

The Panel noted its rulings and comments above. The Panel noted that Celgene had been the subject of PMCPA audits and had subsequently initiated a number of compliance initiatives. The Panel did not consider that this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

An anonymous, contactable complainant complained about a number of 'meetings in a box' materials (refs UK-I&I160318 (a-g)) produced by Celgene UK for use by its representatives. The material related to Otezla

(apremilast) which was indicated for the treatment of adults with psoriatic arthritis or moderate to severe chronic plaque psoriasis.

COMPLAINT

The complainant alleged that the materials were trained to and used by the representative with customers without proper certification or approval. According to the complainant the materials were never approved for use by representatives. The immunology and inflammation (I&I) senior team knew this and sought to repress it rather than be transparent. The complainant stated that there was a big culture of not wanting to put anything in writing for fear of creating evidence for a later date and so the complainant was not convinced that the Authority would find written evidence. It was 'lucky' for Celgene that the prescribing information needed updating and as such it sought to repress the use of improper certified materials by the representatives with the prescribing information update.

When writing to Celgene, the Authority asked it to consider the requirements of Clauses 2, 9.1, 14.1 and 15.9 of the Code.

RESPONSE

Celgene submitted that the meetings in a box consisted of a series of modular PowerPoint presentations which contained a standard set of slides, produced by the I&I department, to be approved for certification under the Code. The PowerPoint presentations were short and designed to cover specific topics; they were prepared based on the information contained in the Otezla detail aid and general information on psoriasis and psoriatic arthritis, which had been previously presented to the representatives. The slide decks were made available to the representatives for use by attendees at on-label, promotional, locally run (Type B) meetings. Type B meetings were representative-led Celgene speaker meetings, hosted by representatives, during which health professional speakers also presented. During some meetings, the health professional would be asked to present the meeting in a box slide decks, rather than the representatives.

The Otezla meeting in a box slide deck (refs UK-I&I 160318(a-g)) was made up of seven modules, referred to by the complainant:

1 Psoriasis- Disease Burden Module (ref UK-I&I160318a)
2 Psoriatic Arthritis- Disease Burden Module (ref UK-I&I160318b)
3 Psoriasis- Unmet Needs Module (ref UK-I&I160318c)
4 Ref UK-I&I160318d (withdrawn, not used)
5 Otezla Clinical Evidence in Psoriasis Module (ref UK-I&I160318e)
6 Otezla Clinical Evidence in Psoriatic Arthritis Module (ref UK-I&I160318f)
7 Otezla Clinical Practice in Psoriasis Module (ref UK-I&I160318g)

The original materials were certified and approved between February and March 2017. This was before the PMCPA re-audit in May 2017 and, following the re-audit, the implementation of 47 compliance-related CAPAs.

In addition to the original set of seven modules, 18 additional slide decks were produced details were provided.

All of the job bags for each module were approved and certified for use by representatives in the UK & Ireland, with the exception of one, which was cancelled, and never distributed or used.

The representatives had been trained on the content of the slide decks from previously approved materials, including the detail aid, and during their initial training course. The meetings in a box briefing document (ref UK-I&I160318y) and the briefing on template slide (ref UK-I&I160318z) were produced specifically to guide the representatives on how to use the materials in the field. Further training was provided during an internal meeting in September 2017 and this included the Psoriatic Arthritis Mode Of Action Slide Deck briefing document (ref UK-I&I160318ae) and the Psoriasis Mode Of Action briefing document (ref UK-I&I160318af).

All four of the briefing documents were certified. However, one of the briefing documents (UK-I&I160318y) was certified on 6 March 2017, which was after the first meeting in a box meeting took place on 28 February. This single use of a briefing document occurred before the PMCPA re-audit in May 2017 after which Celgene put in place 47 corrective and preventative actions, specifically to address a number of compliance issues and to prevent further occurrences. For example, all Zinc account holders had undergone full refresher training and Zinc Maps validation. In addition, a permanent healthcare compliance specialist role had been created and filled, with responsibility for ongoing monitoring of Zinc job map quality and adherence to relevant standard operating procedures (SOPs) and working practices, including active job bag checking and quality and compliance checking of ongoing job bags. All final signatories had been validated following Celgene's established final signature training and validation process.

Celgene explained that the representatives had used the meetings in a box materials or materials modified from the initial slide decks in around 30 meetings between February and December 2017. Ten meetings used meetings in a box materials (UK-I&I160318a, b, c, e, f, g) and the others used other slide decks from the meetings in a box series or materials that were modified versions of the original meetings in a box materials (where, for example, a health professional wished to add slides detailing patient cases). All arrangements and all materials used for these promotional meetings were reviewed and approved by a final nominated medical signatory before each meeting took place.

Celgene noted that the complainant has suggested that the I&I senior team sought to repress the use of uncertified materials, stating that Celgene was

'lucky' that the prescribing information needed updating. Although the prescribing information was due to be updated, this was not the main reason why the materials were withdrawn. In December 2017, one of the final signatories reviewed the meetings in a box materials and noted that the statement contained in the job summary was not completely clear; the wording on the job bag summary stated: "This is the Meetings in a Box (MIB) Slide deck that will be used for by [representatives] in Local Type B meetings". The final signatory did not consider that this wording made it clear that the meetings in a box materials were intended for use by representatives, as well as for use by health professionals. The wording on the job bag summary could be construed to mean that the materials were for use only by the representatives to present, which was not the original intent of the activity. It was decided, therefore, to withdraw the materials and raise new job bags, so that the job bag summary information could be updated to state more clearly that health professionals in addition to representatives could present the meetings in a box material.

Based on the decision to clarify the job bag wording and the additional requirement to update materials following a prescribing information update, all materials pertaining to the meetings in a box were withdrawn on 5 January 2018.

Following receipt of this anonymous complaint, Celgene carried out a number of interviews with members of the Celgene I&I senior team, product team and representatives.

The internal understanding was that the meetings in a box materials were approved for use by representatives and by health professionals in promotional meetings. The materials were based on data in the current detail aids used by the representatives; this was why there was no extensive representative training provided at the start of 2017. However, training was given at the Cycle meeting in September 2017, which the representatives found to be highly valuable.

None of the individuals interviewed were aware of the concerns raised with regard to the meetings in a box material being used without approval, and all representatives understood how the meetings in a box materials were to be used. Meetings in a box materials were approved prior to use at promotional meetings.

Celgene submitted that the compliance environment within the company had improved significantly over the last 18 months. There were no remarks from the interviewees about leadership trying to repress or avoid putting things in writing. One of the outcomes of the May 2017 re-audit was to improve the speak-up culture within the company. Celgene had established a network of compliance champions throughout the affiliate who provided advice, signposting and additional checks within teams. Interviewees noted that these individuals were highly valued. In addition, 24 Speak Up meetings were held in September and October 2017, hosted by the Celgene Leadership Team, seeking feedback on compliance initiatives, to refine processes and approaches, and identify areas that required continuing focus.

With regard to Clause 9.1, Celgene noted that its compliance programme included policies, SOPs and electronic tools for the review and approval of materials. Celgene had reviewed and updated those policies, processes and systems and invested additional compliance resources throughout 2017 and early 2018. All of the 22 job bags for each module comprising the meetings in a box activity were approved and certified for use in the UK & Ireland. Three of the four briefing documents were compiled, approved and certified on time for the meetings in a box meetings with the exception of the first briefing document (ref UK-I&I160318y) which was certified on 6 March 2017, after the first meetings in a box meeting which was held on 28 February 2017.

All job bags for each module of the meetings in a box were approved and certified for use in the both the UK & Ireland before all of the promotional meetings held between February through December 2017 which involved the use of meetings in a box materials in their original or modified form. The representatives were previously trained on the data content of the meetings in a box decks as these same data were included in current promotional materials. Further training was provided in September 2017.

Celgene submitted that the PMCPA should take an overall view, and such an isolated incident should not trigger a breach. While Celgene regretted the failure of the final certification of the briefing document (ref UK-I&I160318y), the company has since been through a full audit procedure. Following the recommendations that came out of the May 2017 re-audit, the company had followed up on 47 compliance-related CAPAs. As a result, Celgene's procedures relating to compliance had been significantly strengthened and improved, which the PMCPA would have found during its re-audit of Celgene on 1 February 2018. Celgene, therefore, believed that high standards had been maintained and there had been no breach of Clause 9.1.

All the material pertaining to the meetings in a box meetings was duly approved and certified by at least one person on behalf of the company in the manner provided for by Clause 14.1, except for the final certification of the briefing document (ref UK-I&I160318y). The company regretted the failure but had put in place a number of measures to ensure that its certification processes followed internal SOPs and were in adherence with the Code.

With regard to Clause 15.9, the representatives were all extensively trained on the content of the meetings in a box materials, as these data were also used in current promotional materials, such as detail aids. The representatives were also extensively trained during their initial training courses. In addition, they received further training on the meetings in a box materials in September 2017, with the involvement of the medical department. All of the briefing materials and all of the meetings in a box materials

were appropriately generated, reviewed and certified by at least one final nominated medical signatory. Three of the four briefing documents were compiled, approved and certified on time for the meetings in a box meetings with the exception of the briefing document (ref UK-I&I160318y) which was certified on 6 March, after the first meetings in a box meeting on 28 February 2017. However as stated above, the representatives had already received extensive training on the content of the meetings in a box decks before the first meeting which used these materials. Celgene denied a breach of Clause 15.9.

Celgene noted that its I&I team had approved and certified all materials and all of the arrangements related to the promotional meetings that took place in 2017 that used either the original meetings in a box materials or modified meetings in a box materials. Briefing material to instruct the representatives on how to use the material had been appropriately compiled, reviewed and certified. The representatives had been extensively trained on the data content of the meetings in a box material. In addition, from the interviews that were conducted with members of the I&I senior team and six representatives, there was no evidence of the intention to suppress the use of improperly certified material used by the representatives. Celgene thus did not consider that the activities of its I&I team had brought discredit upon, or reduced the confidence in the industry; the company denied a breach of Clause 2.

