CASE AUTH/2883/10/16

VOLUNTARY ADMISSION BY ASTELLAS UK

Patient support programmes

Astellas UK voluntarily admitted breaches of the Code with regard to patient support programmes and the conduct of a third party agency. The patient support programmes, Fresh Start and VIP related to Betmiga (mirabegron) and Vesicare (solifenacin succinate) respectively. Both medicines were for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as might occur in patients with overactive bladder syndrome.

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

Astellas explained that on 22 September 2016 a member of staff searched Google for the Betmiga patient support programme (Fresh Start), and found patient support materials for Vesicare and Betmiga clearly displayed on the website of one of Astellas's agencies. The Betmiga material was certified on 3 April 2014, first used on 12 May 2014 and withdrawn on 4 April 2016. The Vesicare material was certified on 28 September 2015. The certified method of dissemination for the material incorrectly identified health professionals including via representatives.

Astellas understood that in displaying the material (without Astellas's permission), the agency's intention was to market its abilities, driven by a new creative director who was not trained on the Code. Astellas immediately asked the agency to remove the material which it did. The webpage went live on 15 April 2016 and was taken down on 22 September 2016.

Astellas discovered that the agency had also used imagery from another Astellas programme which was closed on 22 May 2016 (Remind Me). This imagery was displayed from 15 April 2016 until 22 September 2016. This identified Astellas medicines within the transplantation area and included product brand names and a claim.

Astellas considered that the use of the brand names and therapeutic indications on the agency website went beyond any requirement to market creative capabilities and constituted promotion of prescription only medicines to the public, in breach of the Code. In addition, given the seriousness of this, Astellas UK understood that the Panel might wish to consider the requirements of other clauses including Clause 2.

The detailed response from Astellas UK appears below.

The Panel noted that an Astellas employee had found patient support materials for Betmiga and Vesicare on the agency's website after he/she had specifically searched the internet for the Betmiga patient support programme (Fresh Start). Having discovered the Betmiga and the Vesicare materials on the agency website, Astellas then found material from the Remind Me programme which supported patients taking Prograf (tacrolimus) or Advagraf (tacrolimus SR) for the prophylaxis of transplant rejection. None of the material had been posted on the agency's website with Astellas's knowledge or permission.

The Panel noted that the material shown on the website for Betmiga and Vesicare consisted of the front page of two patient support booklets aimed at those taking one or the other medicines. From the text below, which detailed the client, the brief and the solution, it was clear that both medicines were for the treatment of overactive bladder. The material shown for the Remind Me programme was the nurse guide.

On balance, despite medicines and their indication appearing on an open access website, the Panel did not consider that medicines had been promoted to the public; the website was not aimed at the public *per se*. The company had not failed to maintain high standards. No breaches of the Code were ruled including Clause 2.

Astellas noted that until the events described above, it had run the two patient support programmes; VIP, for all patients prescribed Vesicare and Fresh Start, for those prescribed Betmiga. The third party agency was engaged to develop material and to run the support programmes via its team of nurses who manned a patient support line. Both patient support programmes had now been terminated due to Astellas's concern in relation to its lack of oversight and support as detailed below.

When the programmes started in 2006 (VIP) and 2013 (Fresh Start) the nurses on the patient support line were trained face-to-face by Astellas on the relevant summaries of product characteristics (SPCs) as well as on adverse event reporting. In addition, nurses were given a 'script' to aid their discussions with patients. Although the adverse event training was repeated once a year via an Astellas pharmacovigilance training slide deck, there was no record of any further training on Vesicare or Betmiga despite the SPCs having changed a number of times in intervening years. Although Astellas had not provided revised SPCs to the third party agency, it had confirmed that if nurses needed to refer to an SPC it would always be viewed online via the electronic medicines compendium (eMC) website to provide the latest information.

Although Astellas had monitored the number of patients enrolled into each patient support programme monthly and had continued to pay the agency the monthly fixed fee, it had not provided similar ongoing oversight and support for the nurse helpline in relation to product training. Whilst Astellas recognised that these programmes should have had ongoing consistent oversight, they had been managed by a series of colleagues without appropriate handover or training.

Astellas considered that, given that the nurses interacted directly with patients, this was a failure to maintain high standards. Astellas also understood that the Panel might wish to consider the requirements of Clause 2 in relation to the lack of oversight and supervision.

Astellas submitted that because of errors in setting up job bags in Zinc, some materials from both programmes had gone past the two year period without being re-certified. All of the VIP material including that withdrawn in March 2014 had been reviewed and Astellas considered that the content was still appropriate for use; however, the job bags had been very poorly set up including incorrect audience, poor information on objectives and having been initiated as a promotional item. With regard to Fresh Start, materials were identified in April 2016 that still described Betmiga as 'new' having been previously re-certified in April 2014. The word 'new' should have been removed from this material by February 2014. Other items had been withdrawn in error but remained active. In addition Astellas was concerned that the frequently asked questions section of the nurses' script (certified on 21 July 2015) no longer accurately reflected all adverse events listed in the current SPC (nausea was omitted). In addition, the Betmiga SPC was updated in April 2016 and the nurses' script was not revised to reflect the addition of a number of common side effects (constipation, diarrhoea, headache and dizziness). Astellas thus considered that the nurses' script was inaccurate and did not reflect the available evidence in relation to side effects. In addition, this amounted to a failure to maintain high standards and had the potential to impact on patient safety, which would be contrary to the requirements of Clause 2.

Astellas submitted that the errors noted above with regard to the use of Zinc may have been due to human error and that human error was attributable to the omission in the Fresh Start nurses script.

Astellas considered that, given that the materials at issue were distributed to patients, this amounted to a failure to maintain high standards. Astellas understood that the Panel might wish to consider the requirements of Clause 2 in relation to this lack of oversight and supervision.

In addition, Astellas found out in August 2016 that the third party agency had been sending a survey to patients after 3 months on either programme. This patient feedback information was previously provided to Astellas and outcomes from the questionnaire used in a promotional piece of material in 2009. The agency was instructed to discontinue this activity immediately.

The Panel noted that Astellas's oversight of the agency nurses who delivered the two patient support programmes was extremely poor. Although when both programmes first started, the nurses who were to man the helplines were trained on the relevant medicine (Betmiga or Vesicare), they received no further product specific training despite the fact that the SPCs for both products had since changed a number of times; some of those changes related to changes to Section 4.8, Undesirable effects. Further the telephone scripts which they had initially been given had not been revised; the script for the VIP helpline was dated October 2012. The script for the Fresh Start programme was dated March 2013 and did not reflect the addition to the Betmiga SPC of a number of common side effects (constipation, diarrhoea, headache and dizziness). Both scripts were thus inaccurate and out-of-date and the Panel ruled breaches of the Code. The Fresh Start script did not accurately reflect up-to-date information on possible side effects and in that regard the Panel ruled a breach of the Code. The Panel noted Astellas's submission that if nurses were asked questions about Betmiga or Vesicare that needed reference to the SPC, they would access the eMC website for the latest version. The nurses received annual training on adverse event reporting. It was unclear whether this had been updated annually. It was also unclear why training on other matters outlined above had not been provided. Overall the Panel considered that such inadequate training of those who were expected to interact directly with patients was wholly unacceptable. High standards had not been maintained in breach of the Code. The Panel further considered that the failure to properly train the nurses and keep them updated with product changes was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. It was crucial that out of all of the options available, patients could rely completely upon the industry for up-to-date and accurate information about their medicines. A breach of Clause 2 was ruled.

In addition Astellas's oversight of the patient support materials was very poor. In that regard the Panel noted Astellas's submission that materials had been set up wrongly in Zinc such that although they were withdrawn in Zinc, mostly in 2014, they continued to be used by the agency beyond two years without being re-certified. The Panel ruled a breach of the Code.

Betmiga material which described the medicine as 'new' for more than one year was ruled in breach including that high standards had not been maintained.

