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 The complainant also stated that funding, or part thereof, was withdrawn when the outcome was not as expected.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**