In conclusion, Celgene hoped that the above addressed the PMCPA's questions about the development and use of the meetings in a box materials. The company would be happy to answer any additional questions or provide any further information if required. Celgene noted that the complaint referred to materials certified and approved in early 2017. Since then, the company had been through a full PMCPA audit procedure and had implemented a number of initiatives that had significantly strengthened and improved the company's compliance environment. The company had focused its efforts on further improving its SOPs; building up the Speak Up culture; improving the quality of its materials and undergone a full ZINC review process. This complaint therefore pre-dated a number of significant changes that had been made to Celgene's compliance environment, as the PMCPA would have observed during its recent re-audit in February 2018.

PANEL RULING

The Panel noted that the complainant was initially contactable but the email address given was now no longer in use. The Panel noted that the complainant bore the burden of proof on the balance of probabilities. A judgement had to be made based on the available evidence.

The Panel noted that the complainant referred specifically to materials (refs UK-I&I160318 (a-g)). The Panel noted that Celgene raised a further eighteen materials, the Panel noted that the only material that it considered from that list was the briefing document (ref UK-I&I160318y) because although not specifically referred to by the complainant, it related to the training of the materials at issue which was a matter raised by the complainant.

The Panel noted Celgene's submission that the Otezla meetings in a box modules (UK-I&I 160318 (a-g)) were certified between February and March 2017 for use by the key account managers (KAM) at KAM-led speaker meetings between February and December 2017 with the exception of UKI&I160318d, which was cancelled, and never distributed or used. The Panel noted Celgene's submission that all meetings in a box materials were withdrawn on 5 January 2018 because a final signatory did not consider that the wording on the job bag summary made it clear that the materials were intended for use by health professionals as well as for use by representatives. There was also an additional requirement to update the materials following a prescribing information update.

In the Panel's view it was vital that signatories were given accurate information about the intended use and dissemination of materials. When materials were to be used both by representatives and by health professionals that should be made clear.

The Panel noted Celgene's submission that the wording on the materials' job bag summaries could be construed to mean that the materials were for use only by the representatives to present and that was the information provided to the final signatories when certifying. This was inaccurate and was subsequently noted as such by a final signatory in December 2017. Therefore in the Panel's view the materials (UK-I&I 160318 (a-c) and (e-g)) use by health professionals had not been certified and thus a breach of Clause 14.1 was ruled. The Panel considered that Celgene had failed to maintain high standards on this point and a breach of Clause 9.1 was ruled. Conversely and contrary to the complainant's allegation the use of the materials in question by representatives had been certified and no breach of Clause 14.1 was ruled in that regard.

The Panel noted that Clause 15.9 required that companies must prepare detailed briefing material for medical representatives on the technical aspects of each medicine which they will promote. Briefing material must comply with the relevant requirements of the Code and was subject to the certification requirements of Clause 14. The Panel noted Celgene's submission that representatives were all extensively trained on the content of the meetings in a box materials as these data were also used in the then current promotional materials, such as detail aids and representatives were also extensively trained during their initial training courses. Celgene had not provided a copy of the detail aids and other materials current at the relevant time and did not refer to or provide any relevant briefing on these materials. The Panel queried whether representatives had been properly trained on the specific content of the meetings in a box modules rather than merely being familiar with them. The Panel queried whether familiarity was sufficient and

was concerned, given that the meetings started in February 2017, that representatives only received further specific and detailed training on some of the meetings in a box materials in September 2017, which they found to be highly valuable. Taking all of the circumstances into account the Panel decided on balance that detailed briefing on the clinical content of the meetings in a box modules had not been provided prior to their first use in February 2017 and a breach of Clause 15.9 was ruled. The Panel considered that failure to brief representatives on the clinical content of the meetings in a box slide decks prior to their first use in February 2017 meant that Celgene had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted that a briefing document (UK-I&I160318y) for the meetings in question was certified on 6 March 2017, after the first meeting in a box meeting took place on 28 February. The Panel noted that the briefing material in question covered process: the roll-out of the pre-approved slide decks to the field force and the process for promotional slide approval. It did not cover their clinical content. In the Panel's view the briefing material in question on the approval process should have been certified in advance of the first meeting being planned. The Panel noted Celgene's submission that this single briefing document was used prior to certification and a breach of Clause 14.1 was ruled. The Panel considered that failing to certify the briefing document prior to its first use meant that Celgene had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted that the complainant had provided no evidence in support of his/her allegation that the senior I&I team tried to repress the fact that the team was using uncertified materials and therefore ruled no breach of Clause 9.1.

The Panel noted its rulings and comments above. The Panel noted that Celgene had been the subject of PMCPA audits and had subsequently initiated a number of compliance initiatives. The Panel did not consider that this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

During the consideration of this case the Panel was concerned to note the number of items that were certified with an inaccurate method of dissemination information and that it took almost a year to identify the issue. The Panel noted that the Authority had previously audited Celgene and was aware that in March 2016 it was identified that Type B meeting slides were not certified and was disappointed that there were issues with the certification of said meeting materials discovered in January 2018. The Panel requested that Celgene be advised of its concerns.

Complaint received **31 January 2018**

Case completed **2 August 2018**

BOEHRINGER INGELHEIM and LILLY v NOVO NORDISK

Promotion of Victoza

Boehringer Ingelheim and Eli Lilly and Company (the Alliance) complained about the promotion of Victoza (liraglutide) by Novo Nordisk. The material at issue was an exhibition panel used by Novo Nordisk at the Diabetes UK Professional Congress, March 2018. Victoza was a glucagon-like peptide-1 receptor agonist (GLP-1 RA) indicated for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise.

The Victoza summary of product characteristics (SPC) stated it could be used as monotherapy when metformin was considered inappropriate due to intolerance or contraindications and could be used in addition to other medicinal products for the treatment of diabetes. Section 4.1 of the SPC also stated that study results with respect to combinations, effects on glycaemic control and cardiovascular (CV) events and the populations studied could be found in Sections 4.4, 4.5 and 5.1 of the SPC.

Two thirds of the exhibition panel featured the photograph of a woman walking in the shade towards the viewer and about to turn left around the corner of a large building and into what appeared to be a sunnier aspect. Wrapping around the corner of the building was the text 'In adults with insufficiently controlled type 2 diabetes change the course of treatment by reducing CV [cardiovascular] risk'. This was followed by red text which was mostly about the same height as the woman and which read 'HbA1CV' such that 'CV' was in the foreground of the picture. The headline across the top of the picture read 'Victoza: the only GLP-1 RA superior in preventing CV events vs placebo'. To the right side of the picture, and in the remaining third of the panel were the following two paragraphs in bold font:

> **'Indication : Victoza is indicated for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise.**
>
> **Section 5.1: Both improvement of glycaemic control and reduction of CV morbidity and mortality are an integral part of the treatment of type 2 diabetes.'**

The detailed response from Novo Nordisk is given below.

The Alliance alleged that the overall prominence of the two main claims on the stand 'Change the course of treatment by reducing CV risk' and 'Victoza: the only GLP-1 RA superior in preventing CV events vs placebo' combined with the imagery, would lead observers to conclude that the promotional message was weighted heavily towards the reduction of CV risk. Victoza was not indicated for the reduction of CV risk but for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise. The CV benefits of Victoza were referred to only in Section 5 of the SPC and so should be promoted as added benefits of Victoza rather than as the main indication. The Alliance alleged that the overall balance of the stand promoted Victoza inconsistently with the SPC.

The Panel noted that Victoza had been available as a treatment for diabetes for a number of years. According to Novo Nordisk the SPC had been updated in July 2017 following Marso *et al*, a cardiovascular outcomes trial for Victoza in type 2 diabetes patients with high CV risk (LEADER). Section 5.1 of the SPC which included a section headed 'cardiovascular evaluation' with data from LEADER did not mention that the patients had high CV risk. An earlier part of Section 5.1, headed clinical efficacy and safety, referred to LEADER as a large cardiovascular outcomes trial in 9340 type 2 diabetes patients at high cardiovascular risk. The EMA assessment report referred to the need to include the patient population (Type 2 diabetes) in the indication. The improvement of glycaemic control and the reduction of cardiovascular morbidity and mortality were an integral part of treatment of type 2 diabetes, best expressed in a single indication. A separate cardiovascular prevention indication was not therefore appropriate.

It appeared to the Panel that the exhibition stand was a three dimensional advertisement with the woman and large building part being separated from the rest of the advertisement which framed the picture of the woman and the building. The top of the frame and the right hand side promoted Victoza. The Panel agreed that the message from the exhibition stand was in relation to CV risk. This was set within the context of the treatment of type 2 diabetes. Both parts of the exhibition stand referred to type 2 diabetes and the frame part of the exhibition stand included the indication and details from Section 5.1 of the SPC. The Panel noted that visitors to the stand would be attending the Diabetes UK Professional Congress.

The Panel did not consider that the exhibition stand was unambiguously clear as submitted by Novo Nordisk. However, the Panel considered that on balance, taken as a whole the exhibition stand was not inconsistent with the SPC as alleged and no breach was ruled. The stand overall was not misleading as alleged thus the Panel ruled no breach of the Code.

The Alliance alleged that the claim 'Change the course of treatment by reducing CV risk' promoted Victoza's additional CV benefits as the primary

reason to prescribe. This call to action was misleading and inconsistent with the SPC as it put undue emphasis on CV benefits observed in a clinical trial.

The Alliance noted that the main imagery of the exhibition panel depicted a pavement, adjacent to which was a wall with the word 'HbA1CV'. A woman (presumably a type 2 diabetic) was walking down a shaded pavement, marked by HbA1c, about to turn a corner into the light part of the pavement marked CV. This suggested that Victoza's added benefits with respect to CV risk were at least equally important as the licensed indication, which was glycaemic control of HbA1c. Together with the above claim, the Alliance alleged that this was misleading and inconsistent with the SPC.

The Panel considered that the important factor was that the patient had type 2 diabetes. The outcome of the CV study would be of interest to those that treated type 2 diabetes. There was a change in the Victoza SPC and the company was fully entitled to draw attention to that change. The benefits shown in the LEADER trial were in relation to high cardiovascular risk patients. The Victoza SPC also referred to more general information which showed no increase in CV risk for liraglutide versus all comparators.