The Panel noted Astellas's submission that not all the patient materials were certified in a hard copy final form before use and those that were, were signed by a brand manager and not a nominated signatory. Further, the Panel noted that the patient satisfaction surveys had not been certified at all. Breaches of the Code were ruled including that high

standards had not been maintained. No breach was ruled in relation to certification of promotional materials.

The Panel noted the number of materials which had not been correctly processed for certification. In that regard the Panel considered that Astellas's lack of control of material was such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

During its investigation into the issues noted above, Astellas found out that the nurses manning the patient support lines still also worked for the NHS. This was not previously known, and Astellas considered that this additional information meant that the agency fitted the definition of an institution, organisation or association of health professionals and transfers of value in relation to services provided on behalf of a company were required to be disclosed. This disclosure had not taken place for transfers of value made in 2015. Additionally, payments made to pharmacies in relation to enrolment of patients onto the Fresh Start programme had not been disclosed. The company stated it was addressing this and would upload the relevant data to the ABPI central platform as soon as possible.

The Panel noted that the nurses who manned the patient helplines had been supplied by the agency. Astellas did not know how much of the fee it had paid the agency had gone either to the nurses as a group or to each individual nurse. At the start of the patient support programmes, Astellas had known who the nurses were through face-to-face training for the VIP programme (2006) and the Fresh Start programme (2013).

The Panel noted that the Code required companies to declare transfers of value made directly or indirectly to health professionals and healthcare organisations located in Europe. The definition of healthcare organization included 'an organization through which one or more health professional or other relevant decision makers provide services'. In that regard, the Panel considered that although creative agencies would not normally be considered healthcare organisations, in this case the nurses on the patient helplines had provided their services through the agency. In that regard the Panel considered that Astellas must declare the amount paid to the agency for the nurses on the ABPI central platform. If the company became aware of the individual identity of the nurses then the amount paid should be declared for each individual. It was unacceptable that the contract with the agency did not appear to be such that the company could identify the amount(s) paid. The Panel further noted that monies paid to pharmacies in relation to the enrolment of patients into the Fresh Start programme had not been declared. Breaches of the Code were ruled.

The Panel was extremely concerned about is rulings and comments above. Some of the matters raised went to the heart of self-regulation and patient safety. The company's oversight of the patient support programmes at issue had been lamentable.

Notwithstanding the fact that Astellas UK was currently suspended from membership of the ABPI and already undergoing a series of audits of its procedures under the Code, the Panel decided, in accordance with Paragraph 8.2 of the Constitution and Procedure, to report the company to the Appeal Board for it to consider whether further sanctions were appropriate in this case.

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

The Appeal Board noted that this case had arisen from a voluntary admission by Astellas UK and the company had accepted all breaches of the Code including Clause 2. The Appeal Board also noted that Astellas UK had made a sincere apology for its failings in this case.

The Appeal Board considered that this case raised serious concerns about multiple failings and a complete lack of control in Astellas UK's review and certification process which was entirely unacceptable.

The Appeal Board was very concerned to note that Astellas UK had little or no knowledge about the qualifications of the nurses employed by its agency or of what they did or said to patients. Astellas should have had far greater oversight including feedback and audit of the nurses' interactions with patients. It was an appalling failure in particular that the nurses were not trained or updated on changes to the relevant SPCs. It was essential that patients could rely completely upon the industry for up-to-date and accurate information about medicines. The Appeal Board considered that the deplorable failure of process and oversight in this case raised serious concerns with regard to patient safety and public confidence in the pharmaceutical industry.

The Appeal Board noted that as a consequence of Case AUTH/2780/7/15 Astellas UK was currently suspended from membership of the ABPI. Astellas UK and Astellas Pharma Europe had each been audited twice (December 2015 and September 2016) and each would be audited again in April 2017.

The Appeal Board was minded to report Astellas UK to the ABPI Board but given the exceptional circumstances, including that the re-audits in Case AUTH/2780/7/15 were due to be carried out very shortly, it decided that the issues that had arisen in this case should be looked at as part of the upcoming re-audit of Astellas UK, including examination of patient support programmes and certification of material. On consideration of the report of the re-audits the Appeal Board would reserve its decision on whether to report Astellas UK to the ABPI Board.

The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Astellas UK should be publicly reprimanded for a lamentable lack of concern for patient safety and wholly unsatisfactory oversight and control of the patient support programmes and of the nurses employed to deliver them.

Astellas UK and Astellas Europe were re-audited in April 2017 and the report was considered by the Appeal Board in May 2017.

The Appeal Board noted that Astellas UK and Astellas Europe were now working more closely and there was more open communication with staff. Both companies had been working to implement the recommendations of the previous audits and to ensure compliance was embedded. However, the Appeal Board noted the number of issues highlighted in the report and that there was still much work to be done.

The Appeal Board accepted that it took a long time to change culture but it was not convinced that progress was being made at an appropriate speed particularly given the issues that had come to light in Cases AUTH/2883/10/16, AUTH/2939/2/17 and AUTH/2940/2/17. This was particularly worrying given the level of scrutiny the companies were under. In the view of the Appeal Board, Astellas had much work still to do.

In relation to Case AUTH/2883/10/16 the Appeal Board decided that Astellas UK should be re-audited in October 2017 at the same time as the re-audit required in Case AUTH/2780/7/15 and the audit required in Cases AUTH/2939/2/17 and AUTH/2940/2/17 in relation to both Astellas UK and Astellas Europe.

In relation to Case AUTH/2883/10/16 the Appeal Board noted that it had reserved its position in relation to additional sanctions in this case until it had seen the report of the April 2017 re-audits. Bearing in mind that the case related to patient safety and a lack of control and oversight, the Appeal Board decided that in accordance with Paragraph 12.1 of the Constitution and Procedure, Astellas UK should be reported to the ABPI Board.

The Appeal Board noted the outcome of the audit in Case AUTH/2883/10/16, and the re-audits in Case AUTH/2780/7/15, the decisions to report Astellas UK to the ABPI Board in Cases AUTH/2883/10/16, AUTH/2939/2/17 and AUTH/2940/2/17 in relation to both Astellas UK and Astellas Europe. It also noted its concerns regarding the lamentable lack of concern for patient safety and wholly inadequate oversight and control. Whilst noting this was a matter for the ABPI Board, the Appeal Board's view was that Astellas UK was not ready to resume membership of the ABPI and the suspension should continue.

The ABPI Board noted the rulings of breaches of the Code, the decisions of the Appeal Board regarding audit, re-audit and the public reprimand.

The ABPI Board agreed with the Appeal Board's comments and concerns about the re-audits in April 2017.

The ABPI Board noted and endorsed the Appeal Board's views about the total failure of the companies' systems in relation to the control of prescribing information, the lamentable lack of concern for patient safety, wholly inadequate oversight and control and initial lack of urgency. It was a woeful state of affairs.

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

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

The ABPI Board also decided that it wanted sight of the report of the October 2017 re-audits of Astellas UK and Astellas Europe so that it could review the position before the end of 2017. If the report of the re-audits did not show significant improvement and progress at both companies, then the ABPI Board would consider expelling Astellas UK from membership of the ABPI. The companies should consider undergoing an external assessment of progress, particularly in relation to risk management of compliance in the broadest sense, ie including matters beyond the scope of the Code, with the outcome to be available at the time of the October 2017 re-audits.

The ABPI Board also decided that the MHRA should be advised of the ABPI Board's very serious concerns about the conduct of Astellas UK and Astellas Europe particularly in relation to the matters concerning patient safety. EFPIA should also be updated and asked to ensure the EFPIA Board was informed of the position.

Astellas UK and Astellas Europe were re-audited in October 2017 and the report of the re-audit was considered in November. The Appeal Board noted that as these were the fourth audits of the companies and given that Astellas UK was currently suspended from membership of the ABPI, it expected substantial progress and improvements from both companies. This expectation had not been met. The Appeal Board acknowledged that some progress had been made. The companies must take prompt action to implement the findings and recommendations in the report of the October 2017 re-audits.