The Panel considered that the claim 'Change the course of treatment by reducing CV risk' in conjunction with 'HbA1CV' emphasised the CV risk reduction with Victoza. However the context and audience were important. The frame part of the stand referred to a qualifcation, 'In adults with type 2 diabetes and high CV risk...'. Given its ruling in point 1 above and taking all the circumstances into account the Panel did not consider that Novo Nordisk was promoting the additional CV benefits as the primary reason to prescribe Victoza as alleged. In the Panel's view the mention of the CV benefits was not misleading or inconsistent with the SPC as alleged. The Panel ruled no breach of the Code. The stand was not misleading in this regard and no breach was ruled.

The Alliance alleged that given the position taken by Novo Nordisk during inter-company dialogue, Novo Nordisk had failed to maintain high standards and reduced confidence in the industry, in breach of the Code. Novo Nordisk's promotional stand for Victoza at the Diabetes UK Professional Conference on 13 March 2018 demonstrated that it continued to promote Victoza in the manner complained about in inter-company dialogue.

The Panel noted the important role of inter-company dialogue. Novo Nordisk had withdrawn a leavepiece without prejudice. There were similarities between the leavepiece at issue in the inter-company dialogue and the exhibition stand, the subject of the complaint to the PMCPA. However, Novo Nordisk had not agreed with The Alliance's view that the leavepiece was in breach of the Code. It was disappointing that Novo Nordisk had not given The Alliance more details. Novo Nordisk's letter of 4 January stated that the company now considered the inter-company matter resolved. In the light of the content of the exhibition stand it appeared that The Alliance considered that the inter-company matter was not resolved. The Panel appreciated the frustration for companies when issues raised and considered resolved at inter-company level appeared again in a different format. The main difference with the photograph of the women turning the corner related to the claim 'In adults with type 2 diabetes' used in the leavepiece had been amended to 'In adults with insufficiently controlled type 2 diabetes; in the exhibition stand. The Panel considered that there were differences between the leavepiece and the exhibition stand. It did not accept that Novo Nordisk failed to maintain high standards as alleged and ruled no breach of the Code.

Boehringer Ingelheim Limited and Eli Lilly and Company Limited (the Alliance) complained about the promotion of Victoza (liraglutide) by Novo Nordisk. The material at issue was an exhibition panel (ref UK/VT/0308/0108) used by Novo Nordisk at the Diabetes UK Professional Congress, 14-16 March 2018. Victoza was a glucagon-like peptide-1 receptor agonist (GLP-1 RA) indicated for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise.

The Victoza summary of product characteristics (SPC) stated it could be used as monotherapy when metformin was considered inappropriate due to intolerance or contraindications and could be used in addition to other medicinal products for the treatment of diabetes. Section 4.1 of the SPC also stated that study results with respect to combinations, effects on glycaemic control and cardiovascular (CV) events and the populations studied could be found in Sections 4.4, 4.5 and 5.1 of the SPC.

Two thirds of the exhibition panel featured the photograph of a woman walking in the shade towards the viewer and about to turn left around the corner of a large building and into what appeared to be a sunnier aspect. Wrapping around the corner of the building was the text 'In adults with insufficiently controlled type 2 diabetes change the course of treatment by reducing CV [cardiovascular] risk'. This was followed by red text which was mostly about the same height as the woman and which read 'HbA1CV' such that 'CV' was in the foreground of the picture. The headline across the top of the picture read 'Victoza: the only GLP-1 RA superior in preventing CV events vs placebo'. To the right side of the picture, and in the remaining third of the panel were the following two paragraphs in bold font:

> 'Indication : Victoza is indicated for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise.
>
> Section 5.1: Both improvement of glycaemic control and reduction of CV morbidity and mortality are an integral part of the treatment of type 2 diabetes.'

Boehringer Ingelheim's Product Jardiance (empagliflozin) a selective inhibitor of sodium-

glucose co-transporter 2 (SGLT2) was promoted by The Alliance. Jardiance was indicated for the treatment of adults with insufficiently controlled type 2 diabetes melitis as an adjuct to diet and exercise. Section 4.1 of its SPC referred to, *inter alia*, cardiovascular events, and cross referred to other sections of the SPC. Section 5.1 of the Jardiance SPC referred to cardiovascular outcomes.

1 Overall balance of the stand

COMPLAINT

The Alliance noted that the two main claims on the stand read 'Change the course of treatment by reducing CV risk' and 'Victoza: the only GLP-1 RA superior in preventing CV events vs placebo'. The Alliance alleged that overall prominence of these claims, combined with the imagery, would lead observers to conclude that the promotional message of the stand was weighted heavily towards the reduction of CV risk. The Alliance noted that Victoza was not indicated for the reduction of CV risk but for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise. The CV benefits of Victoza were referred to only in Section 5 of the summary of product characteristics (SPC) and so they should be promoted as added benefits of Victoza rather than as the main indication. The Alliance alleged that the overall balance of the stand promoted Victoza inconsistently with the SPC and in breach of Clauses 3.2, 7.2 and 7.8.

RESPONSE

Novo Nordisk noted that Victoza was not indicated for the reduction of CV risk in isolation and it had not promoted it as such. The claims at issue highlighted the results of the LEADER (The liraglutide effect and action in diabetes evaluation of cardiovascular outcomes results) study, a cardiovascular outcomes trial for Victoza (Marso *et al* 2016). The claims were made in the context of the treatment of type 2 diabetes and the indication for Victoza.

The indication for Victoza was clearly stated in bold type on the right hand side of the exhibition panel. In addition, the statement 'in adults with type 2 diabetes and high CV risk when added to standard of care as demonstrated in the LEADER study' appeared below the headline claim 'Victoza: the only GLP-1 RA superior in preventing CV events vs placebo'. Any mention of 'reducing CV risk' did not suggest CV benefit as a main indication for Victoza, but rather as an inclusive part of the product attribute within the licensed indication for the treatment of adults with type 2 diabetes. This was unambiguously clear.

Novo Nordisk submitted that the Committee for Medicinal Products for Human Use (CHMP) recommended strengthening of the wording of the indication by deleting 'improvement of glycaemic control' from Section 4.1 of the Victoza SPC, as this restriction no longer adequately reflected the demonstrated effects of Victoza. This change in wording was recommended following the incorporation of the results from Marso *et al* in the Victoza European Public Assessment Report EPAR (copy provided).

The European Medicines Agency (EMA) considered that both improvement of glycaemic control and reduction of CV morbidity and mortality were integral to the treatment of type 2 diabetes, which could best be expressed in a single indication for Victoza. The changed wording in Section 4.1 of the Victoza SPC as well as the additional wording in Section 5.1, which further explained the role of glycaemia and CV risk in type 2 diabetes therapy, reflected the regulatory agency's view that a more holistic treatment approach was needed when treating type 2 diabetics.

Novo Nordisk submitted that based on the above, the claims used on the exhibition panel were not misleading or inconsistent with the Victoza SPC and hence there was no breach of Clauses 3.2, 7.2 and 7.8 of the Code.

PANEL RULING

The Panel noted that Clause 3.2 required that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC.

The Panel noted that Victoza had been available as a treatment for diabetes for a number of years. According to Novo Nordisk the SPC had been updated in July 2017 following Marso *et al* which was a cardiovascular outcomes trial for Victoza in type 2 diabetes patients with high CV risk. Section 5.1 of the SPC which included a section headed 'cardiovascular evaluation' with data from LEADER did not mention that the patients had high CV risk. An earlier part of Section 5.1, headed clinical efficacy and safety, referred to LEADER as a large cardiovascular outcomes trial in 9340 type 2 diabetes patients at high cardiovascular risk. The EMA assessment report referred to the need to include the patient population (Type 2 diabetes) in the indication. The improvement of glycaemic control and the reduction of cardiovascular morbidity and mortality were an integral part of treatment of type 2 diabetes, best expressed in a single indication. A separate cardiovascular prevention indication was not therefore appropriate.

The Panel considered the description of the exhibition stand and the photographs provided. It appeared to be a three dimensional advertisement with the woman and large building part being separated from the rest of the advertisement which framed the picture of the woman and the building. The frame part included on the left side an advertisement for Xltophy, (insulin degludec) the top of the frame and the right hand side promoted Victoza. The Panel agreed that the message from the exhibition stand was in relation to CV risk. This was set within the context of the treatment of type 2 diabetes. Both parts of the exhibition stand referred to type 2 diabetes and the frame part of the exhibition stand included the indication and details from Section 5.1 of the SPC. The Panel noted that visitors to the stand would be attending the Diabetes UK Professional Congress.

The Panel did not consider that the exhibition stand was unambiguously clear as submitted by Novo Nordisk. However, the Panel considered that on balance, taken as a whole the exhibition stand was not inconsistent with the SPC as alleged and no breach of Clause 3.2 was ruled. The stand overall was not misleading as alleged thus the Panel ruled no breach of Clauses 7.2 and 7.8 of the Code.

2 Claims and main imagery

COMPLAINT

The Alliance alleged that the claim 'Change the course of treatment by reducing CV risk' promoted Victoza's additional CV benefits as the primary reason to prescribe. This call to action was misleading and inconsistent with the SPC as it put undue emphasis on CV benefits observed in a clinical trial.

The Alliance noted that the main imagery of the exhibition panel depicted a pavement, adjacent to which was a wall with the word 'HbA1CV'. A woman (presumably a type 2 diabetic) was walking down a shaded pavement, marked by HbA1c, about to turn a corner into the light part of the pavement marked CV. This suggested that Victoza's added benefits with respect to CV risk were at least equally important as the licensed indication, which was glycaemic control of HbA1c. Together with the above claim, the Alliance alleged that this was misleading, inconsistent with the SPC and thus in breach of Clauses 3.2, 7.2 and 7.8.

RESPONSE

Novo Nordisk submitted that the claim 'Change the course of treatment by reducing CV risk' did not promote the CV benefits of Victoza as the primary reason to prescribe. It was within the context of treating type 2 diabetes in patients suitable for Victoza (in line with the indication). The claim encouraged health professionals to consider CV risk reduction as part of the treatment goal for patients with type 2 diabetes.