The Appeal Board accepted that it took time to change a company's culture. In this regard, the Appeal Board noted that there had been positive changes in the company culture. However, it was not convinced that the expected progress was being made, especially since the April 2017 re-audits.

Overall, the Appeal Board's view was that the rate of progress was inadequate and that the companies were not where they should be. There was still

much work to do. The Appeal Board queried whether there was an element of structural inertia or perhaps fear of wrongdoing which was inhibiting or slowing the rate of progress.

Despite its criticisms, the Appeal Board noted the positive steps taken by the leadership of Astellas to engage more broadly with staff and drive changes.

The Appeal Board decided that both companies should be re-audited in April 2018. At which point it expected the 2018 global staff survey to demonstrate improvements at Astellas Europe and Astellas UK.

Whilst noting that this was entirely a matter for the ABPI Board, the Appeal Board's view was that if the report of the October 2017 re-audits and Astellas' response had come at the end of the two year suspension limit, then Astellas would have fallen well short of the standard required to resume membership of the ABPI. Unless substantial progress was seen in the report of the re-audits in April 2018, in the Appeal Board's view, Astellas UK would be at serious risk of a recommendation that it be expelled from membership of the ABPI.

The ABPI Board noted the Appeal Board's comments and concerns about the re-audits in October 2017 and the additional information provided by Astellas.

With regard to the external assessment of progress, particularly in relation to risk management of compliance in the broadest sense ie including matters beyond the scope of the Code, the ABPI Board noted the information provided by Astellas.

Following a change in tone from the top of Astellas, the ABPI Board recognised that meaningful progress had been made by the companies. The ABPI Board understood the difficulty inherent in making wide-sweeping cultural changes, and how long it took for those changes to become fully embedded within a large organisation. However, the ABPI Board acknowledged Astellas' clear commitment to further improvement.

The ABPI Board noted Astellas' statement that its materials were compliant in May 2017 in relation to issues of patient safety.

The ABPI Board also decided that it wanted sight of the report of the April 2018 re-audits of Astellas UK and Astellas Europe so that it could review the position before the end of the current suspension in June 2018.

The ABPI Board decided that taking all the circumstances into account it would take no further action at this stage in relation to the expulsion of Astellas from membership of the ABPI. The suspension from membership of the ABPI would remain in place until June 2018.

The ABPI Board also decided that the MHRA should be advised of the position. EFPIA should also be updated and asked to ensure that the EFPIA Board was informed of the position.

Astellas UK and Astellas Europe were re-audited in April 2018 and the report of the re-audits was considered in May 2018.

The Appeal Board noted the detailed responses from Astellas to the report of the April 2018 re-audits including that it was an accurate reflection of the work undertaken.

The Appeal Board noted the results of the 2018 staff survey and the progress made. Numerical increases had been shown in a number of parameters since the previous survey in July 2017. There were concerns about the comments made by staff. The Appeal Board also noted the differences in the Astellas UK results which were generally better than the Astellas Europe results. The Appeal Board considered that the Astellas Europe management committee scores although improved were still not where they should be.

The Appeal Board noted the comments in the report of the April 2018 re-audits and considered that both the leadership of Astellas Europe and Astellas UK had engaged with staff to bring about progress. There was still work to be done. The Appeal Board noted one of the recommendations was that members of the leadership team at Astellas Europe should be held to account and be challenged on compliance matters.

The Appeal Board accepted that it took time to change a company's culture. In this regard, the Appeal Board noted that there had been further positive changes in the company culture and this needed to be continued. The Appeal Board noted that there had been some positive compliance initiatives. The discussion fora and communications continued and progress had been made including ensuring staff had time to complete training.

The Appeal Board noted that whilst as a percentage there had been a significant increase in the number of job bags, the overall number was still low. As Astellas increased its activities it must remain extremely vigilant to compliance requirements in particular in relation to certain higher risk activities such as patient support programmes, product launches etc. The true test of the compliance framework in Astellas and its approach would be when activity levels including higher risk activities were increased and the company was operating at business as usual.

The Appeal Board considered that, at long last, the re-audits in April 2018 showed that progress had been made and that the companies were building on momentum started in summer 2017. The Appeal Board was concerned that these were the fifth audits of each company and that the first audits were in December 2015. It was extraordinary that it had taken so long to demonstrate meaningful change. The overall impression from the report of the April 2018 re-audits was that Astellas was showing improvement and momentum. However, whilst the companies had reached a certain level, given all the circumstances including that Astellas UK had been suspended from membership of the

ABPI and that the Appeal Board still had concerns, the Appeal Board decided that Astellas Europe and Astellas UK should each be re-audited at the end of the first quarter of 2019 to ensure that the improvements and the momentum continued and were built upon.

On the information before it, and noting that Astellas UK was still to respond to the PMCPA in relation to matters raised following completion of the consideration of a complaint concerning Astellas UK, Case AUTH/2984/10/17, the Appeal Board decided 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 when the matter came before the ABPI Board on 5 June 2018.

In June 2018 the ABPI Board noted the comments from both the Appeal Board and Astellas.

The ABPI Board noted the limited information provided about matters raised in Case AUTH/2984/10/17. This was still to be considered by the PMCPA and the Appeal Board and was not before the ABPI Board for consideration.

The view of the Appeal Board was clear. The ABPI Board agreed with the Appeal Board's views and assessment of the re-audits and concluded that meaningful progress had now been made.

The ABPI Board believed that the culture in the companies had improved and noted that much of this had been led by the General Manager of Astellas UK. However, the Board recognised the importance of an ongoing commitment to ensure sustained culture change. On reviewing all the material, the ABPI Board had concerns about the sustainability of the changes made given that there had already been five audits/re-audits, and especially as further types of activity were still to be fully re-introduced across the companies.

The ABPI Board therefore decided that it wanted to see the report of the 2019 re-audits and be informed of major developments including the outcome of Case AUTH/2984/10/17.

In the circumstances, there was no need for the ABPI Board to consider expelling Astellas UK from membership of the ABPI. The suspension would end on 24 June 2018 and Astellas would revert to full membership of the ABPI.

The ABPI Board also decided that the MHRA should be advised of the position and that EFPIA should be updated and asked to ensure that the EFPIA Board was informed of the position.

Astellas UK and Astellas Europe were re-audited in April 2019 and the report of the re-audits was considered in May 2019.

The Appeal Board noted the detailed response from Astellas Europe and Astellas UK to the report of the April 2019 re-audits.

The Appeal Board noted two new senior appointments; a new President EMEA Operations who joined Astellas in July 2018 and a new General Manager, Astellas UK who was appointed from April 2019.

The Appeal Board noted from the report of the April 2019 re-audits that it appeared that a more compliant culture was embedded within Astellas with improved communication. It was essential that this was maintained.

The Appeal Board considered that Astellas UK must ensure a proper professional approach to investigating and responding to any complaint under the Code such that the shortcomings in Case AUTH/2984/10/17 were not repeated. The Appeal Board noted that an audit had not been required in Case AUTH/2984/10/17. The case had, in accordance with established practice, been discussed as part of an examination of the company's culture at the re-audits.

The Appeal Board noted that these were the sixth audits/re-audits of each company and that the first audits were in December 2015. The Appeal Board considered that, on the information provided in the report of the April 2019 re-audits, it appeared that the companies had made further improvements, that this would be maintained and broadly the companies were where they should be. The Appeal Board, however, remained very concerned about the amount of time it had taken Astellas to reach this point. The Appeal Board noted that Astellas stated that it would follow up on the issues identified in the report of the April 2019 re-audits and it was committed to maintaining its approach to embedding a sustainable compliance culture. The Appeal Board noted a number of activities/actions were due to be undertaken. On the understanding that this work was completed, that the progress shown to date was continued and a company-wide commitment to compliance was maintained, the Appeal Board decided that, on the basis of the information in the report of April 2019 re-audits, no further action was required in relation to Case AUTH/2780/7/15, Case AUTH/2883/10/16, Cases AUTH/2939/2/17 and AUTH/2940/2/17.