As explained at point 1 above, the licensed indication for Victoza was no longer glycaemic control of HbA1c, as stated by the Alliance, it was 'treatment of adults with insufficiently controlled type 2 diabetes mellitus...'. Therefore, it was entirely reasonable to encourage consideration of a more holistic approach to adult type 2 diabetes treatment. This was consistent with the National Institute for Health and Care Excellence (NICE) guidelines for treatment of adults with type 2 diabetes, the Scottish Intercollegiate Guidelines Network (SIGN) 154 guideline, as well as the Victoza SPC.

Novo Nordisk submitted that the promotional claims and imagery used on the exhibition panel were not misleading or inconsistent with the Victoza SPC and hence not in breach of Clauses 3.2, 7.2 or 7.8.

PANEL RULING

The Panel noted its ruling in point 1 above. The major inclusion criteria for the LEADER trial were type 2 diabetes patients aged 50 or more with at least one cardiovascular coexisting condition or aged 60 years or more with at least one cardiovascular risk factor.

The LEADER trial showed that Victoza was superior to placebo in preventing MACE (major adverse cardiovascular events (CV death, non fatal myocardial infarction or non-fatal stroke). It also significantly reduced the rist of expanded MACE (primary MACE, unstable angina pectoris leading to hospitalisation, coronary revasculation or hospitalisation due to heart failure).

The Panel considered that the important factor was that the patient had type 2 diabetes. The outcome of the CV study would be of interest to those that treated type 2 diabetes. There was a change in the Victoza SPC and the company was fully entitled to draw attention to that change. The benefits shown in the LEADER trial were in relation to high cardiovascular risk patients. The Victoza SPC also referred to more general information in that, a post hoc analysis of serious major adverse cardiovascular events (cardiovascular death, myocardial infarction, stroke) from intermediate and long term phase 2 and 3 trials showed no increase in CV risk for liraglutide versus all comparators.

The Panel considered that the claim 'Change the course of treatment by reducing CV risk' in conjunction with 'HbA1CV' emphasised the CV risk reduction with Victoza. However the context of the claims was important and needed to be considered as did the audience. The frame part of the stand referred to a qualifcation, 'In adults with type 2 diabetes and high CV risk...'. Given its ruling in point 1 above and taking all the circumstances into account the Panel did not consider that Novo Nordisk was promoting the additional CV benefits as the primary reason to prescribe Victoza as alleged. In the Panel's view the mention of the CV benefits was not misleading or inconsistent with the SPC as alleged. The Panel ruled no breach of Clause 3.2. The stand was not misleading in this regard and no breach of Clauses 7.2 and 7.8 were ruled.

3 Conduct of inter-company dialogue

COMPLAINT

The Alliance alleged that given the position taken by Novo Nordisk during inter-company dialogue, Novo Nordisk had failed to maintain high standards and reduced confidence in the industry, in breach of Clause 9.1.

The Alliance explained that it initiated inter-company dialogue with Novo Nordisk by letter on 27 November 2017, to complain about a Victoza leavepiece (ref UK/VT/0717/0463) (copy provided). The Alliance alleged that the leavepiece breached the Code in several ways and noted eight aspects of concern. The primary concern was that the overall promotional content, the headline claims and the imagery were inconsistent with Victoza's indication for use and the additional benefits of treatment as reflected in section 5 of the SPC. This put excessive promotional emphasis on the additional CV benefits

of the medicine and promoted these as the primary reason to prescribe.

Novo Nordisk replied on 11 December 2017 and stated that it believed the leavepiece complied with the Code and suggested an inter-company teleconference. The teleconference on 19 December 2017 resulted in no agreement or resolution on any aspect discussed. On 4 January 2018, Novo Nordisk wrote to the Alliance to state that it thought the leavepiece was compliant but that 'to avoid any misperceptions' it had decided to withdraw it and that when relevant, it would take the comments from the Alliance into consideration in respect of other assets and when drafting new materials.

The Alliance stated, however, that it was concerned that Novo Nordisk had other similar promotional materials in circulation and so on 10 January it asked Novo Nordisk to withdraw those materials. In reply on 22 January, Novo Nordisk stated that it had re-examined all materials and all complied with the Code; it added that 'no further withdrawal was needed,' and that it would take the Alliance's comments 'into consideration for future materials or activities for Victoza'. The Alliance sought clarity on 29 January and Novo Nordisk replied on 7 February that it 'did not confirm that there are no other materials in circulation to which some aspects identified in the leave piece may refer.'

The Alliance wrote on 15 February 2018 to notify Novo Nordisk that it did not 'consider this matter closed in relation to any other materials affected by the aspects we have raised' and that 'should the Alliance become aware of any further promotional materials affected by any of the aspects raised in the original withdrawn leave piece, we would refer the matter directly to the PMCPA.'

The Alliance alleged that Novo Nordisk's promotional stand for Victoza at the Diabetes UK Professional Conference on 13 March 2018 demonstrated that it continued to promote Victoza in the manner complained about in inter-company dialogue.

RESPONSE

Novo Nordisk stated that it took its responsibility to resolve any complaints through inter-company dialogue extremely seriously and it was disappointed that this matter was unable to be resolved with the Alliance directly. Novo Nordisk stated that it entered into inter-company dialogue with a willingness to discuss the concerns raised by the Alliance.

As a result of the discussions, Novo Nordisk withdrew the leavepiece at issue without prejudice and agreed to re-examine current promotional materials based on the discussions in the inter-company dialogue. As a result of this, the exhibition panel used at the Diabetes UK Professional Conference was created with even more explicit prominence of the licensed indication of Victoza. For the avoidance of doubt, Novo Nordisk stated that it made it clear that it did not confirm that there were no other materials in circulation to which some aspects identified in the leavepiece might refer (letter to the Alliance 7 February 2018). Novo Nordisk stated that it did not agree with the Alliance's concerns about the claims in the leavepiece and so it did not withdraw all materials as requested.

Novo Nordisk stated that it fully engaged in inter-company dialogue and was transparent about not adapting some claims and the imagery as it considered these complied with the Code. Novo Nordisk submitted that it had upheld high standards and hence was not in breach of Clause 9.1.

PANEL RULING

The Panel noted the important role of inter-company dialogue. Novo Nordisk had withdrawn the leavepiece without prejudice. The Panel noted that there were similarities between the leavepiece at issue in the inter-company dialogue and the exhibition stand the subject of points 1 and 2 above. However Novo Nordisk had not agreed with The Alliance's view that the leavepiece was in breach of the Code. It was disappointing that Novo Nordisk had not given The Alliance more details. Novo Nordisk's letter of 4 January stated that the company now considered the inter-company matter resolved. In the light of the content of the exhibition stand it appeared that The Alliance considered that the inter-company matter was not resolved. The Panel appreciated the frustration for companies when issues raised and considered resolved at inter-company level appeared again in a different format. The main difference with the photograph of the women turning the corner related to the claim 'In adults with type 2 diabetes' used in the leavepiece had been amended to 'In adults with insufficiently controlled type 2 diabetes; in the exhibition stand. The Panel considered that there were differences in the leavepiece and the exhibition stand. It did not accept that Novo Nordisk failed to maintain high standards as alleged and ruled no breach of Clause 9.1.

Complaint received **23 April 2018**

Case completed **28 August 2018**

ANONYMOUS CONTACTABLE HEALTH PROFESSIONAL v CONCORDIA

Promotion of Morphgesic SR

An anonymous contactable 'concerned UK health professional' complained about a journal advertisement for Morphgesic SR 10mg tablets (modified release morphine sulphate) placed by Concordia International Rx (UK) and published in Pulse, April 2018.

The complainant alleged that the prescribing information on the advertisement was from May 2013 which seemed unusually old. In an update in 2014 there was additional information on medicines and driving warnings and in 2015 most of the summary of product characteristics (SPC) was updated as were corresponding sections of the patient information leaflet. The complainant alleged that the disparity between the prescribing information in the advertisement and what was currently known, could put patients at risk.

The detailed response from Concordia appears below.

The Panel noted that the Code required prescribing information to include the date that the prescribing information was drawn up or last revised. The prescribing information in the advertisement in question gave the date of preparation as May 2013 and the date of revision as December 2017. The date of preparation for the advertisement as a whole was given as February 2018. The Panel noted, as stated by Concordia that the complainant was incorrect when stating that the prescribing information dated from May 2013. That was not so. May 2013 was when the prescribing information was originally created. The Panel noted Concordia's submission that the advertisement contained the latest certified prescribing information which was in accordance with the current SPC and ruled no breaches of the Code including Clause 2.

An anonymous 'concerned UK health professional' complained about a journal advertisement (ref Con/MOR/PM/0021) for Morphgesic SR 10mg tablets (modified release morphine sulphate) placed by Concordia International Rx (UK) Limited and published in Pulse, April 2018. Morphgesic was indicated for the prolonged relief of severe pain in adults.

COMPLAINT

The complainant alleged that the prescribing information on the advertisement was from May 2013 which seemed unusually old. In an update in 2014 there was additional information on medicines and driving warnings and in 2015 most of the summary of product characteristics (SPC) was updated. The complainant stated that sections 1, 3, 4.1-4.9, 5.1-5.3, and 6.1-6.6 were updated together with corresponding sections of the patient information leaflet. The complainant alleged that the disparity between the prescribing information in the advertisement and what was currently known, could put patients at risk.

When writing to Concordia, the Authority asked it to consider the requirements of Clauses 2, 4.1 and 9.1.

RESPONSE

Concordia submitted that the prescribing information was last updated in December 2017 and was in line with the latest Morphgesic SR 10mg tablets SPC, which was last updated in May 2015. The prescribing information was accurate and was in line with the Code; the 'Date of revision' was correctly stated as December 2017'. Concordia assumed that the complainant must have read the line above which stated 'Date of Preparation: May 2013'. The stated 'Date of Preparation' was when the prescribing information was first created and the 'Date of revision' was the last time the prescribing information was revised which was in accordance with latest SPC. Concordia denied a breach of Clause 4.1.

Concordia submitted that high standards has been maintained as the advertisement in question included the date of revision within the prescribing information, as required by the Code. The company denied a breach of Clause 9.1.

Given that the advertisement included the latest certified prescribing information with a date of revision of December 2017 Concordia did not consider that patient safety was compromised. The company denied a breach of Clause 2.

PANEL RULING

The Panel noted that Clause 4.2 (viii) required prescribing information to include the date that the prescribing information was drawn up or last revised. The Panel noted that the prescribing information in the advertisement in question gave the date of preparation as May 2013 and the date of revision as December 2017. The date of preparation for the advertisement as a whole was given as February 2018. The Panel noted, as stated by Concordia that the complainant was incorrect when stating that the prescribing information dated from May 2013. That was not so. May 2013 was

when the prescribing information was originally created. The Panel noted Concordia's submission that the advertisement contained the latest certified prescribing information which was in accordance with the current SPC and ruled no breach of Clauses 4.1, 9.1 and 2.

Complaint received **25 April 2018**

Case completed **12 July 2018**

CASE AUTH/3037/4/18

ANONYMOUS CONTACTABLE HEALTH PROFESSIONAL v SHIELD

Promotion of Feraccru and unlicensed medicines to the public

An anonymous complainant who described themselves as a 'concerned UK health professional' complained about information on Shield Therapeutics' website. The information in question related to Feraccru (ferric maltol), which was used to treat iron deficiency, and three pipeline products, PT20, PT30 and PT40.

The complainant noted that Shield's website had no separate areas for different groups of people such as prescribers and the public.

Under the heading 'lead products' there was a section for Feraccru and the three pipeline product candidates. The information on Feraccru was clearly promotional, yet the page in question had not been screened from the public and it had no link to prescribing information for health professionals. The complainant stated that the information about the pipeline products promoted them to the public and additionally promoted such medicines before they had been reviewed by the regulatory authorities. In light of the above, the complainant queried whether the material has been adequately reviewed by Shield before it made it available on the Internet.

The detailed response from Shield is given below.

The Panel noted that the website had not been certified and therefore ruled a breach of the Code.

The page for Feraccru positioned Feraccru favourably compared to other iron therapies. The site could be accessed by the public and was promotional, therefore the Panel ruled a breach of the Code.

The failure to include the Feraccru prescribing information or a clear, prominent statement as to where it could be found was ruled in breach of the Code.

The Panel noted that unless access to promotional material about prescription only medicines was limited to health professionals and other relevant decision makers, a pharmaceutical company website or a company sponsored website must provide information for the public as well as promotion to health professionals with the sections for each target audience clearly separated and the intended audience identified. This was to avoid the public needing to access material for health professionals unless they chose to. The Panel noted its comments and rulings above. The website contained promotional material which was not directed towards health professionals and other relevant decision makers as set out in the relevant supplementary information and a breach was ruled.

The Panel ruled a further breach as Shield had failed to maintain high standards. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

The Panel noted its comments above and Shield's submission that although the website was intended to be non-promotional it had become promotional. The Panel noted that the pipeline product candidate pages gave more than a brief summation of the pipeline. The section on PT20 described PT20 as novel and a more efficient phosphate binder compared to iron oxide, that it had generally good tolerability across the dose range and its absorption of phosphate in dialysis-dependent CKD patients was favourably compared with the limitations of current therapies including in relation to GI side effects and significant toxicity. The Panel considered that the section on PT20 was promotional.

The Panel noted Shield's submission that PT20 was a phosphate binder that had completed a Phase II clinical study. It was not licensed and therefore, *de facto*, could not be a prescription only medicine. The Code prohibited the promotion of prescription only medicines to the public. The Panel noted that the product was not currently classified as a prescription only medicine. On this narrow technical point, the Panel ruled no breach of the Code.

The Panel considered that the section on PT20, PT30 and PT40 was promotional and would generate interest in and elicit questions about unlicensed medicines. The Panel noted Shield's submission that both PT30 and PT40 were in early clinical development. The Panel ruled that the website promoted unlicensed medicines in breach of the Code.

The Panel noted that the supplementary information to Clause 2 included promotion prior to the grant of a marketing authorization as an example of an activity that was likely to be in breach of that Clause. The Panel considered that Shield had thus brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

An anonymous complainant who described themselves as a 'concerned UK health professional' complained about information on the website for Shield Therapeutics (www.shieldtherapeutics.com). The information in question related to Feraccru (ferric maltol), which was used to treat iron deficiency, and three pipeline products, PT20, PT30 and PT40.

COMPLAINT

The complainant noted that Shield's website was for a company registered in the UK with two UK offices and apparently no offices in other Anglophone countries. The website had no separate areas for different groups of people such as prescribers and the public.

Under the heading 'lead products' there was a section for Feraccru and pipeline product candidates namely PT20, PT30 and PT40. The information on Feraccru was clearly promotional, yet the page in question had not been screened from the public and it had no link to prescribing information for health professionals.

The information on each of PT20, PT30 and PT40 contained details that appeared to promote the benefits of the products – eg that the product had been designed to be hypoallergenic, potentially overcoming one of the most significant drawbacks of current intravenous iron therapies. The complainant stated that as above, this information promoted the products to the public and additionally promoted such medicines before they had been sufficiently reviewed by the regulatory authorities.

In light of the above, the complainant queried whether the material has been adequately reviewed by Shield before it made it available on the Internet.

When writing to Shield, the Authority asked it to consider the requirements of Clauses 2, 3.1, 4.1, 4.6, 9.1, 14.3, 26.1 and 28.1.

RESPONSE

Shield submitted that the website at issue was intended for investors and members of the public. As such, it was non-promotional with factual and balanced information only in compliance with Clause 26 and it did not require certification under Clause 14, although company procedures required that all such materials were reviewed by the senior leadership team before being posted on the site. As the website was non-promotional, it did not require separate pages for health professionals and patients nor links to the prescribing information as defined in Clauses 4.1 and 4.6, however it clearly provided links to the European Public Assessment Report (EPAR), the summary of product characteristics (SPC) and the patient information leaflet (PIL).

Shield stated that when notified of the complaint, it reviewed the specific pages relating to Feraccru and the pipeline product candidates (PT20, PT30 and PT40) that were live on the website on the date of the complaint.

With regard to the pipeline products, Shield explained that PT20 was a phosphate binder that had completed a Phase II clinical study. It was not licensed and therefore, *de facto*, could not be a prescription only medicine. The paragraph discussed the chemical properties of PT20, the outcome of the Phase II study in general terms and the goal for further development. It made no specific promotional claim, nor did it encourage members of the public to ask their health professionals to prescribe a specific prescription only medicine. Therefore, it did not breach Clauses 26.1, 26.2 or 3.1.

The short paragraph for PT30 and PT40 covered the development goals for the products and discussed some of the challenges of current medicines. Both PT30 and PT40 were in early clinical development. The statements were not promotional and therefore did not breach Clauses 26.1, 26.3 or 3.1. Shield submitted that as these areas were not promotional, Clause 14.3 did not apply and given there were no breaches of Clauses 26.1, 26.2, 3.1 or 14.3, there could be no breach of Clause 2.

Shield submitted that as the website at issue was intended to be non-promotional, it had developed a separate promotional site for Feraccru (www.feraccru.com); this site provided greater information and was appropriately separated into areas for health professionals and those designed for the public. The company was therefore shocked and deeply concerned that the website at issue contained what could be considered promotional claims for Feraccru. Investigation revealed that a contractor had changed the website without following company procedures and had added information to the corporate site. These changes were not seen by the senior team and would not have been sanctioned had they been reviewed. In view of the changes made, it was clear that the site became promotional and so additional requirements of the Code applied. As a promotional site, it followed that there were breaches of Clauses 28.1, 26.1, and 14.3. In view of this, the company accepted that there might be a perception that Shield has failed to maintain high standards in breach of Clause 9.1. Although there were clear links to the Feraccru EPAR, SPC and PIL on the site, these did not carry all the information required in the prescribing information under Clause 4, and as such, there were also breaches of Clauses 4.1 and 4.6.

In view of the findings Shield ensured that the corporate website was amended immediately and stated that the contractor no longer worked at the company. Policies had also been enhanced so that all content of the corporate site must be certified in the same manner as the promotional site to avoid issues in future.

While Shield was extremely disappointed that this error had occurred, it was confident that it had identified and addressed the cause and strengthened its processes to avoid it happening in the future. Given the availability of the EPAR, SPC and PIL on the site, patient safety was not compromised and the company considered that this was a genuine error that did not merit particular censure as indicated by a breach of Clause 2.

PANEL RULING

The Panel disagreed with Sheild's submission that the website at issue was intended for investors and members of the public and as such, it was non-promotional and did not require certification under Clause 14. Clause 14.3 required that educational material for the public or patients issued by companies which relates to diseases or medicines but is not intended as promotion for those medicines must be certified in advance in a manner similar to that provided for by Clause 14.1. The Panel noted that the website had not been certified and therefore ruled a breach of Clause 14.3.

The Panel noted Shield's submission that a contractor had changed the website at issue without following company procedures and had added information to the corporate site which meant that the site became promotional and so additional requirements of the Code applied. The relevant page for Feraccru compared its tolerability, patient outcomes and compliance with salt-based oral iron therapies. It also compared Feraccru to iv iron therapies and stated that iv iron therapies quickly increased iron stores via direct administration of very large doses of iron, causing an increase in Hb levels that was physiologically controlled and occurred over a period of weeks, as was the case with Feraccru. It stated that IV iron therapies, however, were invasive, costly, inconvenient and complex to administer, and also came with potentially life-threatening, spontaneous hypersensitivity reactions. It was clearly promotional and positioned Feraccru favourably compared to other iron therapies. The site could be accessed by the public and was promotional, therefore the Panel ruled a breach of Clause 26.1.

The Panel noted that the website did not include the Feraccru prescribing information or a clear, prominent statement as to where it could be found and breaches of Clauses 4.1 and 4.6 were ruled.

The Panel noted that the supplementary information to Clause 28.1 stated that unless access to promotional material about prescription only medicines was limited to health professionals and other relevant decision makers, a pharmaceutical company website or a company sponsored website must provide information for the public as well as promotion to health professionals with the sections for each target audience clearly separated and the intended audience identified. This was to avoid the public needing to access material for health professionals unless they chose to. The Panel noted its comments and rulings above. The website contained promotional material which was not directed towards health professionals and other relevant decision makers as set out in the relevant supplementary information to Clause 28.1 and a breach of Clause 28.1 was ruled.

The Panel considered that Shield had failed to maintain high standards 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 and reserved for such use.