The Appeal Board noted that the audit/re-audits in these four cases had been required by the Appeal Board. They had not been required by the ABPI Board. Nonetheless, the Appeal Board noted the ABPI Board's request to see the report of the April 2019 re-audits.

At the re-audits in April 2019 it was noted that the MHRA decided that Astellas advertising materials should be submitted for review. This was introduced for all new materials issued since 1 December 2018.

In June 2019 the ABPI Board received an update as requested. It noted the comments from both the Appeal Board and Astellas and the improvements made.

Astellas UK voluntarily admitted breaches of the Code with regard to patient support programmes and the conduct of a third party agency. The patient

support programmes, Fresh Start and VIP related to Betmiga (mirabegron) and Vesicare (solifenacin succinate) respectively. Both medicines were for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as might occur in patients with overactive bladder syndrome.

In addition to the clauses cited by Astellas, the Authority also asked the company to consider the requirements of Clauses 14.1 and 14.3 and noted that the materials might be covered by previous versions of the Code.

1 Actions of an Astellas's agency

VOLUNTARY ADMISSION

Astellas UK explained that on 22 September 2016 a member of its medical team searched for the URL for the Betmiga patient support programme (Fresh Start), and found a page on the website of one of Astellas's third party agencies which clearly displayed a number of patient support materials for Vesicare and Betmiga. The Betmiga material, developed by the agency and certified by Astellas on 3 April 2014, was first used on 12 May 2014 and withdrawn on 4 April 2016; the agency was notified of such by email. The Vesicare material was certified on 28 September 2015. The materials were for patients prescribed either Betmiga or Vesicare respectively; the certified method of dissemination for the material incorrectly identified health professionals including via representatives, but the material was used as part of the patient support programmes managed by the agency. There was never a discussion with, or direction provided to, the agency that the material would be distributed in any other way.

Astellas understood that the agency's intention in publishing the material on its website was to market its abilities and was driven by a new creative director who was not trained on the Code. Astellas had not been aware of this previously; the agency had not asked the company if it could use its materials in this way. Astellas immediately asked the agency to remove the material which it did on the same day.

Astellas stated that the webpage went live on 15 April 2016 and was taken down on 22 September 2016; during the 27 weeks that it was available with unrestricted access, 116 visits were recorded. The agency did not solely work within the pharmaceutical industry and therefore it was likely that individuals from other industries, who Astellas UK considered members of the public, had accessed the site during that time.

Astellas's investigation also revealed that the agency had used imagery from another Astellas programme which was closed on 22 May 2016 (Remind Me). This imagery was displayed from 15 April 2016 until 22 September 2016 and was visited 121 times. This identified Astellas medicines within the transplantation area and included product brand names and a claim.

Although the PMCPA recognised in Cases AUTH/2576/2/13 and AUTH/2679/11/13 that agencies might wish to highlight their work, Astellas considered that the use of the brand names and therapeutic indications on the agency website went beyond any requirement to market creative capabilities and constituted promotion of prescription only medicines to the public, in breach of Clause 26.1. In addition, given the seriousness of this, Astellas UK could understand that the Panel might wish to consider the requirements of Clauses 9.1 and 2.

The agency confirmed that it had not discussed this with, or sought prior permission from, Astellas for the use of the graphics or their presentation on its website. The agency staff were last trained on the Code in April 2016.

Whilst this material was published on the agency's website without Astellas UK's knowledge or approval, the company stated that it was fully accountable for the actions of its agencies and acknowledged the failing in this regard. Astellas stated that it would now review the working practices of all of its UK agencies in relation to compliance, and its oversight, to ensure that it maintained the high standards expected.

RESPONSE

Astellas explained that the material on the agency website featured on a page entitled 'Our Work' which was accessible from the home page. The home page itself did not signpost to this section or refer to the type of work featured in this section or to Astellas. 'Our Work' could only be accessed via the menu at the top of the home page. In the website section 'Our Work' there was no separation of the Astellas material from non-pharmaceutical work and no information was provided to highlight that the Astellas work was aimed specifically at the pharmaceutical industry.

The agency was trained on the Code in April 2016 by another pharmaceutical company prior to the introduction of its patient support programme. The training specifically focused on:

- Clause 2 in terms of the non-promotional nature of nurse support
- Clause 4 in relation to governing the limits of information given to patients
- Clause 16 on pharmacovigilance and the requirements of the marketing authorization holder to ensure all agencies acting on its behalf followed the guidelines on adverse event reporting and the timelines for doing so and
- Clause 19 relating to patient confidentiality.

Attendees were provided with a copy of the 2016 Code.

PANEL RULING

The Panel noted that an Astellas employee had found patient support materials for Betmiga and Vesicare on the agency's website after searching for the URL

for the Betmiga patient support programme (Fresh Start). In that regard the employee had actively searched the internet for specific material. Having discovered the Betmiga material and the Vesicare material on the agency website, Astellas then found material from the Remind Me programme which supported patients taking Prograf (tacrolimus) or Advagraf (tacrolimus SR) for the prophylaxis of transplant rejection. None of the material had been posted on the agency's website with Astellas's knowledge or permission.

The Panel noted Astellas's submission that the material on the agency website was in the 'Our Work' section, accessible only via the menu at the top of the home page. According to Astellas, the 'Our Work' section did not separate Astellas material from non-pharmaceutical work.

The Panel acknowledged that creative agencies were entitled to promote their work and that as a result, examples of pharmaceutical material might appear on their open access websites. Whether this was acceptable would depend on the circumstances of each case. The Panel considered it would be prudent if the potential for such use was addressed in the contract between the pharmaceutical company and its agency at the outset. The website in this case was the agency's own website and anyone could access it. Anyone who landed on the home page of the website would have to consciously look further for examples of the agency's work, including that of Astellas, by using the menu.

The Panel noted that the material shown on the website for Betmiga and Vesicare consisted of the front page of two patient support booklets aimed at those taking one or the other medicines. From the text below, which detailed the client, the brief and the solution, it was clear that both medicines were for the treatment of overactive bladder. The material shown for the Remind Me programme was the nurse guide. In the accompanying text, the brief was stated to be 'Increase drug adherence by finding a way to help transplant patients remember to take their Prograf or Advagraf medication ensuring their new transplant does not fail'.

On balance, despite medicines and their indication appearing on an open access website, the Panel did not consider that medicines had been promoted to the public; the website was not aimed at the public *per se*. No breach of Clause 26.1 was ruled. The company had not failed to maintain high standards. No breach of Clause 9.1 was ruled.

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

During its consideration of this matter, the Panel noted its concern about the claim that Prograf and Advagraf would *ensure* (emphasis added) that new transplants did not fail and questioned whether such an all-embracing claim for efficacy was acceptable in an agency brief. The Panel requested that Astellas be advised of its concerns in this regard.

2 Patient support programmes

VOLUNTARY ADMISSION

Astellas noted that until the events described in Point 1 above, it had run two patient support programmes; VIP, for all patients prescribed Vesicare and Fresh Start, for those prescribed Betmiga. The agency was engaged to develop material for both programmes and also to run them via its team of nurses who manned a patient support line. Both patient support programmes had now been terminated due to Astellas's concern in relation to its lack of oversight and support as detailed below. These issues became apparent during the investigation described above.

Issues about adverse event reporting at the agency was the subject of a separate investigation that was raised in March 2016 but there was no conclusive evidence to uphold the issues raised.

Description of patient support programmes

The patient support programmes were designed to support patients taking Vesicare (VIP) or Betmiga (Fresh Start). When the first prescription was filled, patients were given details on how to enrol in the relevant programme via a leaflet from their health professional or, in the case of the VIP, via the Vesicare patient information leaflet and carton. Patients could enrol either by telephoning a careline manned by the agency staff or by going to a website, hosted by the agency, and certified by Astellas; in both cases, patients could only register on the programmes if they provided a batch code from their medicine packaging. This ensured that the programmes were only available to those already prescribed the relevant medicine.

Once registered, patients would receive a welcome pack and a call from a nurse at weeks 3, 7 and 11 to discuss their treatment and any questions they might have. After three months, proactive contact by a nurse as part of the patient support programme stopped, however patients were able to call the nurse support line at any point during their treatment (either during that three month period or beyond).

Astellas oversight of patient support programmes

A master services agreement (MSA) was put in place between Astellas and the agency in 2010, initially to cover the Vesicare patient support programme (VIP); although the programme had operated since 2006, no record of a contract with the agency before 2010 could be found.

When the programme started in 2006 the nurses on the patient support line were trained on the Vesicare summary of product characteristics (SPC) as well as on adverse event reporting. This was face-to-face training conducted by the Astellas medical and marketing department; training materials were also provided. In addition, nurses were given a 'script' to aid their discussions with patients. Although the adverse event training was repeated once a year via an Astellas pharmacovigilance training slide deck, which was rolled out to all the agency

nurses and confirmed back to Astellas that this had been completed, there was no record of any further training on Vesicare despite the SPC having changed nine times. Although Astellas had not provided revised SPCs to the agency over this period, the agency had confirmed that if nurses were asked a question about Vesicare which needed reference to the SPC then this would always be viewed online via the electronic medicines compendium (eMC) website to provide the latest information.

In 2013, the Fresh Start patient support programme was introduced for patients prescribed Betmiga. This coincided with the launch of Betmiga and, as with all new chemical entities, material was pre-vetted by the Medicines and Healthcare products Regulatory Agency (MHRA), including material for the patient support programme.

The nurse support line for Fresh Start was also staffed by the same agency nurses as the VIP programme, although Astellas had no copy of an MSA that reflected this additional arrangement. However, the additional arrangements were covered via estimates provided relating to the project and the approval of the relevant purchase orders (including Astellas standard Terms and Conditions). Astellas understood that in 2013 the nurses on the patient support line were trained on the Betmiga SPC current at that time. This face-to-face training was conducted by the medical and marketing department and training material was provided. As with the Vesicare training, there was no record of any further training on Betmiga, despite the SPC having changed six times. Although Astellas had not provided revised SPCs to the agency over this period, the agency had confirmed that if nurses were asked a question about the medicine that needed reference to the SPC then it would always be viewed online via the eMC website. In addition, nurses were provided with a 'script' to aid their discussions with patients; however, as identified below, this had not been kept up-to-date.

Although Astellas had monitored the number of patients enrolled into each patient support programme monthly and had continued to pay the agency the monthly fixed fee, it had not provided similar ongoing oversight and support for the nurse helpline in relation to product training. Whilst Astellas recognised that these programmes should have had ongoing consistent oversight, they had been managed by a series of colleagues without appropriate handover or training which had led to the current situation.

Astellas considered that, given that the nurses interacted directly with patients, this was a failure to maintain high standards, contrary to the requirements of Clause 9.1. Astellas also understood that the Panel might wish to consider the requirements of Clause 2 in relation to this lack of oversight and supervision.

Patient support programme materials

The material relating to VIP and Fresh Start was provided. Given that all material was printed/produced and sent out by the agency, Astellas did not keep any copies of the material at its offices. Astellas would receive an invoice as and when there was a need to print more material. The last such invoice was received in March 2014 for materials for the VIP programme and December 2015 for the Fresh Start programme.

VIP

Astellas had reviewed all of the VIP patient support programme materials and found that four job bags were, in error, set up as items that would be used only once, rather than those that would require re-approval if still in use before the end of the two year period post-certification (Clause 14.5). Details were provided.

Material set up in such a way was automatically withdrawn on Zinc after a stated time period, without those who might have it in their possession being notified. In addition, such material would not be flagged in Zinc as requiring re-approval, meaning in this case that some materials that were, until recently, still being used by the agency and sent to patients on the VIP patient support programme, had in fact been withdrawn on Zinc and had gone past the two year period before which they would need to be re-certified.

Astellas reviewed all VIP material including that withdrawn in March 2014 and considered that the content of these items was still appropriate for use; however, the above job bags were of a very poor quality regarding the way they had been set up including incorrect audience, poor information on objectives and having been initiated as a promotional item, contrary to Clause 9.1, and the material was in continued use past the two year period noted above, contrary to the requirements of Clause 14.5.

Astellas had also identified a number of other issues relating to four other materials for the VIP programme. Details were provided.

Astellas submitted that human error might have contributed to why certain job bags were set up or withdrawn inaccurately in Zinc and, in view of this finding, the company would continue to emphasise to staff the importance of appropriate job bag creation in relevant training. In addition, Astellas had incorporated these specific requirements into its peer review checklist to ensure that the quarterly reviews of job bags that were conducted internally assessed accurate job bag set up including the 'one-off use' status in Zinc.

Fresh Start

Astellas had reviewed material relating to the Fresh Start patient support programme and was concerned that the frequently asked questions section of the nurses' script (certified on 21 July 2015) no longer accurately reflected all adverse events listed in the current SPC (nausea was omitted). In addition, the Betmiga SPC was updated in April 2016 and the nurses' script was not revised to reflect the addition of a number of common side effects (constipation,

diarrhoea, headache and dizziness). Both of these omissions were attributable to human error by the signatory in the first instance and the owner of the material in the second; the issue was being addressed with both.

Astellas thus considered that the nurses' script was inaccurate and did not reflect the available evidence in relation to side effects, contrary to the requirements of Clauses 7.2 and 7.9. In addition, this amounted to a failure to maintain high standards, in breach of Clause 9.1 and had the potential to impact on patient safety, which would be contrary to the requirements of Clause 2. Impact on patient safety would be a matter of a separate assessment and communication with the relevant competent authorities where required.

Astellas also discovered that one item from the Fresh Start programme was, in error, set up as an item that would be used only once, rather than one that would require re-approval if still in use before the end of the two-year period post-certification. This item had therefore been used past the two year period.

In addition, two items were identified in April 2016 that still described Betmiga as 'new' at re-certification having been previously been re-certified in April 2014. These materials were immediately withdrawn. Astellas recognised that the word 'new' should have been removed from this material by February 2014 and thus after this date the material was in effect in breach of Clause 7.11. In addition, one item which was for re-certification was withdrawn to be updated with the new side effects and two other items had been withdrawn in error but remained active.

Astellas considered that, given that these materials were distributed to patients, as well as being contrary to the requirements of Clause 7.11, this amounted to a failure to maintain high standards, contrary to the requirements of Clause 9.1. Astellas also understood that the Panel might wish to consider the requirements of Clause 2 in relation to this lack of oversight and supervision.
In addition, Astellas found out on 26 August 2016 that the agency had been sending a survey to patients after 3 months on either programme. This had happened since the programmes were initiated and was intended to collect patient feedback on each programme. This information was previously provided to Astellas and outcomes from the questionnaire used in a promotional piece of material in 2009. As soon as the current team became aware, it instructed the agency to discontinue this activity immediately.

RESPONSE

Regarding Clauses 14.1 and 14.3, Astellas confirmed that all of the materials at issue were electronically certified before use. Not all materials were certified in a hard copy final form before use in breach of Clauses 14.1 and 14.3. Copies of all electronic certificates and hard copy certificates, where available, were provided for the items referred to above. As detailed in the sections below, some materials were withdrawn in Zinc in error but remained in use post the Zinc withdrawal.
Items related to the VIP and Fresh Start programmes and details of approval certificates

Details of the items were provided including whether the job bag was available at Astellas and whether a 'Hard copy (signed) certificate available' which denoted that a signed copy of the Zinc final certificate was contained within the job bag. These certificates were signed by a brand manager and not by a nominated signatory.