The Panel noted its comments above and Shield's submission that although the website was intended to be non-promotional it had become promotional. The Panel noted that the pipeline product candidate pages gave more than a brief summation of the pipeline. The section on PT20 described PT20 as novel and a more efficient phosphate binder compared to iron oxide, that it had generally good tolerability across the dose range and its absorption of phosphate in dialysis-dependent CKD patients was favourably compared with the limitations of current therapies including in relation to GI side effects and significant toxicity. The Panel considered that the section on PT20 was promotional.

The Panel noted Shield's submission that PT20 was a phosphate binder that had completed a Phase II clinical study. It was not licensed and therefore, *de facto*, could not be a prescription only medicine. Clause 26.1 prohibited the promotion of prescription only medicines to the public. The Panel noted that the product was not currently classified as a prescription only medicine. On this narrow technical point, the Panel ruled no breach of Clause 26.1 of the Code.

The Panel noted that Clause 3.1 which required that a medicine must not be promoted prior to the grant of the marketing authorization which permits its sale or supply. The Panel noted that Shield considered the site to be promotional. PT30 was described as a novel IV iron formulation that was designed to be hypoallergenic, potentially overcoming one of the most significant drawbacks of current IV iron therapies. It stated that PT40 was designed to be the first generic version of IV iron sucrose, which would significantly lower the cost of IV iron sucrose. The Panel considered that the section on PT20, PT30 and PT40 was promotional and would generate interest in and elicit questions about unlicensed medicines. The Panel noted Shield's submission that both PT30 and PT40 were in early clinical development. The Panel considered that the website at issue promoted unlicensed medicines and a breach of Clause 3.1 was ruled.

The Panel noted that the supplementary information to Clause 2 included promotion prior to the grant of a marketing authorization as an example of an activity that was likely to be in breach of that Clause. The Panel considered that Shield had thus brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

Complaint received **26 April 2018**

Case completed **24 August 2018**

CASE AUTH/3039/5/18

TILLOTTS v DR FALK

Promotion of Budenofalk

Tillotts Pharma UK complained about a Budenofalk (budesonide) advertisement used by Dr Falk Pharma UK. Budenofalk was available as 3mg gastro-resistant capsules, 9mg gastro-resistant granules and a 2mg/dose foam enema.

Budenofalk capsules was indicated for the induction of remission of mild to moderate active Crohn's disease in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon, the induction of remission of active collagenous colitis and for the treatment of autoimmune hepatitis whilst Budenofalk granules was indicated for the induction of remission of mild to moderate active Crohn's disease in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon and the induction of remission of active collagenous colitis. Budenofalk foam was only indicated for the treatment of active ulcerative colitis that was limited to the rectum and the sigmoid colon.

Tillotts was concerned that the pharmaceutical form was not clearly stated on the advertisement given that Budenofalk was the root name for three separate products. The advertisement was headed by three indications: autoimmune hepatitis, Crohn's disease and collagenous colitis however only Budenofalk 3mg capsules was licensed for all three indications. Tillotts alleged that the advertisement was thus misleading. The ambiguity surrounding which product was being advertised might also represent a further breach, as the specific marketing authorisation being advertised was not clear. The advertisement implied that all forms of Budenofalk were indicated for all three conditions.

Tillotts further noted the ambiguity in the first of three bullet points which stated 'The only budesonide with three indications'. Given that the specific preparation was not clearly identified, the claim was inaccurate as neither the granule nor the foam formulation had three indications (they had two and one indication, respectively). In addition, the claim should specify that it referred to an orally administered budesonide, as certain inhaled budesonides offer three indications, such as Rhinocort Aqua nasal spray.

Tillotts noted that the prescribing information referred to Budenofalk granules and capsules and stated in the indication section that autoimmune hepatitis related to the capsules only. The prescribing information was the only place on the page where the product names were mentioned and Tillotts alleged that this needed to be stated more prominently in the body of the advertisement. The reader should not be relied upon to read the prescribing information to understand the subject of the advertisement.

The detailed response from Dr Falk appears below.

The Panel noted that the top half of the advertisement bore photographs of 3 separate woman and the claim 'Getting on with their lives By getting on with their steroid'. Above each woman was a description of her condition: autoimmune hepatitis, Crohn's disease and collagenous colitis respectively. A bold red strip beneath the photographs read, on the right, 'Budenofalk' above in smaller font 'Budesonide, the Dr Falk way'. To the left appeared three bullet point claims, the first of which read 'The only budesonide with three indications'. The prescribing information appeared beneath.

The Panel noted the prominent reference to 'Budenofalk' and that there were three relevant products which had Budenofalk as the root name. Only one product, Budenofalk 3mg capsules was indicated for all three conditions. In the Panel's view the failure to clearly identify the product in the body of the advertisement either implied that all three Budenofalk products were each licensed for all three conditions and that was not so, or was otherwise unclear which Budenofalk product was so licensed. The advertisement was misleading in this regard. The Panel also considered that Dr Falk had failed to maintain high standards. Breaches of the Code were ruled.

In the Panel's view the claim 'the only budesonide with three indications' in isolation was inaccurate, however, the context in which it appeared was relevant. The Panel noted that the claim in question appeared in relatively small font on the left-hand side of a red box, to the right of which appeared the prominent brand name Budenofalk followed by Budesonide, the Dr Falk way beneath. In the Panel's view, the relevant qualification, namely that the budesonide product in question was a Budenofalk product, appeared prominently and within the immediate visual field of the claim in question. In addition, it was clear that the three indications referred to were autoimmune hepatitis, Crohn's disease and collagenous colitis as stated at the top of the advertisement. On balance, the Panel considered that the claim in question 'The only budesonide with three indications' was sufficiently qualified such that, within the context of the advertisement, it was not misleading as alleged and thus ruled no breaches of the Code.

Tillotts Pharma UK Limited complained about a Budenofalk (budesonide) advertisement (ref DrF17/159) used by Dr Falk Pharma UK Ltd. Budenofalk was available as 3mg gastro-resistant capsules, 9mg gastro-resistant granules and a 2mg/dose foam enema.

Budenofalk capsules was indicated for the induction of remission of mild to moderate active Crohn's disease in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon, the induction of remission of active collagenous colitis and for the treatment of autoimmune hepatitis whilst Budenofalk granules was indicated for the induction of remission of mild to moderate active Crohn's disease in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon and the induction of remission of active collagenous colitis. Budenofalk foam was only indicated for the treatment of active ulcerative colitis that was limited to the rectum and the sigmoid colon.

COMPLAINT

Tillotts was concerned that the pharmaceutical form was not clearly stated on the advertisement given that Budenofalk was the root name for three separate products ie Budenofalk 3mg capsules, Budenofalk 9mg granules and Budenofalk foam enema all of which contained budesonide. The advertisement was headed by three indications: autoimmune hepatitis, Crohn's disease and collagenous colitis however only Budenofalk 3mg capsules were licensed for all three indications. Tillotts alleged that the advertisement was thus misleading, and in breach of the Code. The ambiguity surrounding which product was being advertised might also represent a further breach, as the specific marketing authorisation being advertised was not clear. The advertisement implied that all forms of Budenofalk were indicated for all three conditions.

Tillotts further noted the ambiguity in the first of three bullet points which stated 'The only budesonide with three indications'. Given that the specific preparation was not clearly identified, the claim was inaccurate as neither the granule nor the foam formulation had three indications (they had two and one indication, respectively). In addition, the claim should specify that it referred to an orally administered budesonide, as certain inhaled budesonides offer three indications, such as Rhinocort Aqua nasal spray.

Tillotts noted that the prescribing information referred to Budenofalk granules and capsules and stated in the indication section that autoimmune hepatitis indicated related to the capsules only. The prescribing information was the only place on the page where the product names were mentioned and Tillotts considered that this needed to be stated more prominently in the body of the advertisement. The reader should not be relied upon to read the prescribing information to understand the subject of the advertisement.

Tillotts alleged that the advertisement was misleading, in breach of Clause 7.2. The matter also appeared to be a failure to uphold high standards by Dr Falk and in breach of Clause 9.1.

RESPONSE

Dr Falk submitted that the complaint was not succinct and did not allege more than one breach of the Code. The complaint appeared to be concerned with the fact that there were three licensed indications stated at the top of the advertisement along with the statement 'The only budesonide with three indications', without listing specific formulations within the Budenofalk range.

Budenofalk 3mg capsules were licensed for the three indications listed. The statement 'The only budesonide with three indications' was a fact. It was also a fact that this budesonide was in the Budenofalk range. Budenofalk, budesonide, was clearly stated in the advertisement. The advertisement was very brief and there was no suggestion in it that other formulations might or might not have these indications as the prescribing information clearly showed the indications and it was a general expectation and practice that readers consulted the prescribing information and/or the summary of product characteristics (SPC) and/or referenced works such as the British National Formulary (BNF) and MIMS. Indeed, the Code itself expected the reader to 'form their own opinion of the therapeutic value of the medicine'.

Dr Falk noted that the complainant also suggested inaccuracy because a product in a different therapeutic area, Rhinocort Aqua nasal spray, was indicated for seasonal and perennial allergic rhinitis, vasomotor rhinitis and nasal polyps. Dr Falk thus agreed that there was a budesonide product in a different therapeutic area with three indications but did not consider that it was relevant because health professionals dealing with autoimmune hepatitis, Crohn's disease and collagenous colitis, diseases of the lower gastrointestinal tract, were not likely to confuse Budenofalk with a treatment for nasal conditions, even in the unlikely event that they worked in both therapeutic areas. In addition, the advertisement was only placed in specialist publications targeted at gastroenterologists, such as Frontline Gastroenterology, Colorectal Disease, Journal of Crohn's and Colitis and IBD News.

Dr Falk did not consider that any health professional would be misled by the advertisement in question nor find it ambiguous. Dr Falk stated that in its view, the complainant had not proven that the advertisement breached Clause 7.2.

Finally, Dr Falk noted that the complainant had not explained how the advertisement failed to uphold high standards. Dr Falk maintained that the advertisement met the high standards required, particularly when considered in the light of the supplementary information to Clause 9.1.