Astellas explained that the withdrawal dates for the items mentioned above referred to the date withdrawn from Zinc. Items were withdrawn from use at various times between the Zinc withdrawal date and the withdrawal of the whole programme. Details were provided of the eight VIP materials and the six Fresh Start materials where the withdrawal dates in Zinc did not match the withdrawal from use dates.

The Fresh Start website content was withdrawn from use on 1 April 2016 and subsequently withdrawn from Zinc on 4 April 2016, whilst an update was made to remove the word 'new' and reflect the most recent SPC. It was replaced by the holding page which was certified and went live on 11 April 2016 and remained in place until the closure of the programme. There was no site available between 1 and 11 April.

No patient support packs or letters were sent to patients after 22 September 2016 and no new patients were registered on either programme after the closure date on 10 October 2016.

PANEL RULING

The Panel noted that Astellas's oversight of the agency nurses who delivered the two patient support programmes was extremely poor. Although when both programmes first started, the nurses who were to man the helplines were trained on the relevant medicine (Betmiga or Vesicare), they received no further product specific training despite the fact that the SPCs for both products had since changed a number of times; some of those changes related to changes to Section 4.8, Undesirable effects. Further the telephone scripts which they had initially been given had not been revised; the script for the VIP helpline was dated October 2012. The script for the Fresh Start programme was dated March 2013 and did not reflect the addition to the Betmiga SPC of a number of common side effects (constipation, diarrhoea, headache and dizziness). Both scripts were thus inaccurate and out-of-date and in that regard the Panel ruled a breach of Clause 7.2. The Fresh Start script did not accurately reflect up-to-date information on possible side effects and in that regard the Panel ruled a breach of Clause 7.9. The Panel noted Astellas's submission that if nurses were asked questions about Betmiga or Vesicare that needed reference to the SPC, they would access the eMC website for the latest version. The nurses did receive annual training on adverse event reporting, certainly in relation to VIP. It was unclear whether

this had been updated annually, a copy had not been provided. It was also unclear why training on other matters outlined above had not been provided. Overall the Panel considered that such inadequate training of those who were expected to interact directly with patients was wholly unacceptable. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel further considered that the failure to properly train the nurses and keep them updated with product changes was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. It was crucial that out of all of the options available, patients could rely completely upon the industry for up-to-date and accurate information about their medicines. A breach of Clause 2 was ruled.

In addition to its failure to properly train the nurses who manned the helplines, the Panel noted that Astellas's oversight of the patient support materials was very poor. In that regard the Panel noted Astellas's submission that materials had been set up wrongly in Zinc such that although they were withdrawn in Zinc, mostly in 2014, they continued to be used by the agency beyond two years without being re-certified. In that regard the Panel ruled a breach of Clause 14.5.

The Panel further noted that some of the Betmiga material which was in use up to April 2016, continued to describe the medicine as 'new' when in fact that description could only be used for one year and should have been removed from the material in February 2014. A breach of Clause 7.11 was ruled. The Panel noted its rulings with regard to the oversight of material. The Panel noted that despite the withdrawal of certain materials in Zinc, the company had nonetheless paid the agency for the cost of printing materials for the Fresh Start programme in 2015. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The supplementary information to Clause 14.1 stated that when certifying material where the final form was to be printed companies could certify the final electronic version of the item to which no subsequent amendments would be made. When such material was printed the company must ensure that the printed material could not be used until any one of the company's signatories had checked and signed the item in its final form. In such circumstances the material would have two certificates and both must be preserved. The Panel noted Astellas's submission that not all materials were certified in a hard copy final form before use and those that were, were signed by the relevant brand manager and not by a nominated signatory. Further, the Panel noted that the patient satisfaction surveys had not been certified at all as no job bag had been raised in Zinc. The Panel ruled a breach of Clause 14.3. High standards had not been maintained. A breach of Clause 9.1 was ruled. As the material at issue was not promotional material, Clause 14.1 was not relevant and so the Panel ruled no breach of that clause.

The Panel noted its rulings and comments above. In the Panel's view, a certification process, correctly implemented, underpinned self-regulation. The Panel noted the number of materials which had not been correctly processed through Zinc, and some that had not been through Zinc at all. In that regard the Panel considered that Astellas's lack of control of material was such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

3 Transparency and disclosure

VOLUNTARY ADMISSION

During its investigation into the issues noted above, Astellas found out that the nurses manning the support line for both patient support programmes still also worked for the NHS. This was not previously known, and Astellas considered that this additional information meant that the agency fitted the definition of an institution, organisation or association of health professionals noted in Clause 21. This clause required that any transfers of value made to such bodies in relation to services that they provided on behalf of a company were disclosed in accordance with the requirements of Clause 24. This disclosure had not taken place for transfers of value made to the agency in 2015, in breach of Clauses 21 and 24. Additionally, Astellas had found out that payments made to pharmacies in relation to enrolment of patients onto the Fresh Start programme had not been disclosed. The company stated it was addressing this and would upload the relevant data to the ABPI central platform as soon as possible.

RESPONSE

With regard to payment, Astellas explained that £7.50 was paid for each eligible patient enrolled on Fresh Start to pharmacies through the specific local pharmaceutical committees (LPCs) that Astellas worked with. To be eligible, patients must have been enrolled within 6 months of taking Betmiga. In 2015, 25 patients were enrolled, ie 25 payments were made. In 2016 only 1 patient was enrolled via a pharmacy. The same payment amount and eligibility criteria applied to the Vesicare programme. Only one LPC was involved in pharmacy enrolment for VIP during the period 2015 to 2016; it enrolled 5 patients via pharmacies in 2015 and 3 in 2016.

In response to a request for further information, Astellas explained that its agency had a UK business address and engaged the services of health professionals (nurses) to deliver support services to patients. In its capacity as an agency to deliver the patient support programme for Astellas the nature of its work was to deliver healthcare services to patients via a telephone support line. In Astellas's view the definition of a healthcare organisation as stated in Clause 1.9 applied.

Astellas noted that Clause 21 covered:

> 'Contracts between companies and institutions, organisations or associations of health professionals under which such institutions, organisations or associations provide any type

of services on behalf of companies *(or any other type of funding by the company not otherwise covered by the Code) are only allowed if such services (or other funding)'* [emphasis added].

Astellas acknowledged that Clause 21 referred to, *inter alia*, the requirements of Clause 19.1 (which covered medical and educational goods and services (MEGS)); however, it considered that it was also a 'catch all' clause to cover transfers of value (ToVs) made to a healthcare organisation that was not covered in any other clause of the Code. Given that Astellas did not know exactly how much was paid to each nurse, it considered that Clause 21 was relevant, even if the services provided were not related to MEGS.

Astellas submitted that the identity of individuals who were initially trained could be accessed by Astellas from the training records provided by the agency.

The agency offered nurse teams to its clients. The Astellas support lines were adapted to the needs of patients with overactive bladder, however the agency had confirmed that the provision of nurses via a support line was not a unique offering to Astellas and that the nurses were not sub-contracted from another agency/organisation. The agency engaged directly with the nurses manning the telephone support line.

Within clause 19.1 of the MSA the agency must gain prior consent from Astellas in order to sub-contract works. No such requests are known to have been made to Astellas.

Astellas submitted that it did not have the relevant information to be able to make a disclosable ToV to the nurses either in aggregate nor individually; Astellas only knew what it had paid to the agency.

The methodological note outlining how Astellas disclosed ToVs in these situations was publicly available on the ABPI website and stated:

'Where services for Astellas are rendered by an HCP [healthcare professional] on behalf of an HCO [healthcare organisation] (for example, Astellas enters into a service contract with an HCO and the services are provided by the HCO's employee), the associated fees and expenses paid by Astellas to the HCO are disclosed as Transfers of Value made to the HCO. This is the case unless Astellas can confirm that the HCP received a benefit from the Transfer of Value, either directly from Astellas or via the HCO, (e.g., fees paid to the HCP in connection with the services he/she rendered and/or reimbursement of any related expenses the HCP incurred), in which case Astellas discloses those Transfers of Value as being transfers to the HCP. Where Astellas can identify the HCP and know that the HCO will make the full Transfer of Value to the HCP on Astellas' behalf, the Transfer of Value is disclosed as being a Transfer of Value to the HCP.'