PANEL RULING

The Panel noted that the top half of the advertisement bore photographs of 3 separate woman and the claim 'Getting on with their lives By getting on with their steroid'. Above each woman appeared a description of her condition: autoimmune hepatitis, Crohn's disease and collagenous colitis respectively. A bold red strip beneath the photographs read, on the right, 'Budenofalk' above in smaller font 'Budesonide, the Dr Falk way'. To the left appeared three bullet point claims, the first

of which read 'The only budesonide with three indications'. The prescribing information appeared beneath.

The Panel noted Tillotts' submission that Budenofalk was the root name given to three separate products. The Panel noted that according to their respective SPCs Budenofalk 9mg granules were indicated for induction of remission in mild to moderate active Crohn's disease of the ileum and/or ascending colon and induction of remission in patients with active collagenous colitis; Budenofalk 2mg rectal foam for the treatment of active rectum and colon ulcerative colitis; and Budenofalk 3mg capsules for induction of remission in patients with mild to moderate active Crohn's disease of the ileum and ascending colon, induction of remission in patients with active collagenous colitis and for autoimmune hepatitis.

The Panel noted the prominent reference to 'Budenofalk' and that there were three relevant products which had Budenofalk as the root name. Only one product, Budenofalk 3mg capsules was indicated for all three conditions. In the Panel's view the failure to clearly identify the product in the body of the advertisement either implied that all three Budenofalk products were each licensed for all three conditions and that was not so, or was otherwise unclear which Budenofalk product was so licensed. The advertisement was misleading in this regard. In the Panel's view, that the prescribing information made it clear that only the capsules were indicated for autoimmune hepatitis did not alter the otherwise misleading implication of the advertisement. The main body of the advertisement had to be capable of standing alone with regard to the requirements of the Code and, on this point, could not be qualified by the use of footnotes or by reference to the content of prescribing information. In addition, the Panel noted that the prescribing information referred to Budenofalk granules under presentation and only referred to the capsule formulation in brackets beside the autoimmune hepatitis indication. A breach of Clause 7.2 was ruled. The Panel considered that Dr Falk had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted Dr Falk's submission that although there was a budesonide product in a different therapeutic area with three rhinitis indications, it was not relevant because health professionals dealing with diseases of the lower gastrointestinal tract were not likely to confuse Budenofalk with a treatment for nasal conditions. The Panel noted that Tillott's allegation was not about health professionals confusing Budenofalk with the treatment of nasal conditions; Tillotts alleged that by not referring to orally administered budesonide, the claim 'the only budesonide with three indications' was inaccurate as certain inhaled budesonides such as Rhinocort Aqua nasal spray offered three indications. In the Panel's view the claim 'the only budesonide with three indications' in isolation was inaccurate, however, the context in which it appeared was relevant. The Panel noted that the claim in question appeared in relatively small font on the left-hand side of a red box, to the right of which appeared the prominent brand name Budenofalk followed by Budesonide, the Dr Falk way beneath. In the Panel's view, the relevant qualification, namely that the budesonide product in question was a Budenofalk product, appeared prominently and within the immediate visual field of the claim in question. In addition, it was clear that the three indications referred to were autoimmune hepatitis, Crohn's disease and collagenous colitis as stated at the top of the advertisement. On balance, the Panel considered that the claim in question 'The only budesonide with three indications' was sufficiently qualified such that, within the context of the advertisement, it was not misleading as alleged and thus ruled no breach of Clause 7.2 and subsequently no breach of Clause 9.1 was ruled.

During its consideration of this case the Panel noted that Budenofalk 3mg capsules and 9mg granules were both indicated for the induction of remission of mild to moderate active Crohn's disease in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon and Budenofalk foam was indicated for the treatment of active ulcerative colitis that was limited to the rectum and the sigmoid colon. The Panel noted that the advertisement simply listed Crohn's disease as one of the indications of Budenofalk thereby implying that they were indicated for all presentations of Crohn's disease and that was not so. The Panel queried whether this was in line with the requirements of Clause 3.2 which stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics.

The Panel also noted its comments above about the content of the prescribing information and considered it would be advisable for Dr Falk to review its prescribing information to ensure that it was accurate and complied with the Code.

The Panel requested that Dr Falk be advised of its concerns.

Complaint received **11 May 2018**

Case completed **13 July 2018**

CASE AUTH/3047/6/18

ANONYMOUS CONTACTABLE HEALTH PROFESSIONAL V A MENARINI

Promotion of Migard

An anonymous contactable complainant who described themselves as a 'concerned UK health professional' complained about an advertisement for Migard (frovatriptan) on the BMJ website.

The complainant noted that instead of prescribing information, there was a link to an out-of-date summary of product characteristics (SPC).

The detailed response from A Menarini is given below.

The Panel noted A Menarini's submission that the material at issue was placed on the BMJ website by global colleagues without any knowledge, review or approval from the UK.

The Panel noted that it was an established principle under the Code that UK companies were responsible for acts and omissions of their overseas affiliates that came within the scope of the Code. The Panel considered that the Migard advertisement published in the BMJ came within the scope of the Code and A Menarini UK was thus responsible for it.

The Panel noted that prescribing information was required to be included in promotional material. The summary of product characteristics might be provided in certain situations providing that the legal classification and cost of the medicine were also provided. Although the SPC had been provided, the legal classification and cost of the medicine had not been. The Panel ruled a breach of the Code. As the material did not include the prescribing information or the link to it as required a further breach was ruled.

The Panel noted that the SPC that was linked to the advertisement appeared to be for frovatriptan 2.5mg and was dated November 2014. The current Migard SPC was dated April 2017. The Panel noted its comments and rulings above and considered that it appeared that A Menarini had been badly let down by its global affiliate. An old version of the SPC had been used in the advertisement. High standards had not been maintained and a breach of the Code was ruled.

The Panel noted that there did not appear to be any major differences between the two SPCs. Neither the complainant nor A Menarini had made any comments in this regard. The Panel did not consider that this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

An anonymous complainant who described themselves as a 'concerned UK health professional' complained about an advertisement for Migard (frovatriptan) which appeared on the BMJ website. Migard was marketed by A Menarini and indicated for the acute treatment of the headache phase of migraine in adults.

COMPLAINT

The complainant noted that instead of prescribing information, there was only a link from the website to an out-of-date summary of product characteristics (SPC).

When writing to A Menarini, the Authority asked it to consider the requirements of Clauses 2, 4.1, 4.2, 4.4 and 9.1 of the Code.

RESPONSE

A Menarini explained that the Migard material at issue was generated, approved and placed on the BMJ website by global colleagues around January 2016, without any knowledge, review or approval from the UK. A Menarini believed that the material was intended for health professionals and because of the BMJ placement, this was likely to include UK health professionals.

A Menarini was aware of its responsibilities under the Code in relation to the review and approval of materials created by global when materials might be accessed by UK health professionals, patients or members of the public. However, on this occasion, the UK had no knowledge of the material and it was not included in the review and approval process.

A Menarini believed that the Migard material was accessible to UK health professionals. Migard was available in the UK at the time, although not actively promoted. During the review process, one member of the global team commented that 'Since the Brand Migard is also available in UK, please see my comments into the material related to the UK compliance', however, this direction was not followed.

A Menarini noted the difference between the SPC provided with the material at issue and the current UK SPC; copies of both were provided. A Menarini was not aware of the circumstances that seem to have led to the Migard material SPC being out-of-date, as alleged.

A Menarini had informed its global colleagues about the matter who were looking into it and making the necessary arrangements to remove the Migard material from the BMJ website.

A Menarini noted that it might not be appropriate for it to provide responses on behalf of global whilst its review on this matter was still ongoing. However, it provided the available information and comments in relation to the clauses from the UK perspective.

A Menarini explained that as the material at issue was intended for health professionals, global considered it appropriate to add the Migard SPC, sourced from the corporate regulatory department, instead of the prescribing information as required by the Code. The SPC was linked to all the webpages of the material by a single click link highlighted as a 'SmPC' box. However, A Menarini submitted that the material fell within the scope of the Code and should have met all of its relevant requirements. Therefore, A Menarini acknowledged that it had breached Clauses 4.1, 4.2 and 4.4.

A Menarini considered that its global colleagues should have included the UK in the review and approval process. The material fell within the scope of the Code and should have met all of its relevant requirements. A Menarini accepted a breach of Clauses 2 and 9.1.

PANEL RULING

The Panel noted A Menarini's submission that the material at issue was generated, approved and placed on the BMJ website by global colleagues without any knowledge, review or approval from the UK. A Menarini believed that the material was intended for health professionals and because of the BMJ placement, was likely to include UK health professionals.

The Panel noted that it was an established principle under the Code that UK companies were responsible for acts and omissions of their overseas affiliates that came within the scope of the Code. The Panel considered that the Migard advertisement published in the BMJ came within the scope of the Code and A Menarini UK was thus responsible for it.
The Panel noted that material published on the BMJ included a picture of a woman with her hands on her head, the brand name (Migard) and generic name (frovatriptan) appeared on one side of the picture and the A Menarini group logo on the other. The footer stated that migraine was a chronic disorder occurring in both genders, although large surveys showed higher prevalence of this condition in women and went on to give the ratio of men to women and some information on the factors that might play a role in the pathogenesis of migraine. Below this was the statement 'Discover how a single treatment can prove useful for the many kinds of migraine patients' followed by 4 different photographs of patients titled Migraine, migraine with aura, menstrual migraine and weekend migraine with buttons on each to click for more information. At the bottom of the page was a link to the SPC and an adverse event reporting statement. In the Panel's view it was clearly an advertisement for Migard.

The Panel noted that Clause 4.1 required prescribing information to be included in promotional material. Clause 4.2 listed the elements of the prescribing information and stated that the summary of product characteristics might be provided instead of information listed under sections i-viii of Clause 4.2 providing that the legal classification and cost of the medicine were also provided. Although the SPC had been provided in this case, the legal classification and cost of the medicine had not been. The Panel noted that Clause 4.2 listed the content of prescribing information which was required by Clause 4.1 to be provided with all promotional material. Failure to satisfy Clause 4.2 was therefore a breach of Clause 4.1. The Panel noted that the advertisement for Migard did not include the prescribing information as listed in Clause 4.2 and a breach of Clause 4.1 was ruled.

Clause 4.4 required that in the case of digital material such as advertisements in electronic journals, emails, electronic detail aids and suchlike, the prescribing information as required by Clause 4.1 might be provided either by inclusion in the digital material itself, or by way of a clear and prominent direct single click link. Although the advertisement included a link to the SPC, the material did not include the prescribing information or the link to it as required by Clause 4.1 and a breach of Clause 4.4 was ruled.

The Panel noted that the SPC linked to the advertisement in question as provided by A Menarini appeared to be for frovatriptan 2.5mg and was dated November 2014. The current Migard SPC provided by A Menarini was dated April 2017. Both SPCs listed Menarini International Operations Luxembourg S.A as the marketing authorisation holder and PL16239/0017 as the marketing authorisation number. The Panel noted its comments and rulings above and considered that it appeared that A Menarini had been badly let down by its global affiliate. Irrespective of the failure to comply with Clause 4.1 an old version of the SPC had been used in the advertisement. High standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that there did not appear to be any major differences between the two SPCs. Neither the complainant nor A Menarini had made any comments in this regard. The Panel did not consider that this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

Complaint received **8 June 2018**

Case completed **3 September 2018**

CASE AUTH/3049/6/18

ANONYMOUS, NON CONTACTABLE v BRISTOL-MYERS SQUIBB

Colour of inverted triangle

An anonymous, non-contactable complainant complained about the incorrect colour of the inverted triangle used by Bristol-Myers Squibb Pharmaceuticals on its 'Current products' website page. The complainant stated that the website had been recently certified with the date of preparation listed as May 2018 and the inverted triangle had been used 6 times and none with the correct black colour.

The detailed response from Bristol-Myers Squibb is given below.

The Panel noted that Bristol-Myers Squibb had immediately removed the webpage when it was informed of the complaint as four triangles on the webpage were dark navy and a further two were dark grey.

The Panel noted Bristol-Myers Squibb's submission that the website in question was a publicly visible, non-promotional, UK corporate website. The Panel considered that the complainant had not established that the website was promotional and required the black inverted triangle symbol thus no breach of the Code was ruled.

The Panel noted that contrary to Bristol-Myers Squibb's view, it was not only promotional material that required the inclusion of a black triangle. The Panel noted that in addition, the inverted black triangle symbol needed to be included on material which related to a medicine which was subject to additional monitoring and which was intended for a patient taking that medicine.

The webpage in question included the medicine name and links to the electronic Medicines Compendium to enable the visitor to view the relevant summary of product characteristics (SPC) or patient information leaflet (PIL). In the Panel's view, the inverted black triangle was a well-known and established symbol. Its appropriate use was an important part of medicines regulation. Thus, in the Panel's view failure to publish the triangle in the correct colour was, at the very least, inappropriate and might potentially cause confusion. This was a serious matter. The Panel ruled that high standards had not been maintained in breach of the Code.

An anonymous, non-contactable complainant complained about the colour of the inverted triangle used by Bristol-Myers Squibb Pharmaceuticals Limited on its 'Current products' website page (URL https://www.bms.com/gb/our-medicines.html).

COMPLAINT

The complainant stated that the website (ref MLTUK1701479-04) had been recently certified with the date of preparation listed as May 2018. The complainant alleged that Bristol-Myers Squibb's UK website displayed the inverted triangle in incorrect colours for the relevant medicines. The triangle appeared in a shade of navy blue four times and in grey twice on the 'Current products' website page. Thus, the inverted triangle had been used 6 times on the webpage and none with the correct black colour.

The complainant submitted that the company should have maintained better oversight of the content of the website through the approval process and that high standards had not been maintained.

The complainant stated that the appropriate use of the black triangle was an important part of medicines regulation. Thus, the failure to publish the triangle in the correct colour on the website, at the very least was inappropriate and might potentially cause confusion.

When writing to Bristol-Myers Squibb, the Authority asked it to consider the requirements of Clauses 4.10 and 9.1.

RESPONSE

Bristol-Myers Squibb stated that the website in question was a publicly visible, non-promotional, UK corporate website, intended and approved for a UK audience only.

As identified by the complainant, the website included a page which listed Bristol-Myers Squibb's UK current marketed products. The page was certified as a non-promotional item on 3 May 2018 and the entire corporate website went live on 15 May. A copy of the approval certificate was provided.

Bristol-Myers Squibb noted that Clause 4.10 stated that, when required by the licensing authority, all promotional material must show an inverted black equilateral triangle to denote that additional monitoring was required in relation to adverse events. It was decided to include the black triangle symbol on the webpage at issue on the relevant products in the spirit of transparency, to indicate the monitoring requirements of those products even though there was no requirement under the Code to do so. The page included the medicine name and links to the electronic Medicines Compendium to

enable the visitor to view the relevant summary of product characteristics (SPC) or patient information leaflet (PIL).

The complainant correctly highlighted that four triangles on the page were dark navy and a further two were dark grey, which appeared next to statements explaining what the symbol indicated. Bristol-Myers Squibb was grateful to the complainant for noting this. Bristol-Myers Squibb noted that on 11 June 2018 when it was informed of the compliant, it immediately removed the page at issue from the corporate website.

Bristol-Myers Squibb acknowledged that the triangles should be black and this was an oversight on its part. However, it denied a breach of Clause 4.10 which specifically related to promotional material. The page referred to by the complainant was not promotional in nature or intent and therefore the colour of the triangles was not subject to that specific clause requirement, which remained an important distinction.

Bristol-Myers Squibb stated that it was fully committed to compliance with the Code and denied any breach of Clause 9.1. The proposed corporate website page was checked and certified as a non promotional item. The working website was also checked for appearance and functionality before being published. The triangles were a very dark navy and dark grey in colour. On some screens, depending on screen and software, the triangles appeared black. They also appeared black on screen to those involved in checking it. However, Bristol-Myers Squibb accepted that it was a mistake on its part that they were not black.

Bristol-Myers Squibb reiterated that on first being notified about the issue, it pulled the page from the website. The company did not therefore believe that it had failed to maintain high standards in that respect.

PANEL RULING

The Panel noted that Clause 4.10 stated that when required by the licensing authority, all promotional material must show an inverted black equilateral triangle to denote that additional monitoring was required in relation to adverse reactions. The Panel noted that Bristol-Myers Squibb had immediately removed the webpage at issue from the corporate website when it was informed of the complaint as the complainant had correctly highlighted that four triangles on the webpage were dark navy and a further two were dark grey.

The Panel noted Bristol-Myers Squibb's submission that the website in question was a publicly visible, non-promotional, UK corporate website. The Panel noted that Clause 4.10 only required a black triangle to be included on promotional material and considered that the complainant had not established that the website was promotional and thus no breach of Clause 4.10 of the Code was ruled.

The Panel noted Bristol-Myers Squibb's submission that it had decided to include the black triangle symbol on the webpage at issue on the relevant products' section in the spirit of transparency, to indicate the monitoring requirements of those products even though it considered that there was no requirement under the Code to do so. That was not so. The Panel noted that contrary to Bristol-Myers Squibb's view, it was not only promotional material that required the inclusion of a black triangle. The Panel noted that in addition, Clause 26.3 required the inverted black triangle symbol to be included on material which related to a medicine which was subject to additional monitoring and which was intended for a patient taking that medicine. The Panel noted that Clause 26.3 had not been raised by the case preparation manager and thus considered the matter in relation to Clause 9.1 of the Code.

The webpage in question included the medicine name and links to the electronic Medicines Compendium to enable the visitor to view the relevant summary of product characteristics (SPC) or patient information leaflet (PIL). In the Panel's view, the inverted black triangle was a well-known and established symbol. Its appropriate use was an important part of medicines regulation. Thus, in the Panel's view failure to publish the triangle in the correct colour was, at the very least, inappropriate and might potentially cause confusion. This was a serious matter. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

Complaint received **8 June 2018**

Case completed **15 August 2018**

CODE OF PRACTICE REVIEW – November 2018

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

AUTH/2984/10/17	**Health professional v Astellas UK**	**Provision of funding linked to use of Advagraf and a failure to provide comprehensive accurate information**	**Breaches Clauses 2, 9.1 and 18.5**	**Appeal by complainant** **Report from the Panel to the Appeal Board** **Report from the Appeal Board to the ABPI Board**	**Page 3**
AUTH/2987/10/17	**Anonymous, contactable v Shire**	**Alleged promotion prior to the grant of a marketing authorisation**	**Three breaches Clause 9.1 Breach Clause 12.2**	**Appeal by respondent**	**Page 35**
AUTH/2997/12/17	**Anonymous, contactable health professional v AbbVie**	**Promotion of Synagis**	**Breaches Clauses 9.1 and 14.1**	**No appeal**	**Page 53**
AUTH/3017/2/18	**Anonymous, contactable v Celgene**	**Certification and approval of material for meetings**	**Three breaches Clause 9.1.** **Two breaches Clause 14.1** **Breach Clause 15.9**	**No appeal**	**Page 58**
AUTH/3033/4/18	Boehringer Ingelheim and Lilly v Novo Nordisk	Promotion of Victoza	No breach	No appeal	Page 63
AUTH/3036/4/18	Anonymous, contactable health professional v Concordia	Advertisement for Morphgesic SR	No breach	No appeal	Page 68
AUTH/3037/4/18	**Anonymous, contactable health professional v Shield**	**Promotion of Feraccru and unlicensed medicines to the public**	**Breaches Clauses 2, 3.1, 4.1, 4.6, 9.1, 14.3, 26.1 and 28.1**	**No appeal**	**Page 70**
AUTH/3039/5/18	**Tillotts v Dr Falk**	**Promotion of Budenofalk**	**Breaches Clauses 7.2 and 9.1**	**No appeal**	**Page 73**
AUTH/3047/6/18	**Anonymous, contactable health professional v A Menarini**	**Promotion of Migard**	**Breaches Clauses 4.1, 4.4 and 9.1**	**No appeal**	**Page 76**
AUTH/3049/6/18	**Anonymous non-contactable v Bristol-Myers Squibb**	**Colour of inverted triangle**	**Breach Clause 9.1**	**No appeal**	**Page 78**

PMCPA | Prescription Medicines Code of Practice Authority

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

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

It covers:

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

It also covers:

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

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

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

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

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

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

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

CODE OF PRACTICE REVIEW

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