PANEL RULING

The Panel noted that the nurses who manned the patient helplines had been supplied by the agency. Astellas did not know how much of the fee it had paid the agency had gone either to the nurses as a group or to each individual nurse. At the start of the patient support programmes, Astellas had known who the nurses were through face-to-face training for the VIP programme (2006) and the Fresh Start programme (2013).

The Panel noted that the Code required companies to declare transfers of value made directly or indirectly to health professionals and healthcare organisations located in Europe. The definition of healthcare organization as stated in Clause 1.9 included 'an organization through which one or more health professional or other relevant decision makers provide services'. In that regard, the Panel considered that although creative agencies would not normally be considered healthcare organisations, in this case the nurses on the patient helplines had provided their services through the agency. In that regard the Panel considered that Astellas must declare the amount paid to the agency for the nurses on the ABPI central platform in accordance with Clause 24.1. If the company became aware of the individual identity of the nurses then the amount paid should be declared for each individual. It was unacceptable that the contract with the agency did not appear to be such that the company could identify the amount(s) paid. The Panel further noted that monies paid to pharmacies in relation to the enrolment of patients into the Fresh Start programme had not been declared. A breach of Clauses 21 and of 24.1 was ruled.

* * * *

The Panel was extremely concerned about is rulings and comments above. Some of the matters raised went to the heart of self-regulation and patient safety. The company's oversight of the patient support programmes at issue had been lamentable. Notwithstanding the fact that Astellas UK was currently suspended from membership of the ABPI and already undergoing a series of audits of its procedures under the Code, the Panel decided, in accordance with Paragraph 8.2 of the Constitution and Procedure, to report the company to the Appeal Board for it to consider whether further sanctions were appropriate in this case.

COMMENTS FROM ASTELLAS UK ON THE REPORT FROM THE PANEL

Astellas fully accepted and agreed with all of the Panel's rulings and sincerely apologised for the issues highlighted in this case. Astellas noted the Panel's comment that its oversight of the patient support programmes was lamentable. Whilst the patient support programmes were established some years ago, Astellas recognised that this was no excuse for the findings in this case.

Astellas had been aware for some time of failings in its review and certification process, both in relation to the quality of material and the technical accuracy of setting up a job bag in Zinc. In that regard it had, since 6 June 2016 regularly monitored the situation and shared findings with all relevant staff with the aim of achieving continuous quality improvement.

Astellas recognised the lack of oversight in relation to the patient support programmes at issue and acknowledged that this was due to its failure to provide clear process and training on the development, implementation and oversight of such programmes. When it discovered the issues in this case, Astellas ceased all patient support programmes and no more would be developed and put in place until such training and process had been implemented.

In relation to the transfers of value that had not been disclosed, Astellas submitted that all of those made to the agency as a healthcare organisation would be uploaded to the Astellas 2015 disclosure report on the ABPI portal, including the payments made to the nurse teams and pharmacies in running the programme.

At the consideration of the report the representatives from Astellas UK apologised to the Appeal Board for the failures outlined above which it accepted could bring discredit upon or reduce confidence in the industry.

Astellas stated that it was lamentable that due to process failure and human error its oversight of the patient support programmes fell well below acceptable standards and some of the matters raised went to the heart of self-regulation and patient safety.

Astellas knew that from previous PMCPA audits, there had, historically been issues with the company culture and processes relating to compliance. Astellas recognised that projects initiated some years ago did not have the rigour of oversight that it would apply to projects initiated today.

Astellas noted that this issue had come to light because an agency that it had worked with for many years had posted materials, which included brand names and indications, on its website without the company's knowledge or approval. However, once Astellas became aware of this issue it carried out a full investigation and self-reported all the related potential breaches of the Code.

Astellas did not seek to defend its actions taken in 2006 and 2013, or since, nor did it provide excuses. Astellas gave reassurance that it had learned from these events and although the journey to improve its compliance with the Code by addressing its culture and processes was in no way complete, progress had been made. Astellas submitted that the progress had been acknowledged by the Appeal Board and the ABPI Board. Events such as this made Astellas even more determined to get it right.

Astellas stated that the current UK team took full responsibility for these events and it sincerely apologised for these failures.

The representatives from Astellas UK stated that to help ensure that such failings did not recur, the company either planned to start or had a number of new processes and procedures in place including annual examinations for signatories, compliance risk assessments, compliance monitoring and regular material quality review. In addition, all job descriptions would be amended to include specific compliance training for the role and reporting structures for key roles including, *inter alia*, those for ethics and compliance, would change such that staff would report directly to global.

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board noted that this case had arisen from a voluntary admission by Astellas UK and the company had accepted all breaches of the Code including Clause 2. The Appeal Board also noted that Astellas UK had made a sincere apology for its failings in this case. However, the Appeal Board noted the Panel's comments and rulings above.

The Appeal Board considered that this case raised serious concerns about multiple failings and a complete lack of control in Astellas UK's review and certification process which was entirely unacceptable. In that regard the Appeal Board noted with concern a number of examples where signatories had taken an extremely short period of time to certify material in Zinc.

The Appeal Board was very concerned to note that Astellas UK had little or no knowledge about the qualifications of the nurses employed by its agency or of what they did or said to patients. Astellas should have had far greater oversight including feedback and audit of the nurses' interactions with patients. It was an appalling failure in particular that the nurses were not trained or updated on changes to the relevant SPCs. It was essential that patients could rely completely upon the industry for up-to-date and accurate information about medicines. The Appeal Board considered that the deplorable failure of process and oversight in this case raised serious concerns with regard to patient safety and public confidence in the pharmaceutical industry.

The Appeal Board noted that as a consequence of Case AUTH/2780/7/15 Astellas UK was currently suspended from membership of the ABPI. Astellas UK and Astellas Pharma Europe had each been audited twice (December 2015 and September 2016) and each would be audited again in April 2017. The Appeal Board was minded to report Astellas UK to the ABPI Board but given the exceptional circumstances, including that the re-audits in Case AUTH/2780/7/15 were due to be carried out very shortly, it decided that the issues that had arisen in this case should be looked at as part of the upcoming re-audit of Astellas UK, including examination of patient support programmes and certification of material. On consideration of the report of the re-audits the Appeal Board would reserve its decision on whether to report Astellas UK to the ABPI Board.

The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Astellas UK should be publicly reprimanded for a lamentable lack of concern for patient safety and wholly unsatisfactory oversight and control of the patient support programmes and of the nurses employed to deliver them.

APPEAL BOARD FURTHER CONSIDERATION

Astellas UK and Astellas Europe were re-audited in April 2017 and the report was considered by the Appeal Board in May 2017.

The Appeal Board noted that Astellas UK and Astellas Europe were now working more closely and there was more open communication with staff. Both companies had been working to implement the recommendations of the previous audits and to ensure compliance was embedded. However, the Appeal Board noted the number of issues highlighted in the report and that there was still much work to be done.

The Appeal Board accepted that it took a long time to change culture but it was not convinced that progress was being made at an appropriate speed particularly given the issues that had come to light in Cases AUTH/2883/10/16, AUTH/2939/2/17 and AUTH/2940/2/17. This was particularly worrying given the level of scrutiny the companies were under. In the view of the Appeal Board, Astellas had much work still to do.

In relation to Case AUTH/2883/10/16 the Appeal Board decided that Astellas UK should be re-audited in October 2017 at the same time as the re-audit required in Case AUTH/2780/7/15 and the audit required in Cases AUTH/2939/2/17 and AUTH/2940/2/17 in relation to both Astellas UK and Astellas Europe.

In relation to Case AUTH/2883/10/16 the Appeal Board noted that it had reserved its position in relation to additional sanctions in this case until it had seen the report of the April 2017 re-audits. Bearing in mind that the case related to patient safety and a lack of control and oversight, the Appeal Board decided that in accordance with Paragraph 12.1 of the Constitution and Procedure, Astellas UK should be reported to the ABPI Board.

The Appeal Board noted the outcome of the audit in Case AUTH/2883/10/16, and the re-audits in Case AUTH/2780/7/15, the decisions to report Astellas UK to the ABPI Board in Cases AUTH/2883/10/16, AUTH/2939/2/17 and AUTH/2940/2/17 in relation to both Astellas UK and Astellas Europe. It also noted its concerns regarding the lamentable lack of concern for patient safety and wholly inadequate oversight and control. Whilst noting this was a matter for the ABPI Board, the Appeal Board's view was that Astellas UK was not ready to resume membership of the ABPI and the suspension should continue.

ABPI BOARD CONSIDERATION OF THE REPORT FROM THE APPEAL BOARD

The ABPI Board noted the rulings of breaches of the Code, the decisions of the Appeal Board regarding audit, re-audit and the public reprimand.

The ABPI Board agreed with the Appeal Board's comments and concerns about the re-audits in April 2017.

The ABPI Board noted and endorsed the Appeal Board's views about the total failure of the companies' systems in relation to the control of prescribing information, the lamentable lack of concern for patient safety, wholly inadequate oversight and control and initial lack of urgency. It was a woeful state of affairs.

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

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

The ABPI Board also decided that it wanted sight of the report of the October 2017 re-audits of Astellas UK and Astellas Europe so that it could review the position before the end of 2017. If the report of the re-audits did not show significant improvement and progress at both companies, then the ABPI Board would consider expelling Astellas UK from membership of the ABPI. The companies should consider undergoing an external assessment of progress, particularly in relation to risk management of compliance in the broadest sense, ie including matters beyond the scope of the Code, with the outcome to be available at the time of the October 2017 re-audits.

The ABPI Board also decided that the MHRA should be advised of the ABPI Board's very serious concerns about the conduct of Astellas UK and Astellas Europe particularly in relation to the matters concerning patient safety. EFPIA should also be updated and asked to ensure the EFPIA Board was informed of the position.

APPEAL BOARD FURTHER CONSIDERATION

Astellas UK and Astellas Europe were re-audited in October 2017 and the report of the re-audit was considered in November. The Appeal Board noted that as these were the fourth audits of the companies and given that Astellas UK was currently suspended from membership of the ABPI, it expected substantial progress and improvements from both companies. This expectation had not been met. The Appeal Board acknowledged that some progress had been made. The companies must take prompt action to implement the findings and recommendations in the report of the October 2017 re-audits.

The Appeal Board accepted that it took time to change a company's culture. In this regard, the Appeal Board noted that there had been positive changes in the company culture. However, it was not convinced that the expected progress was being made, especially since the April 2017 re-audits.

Overall, the Appeal Board's view was that the rate of progress was inadequate and that the companies were not where they should be. There was still much work to do. The Appeal Board queried whether there was an element of structural inertia or perhaps fear of wrongdoing which was inhibiting or slowing the rate of progress.

Despite its criticisms, the Appeal Board noted the positive steps taken by the leadership of Astellas to engage more broadly with staff and drive changes.

The Appeal Board decided that both companies should be re-audited in April 2018. At which point it expected the 2018 global staff survey to demonstrate improvements at Astellas Europe and Astellas UK.

Whilst noting that this was entirely a matter for the ABPI Board, the Appeal Board's view was that if the report of the October 2017 re-audits and Astellas' response had come at the end of the two year suspension limit, then Astellas would have fallen well short of the standard required to resume membership of the ABPI. Unless substantial progress was seen in the report of the re-audits in April 2018, in the Appeal Board's view, Astellas UK would be at serious risk of a recommendation that it be expelled from membership of the ABPI.

ABPI BOARD FURTHER CONSIDERATION

The ABPI Board noted the Appeal Board's comments and concerns about the re-audits in October 2017 and the additional information provided by Astellas.

With regard to the external assessment of progress, particularly in relation to risk management of compliance in the broadest sense ie including matters beyond the scope of the Code, the ABPI Board noted the information provided by Astellas.

Following a change in tone from the top of Astellas, the ABPI Board recognised that meaningful progress had been made by the companies. The ABPI Board understood the difficulty inherent in making wide-sweeping cultural changes, and how long it took for those changes to become fully embedded within a large organisation. However, the ABPI Board acknowledged Astellas' clear commitment to further improvement.

The ABPI Board noted Astellas' statement that its materials were compliant in May 2017 in relation to issues of patient safety.

The ABPI Board also decided that it wanted sight of the report of the April 2018 re-audits of Astellas UK and Astellas Europe so that it could review the position before the end of the current suspension in June 2018.

The ABPI Board decided that taking all the circumstances into account it would take no further action at this stage in relation to the expulsion of Astellas from membership of the ABPI. The suspension from membership of the ABPI would remain in place until June 2018.

The ABPI Board also decided that the MHRA should be advised of the position. EFPIA should also be updated and asked to ensure that the EFPIA Board was informed of the position.

APPEAL BOARD FURTHER CONSIDERATION

In response to a request from the Appeal Board Astellas provided further information which showed that matters raised by the Appeal Board in November were being addressed more promptly than previously indicated.

APPEAL BOARD FURTHER CONSIDERATION

Astellas UK and Astellas Europe were re-audited in April 2018 and the report of the re-audits was considered in May 2018.

The Appeal Board noted the detailed responses from Astellas to the report of the April 2018 re-audits including that it was an accurate reflection of the work undertaken.

The Appeal Board noted the results of the 2018 staff survey and the progress made. Numerical increases had been shown in a number of parameters since the previous survey in July 2017. There were concerns about the comments made by staff. The Appeal Board also noted the differences in the Astellas UK results which were generally better than the Astellas Europe results. The Appeal Board considered that the Astellas Europe management committee scores although improved were still not where they should be.

The Appeal Board noted the comments in the report of the April 2018 re-audits and considered that both the leadership of Astellas Europe and Astellas UK had engaged with staff to bring about progress. There was still work to be done. The Appeal Board noted one of the recommendations was that members of the leadership team at Astellas Europe should be held to account and be challenged on compliance matters.

The Appeal Board accepted that it took time to change a company's culture. In this regard, the Appeal Board noted that there had been further positive changes in the company culture and this needed to be continued. The Appeal Board noted that there had been some positive compliance initiatives. The discussion fora and communications continued and progress had been made including ensuring staff had time to complete training.

The Appeal Board noted that whilst as a percentage there had been a significant increase in the number of job bags, the overall number was still low. As Astellas increased its activities it must remain extremely vigilant to compliance requirements in particular in relation to certain higher risk activities such as patient support programmes, product launches etc. The true test of the compliance framework in Astellas and its approach would be when activity levels including higher risk activities were increased and the company was operating at business as usual.

The Appeal Board considered that, at long last, the re-audits in April 2018 showed that progress had been made and that the companies were building on momentum started in summer 2017.

The Appeal Board was concerned that these were the fifth audits of each company and that the first audits were in December 2015. It was extraordinary that it had taken so long to demonstrate meaningful change. The overall impression from the report of the April 2018 re-audits was that Astellas was showing improvement and momentum. However, whilst the companies had reached a certain level, given all the circumstances including that Astellas UK had been suspended from membership of the ABPI and that the Appeal Board still had concerns, the Appeal Board decided that Astellas Europe and Astellas UK should each be re-audited at the end of the first quarter of 2019 to ensure that the improvements and the momentum continued and were built upon.

On the information before it, and noting that Astellas UK was still to respond to the PMCPA in relation to matters raised following completion of the consideration of a complaint concerning Astellas UK, Case AUTH/2984/10/17, the Appeal Board decided 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 when the matter came before the ABPI Board on 5 June 2018.

ABPI BOARD FUTHER CONSIDERATION

In June 2018 the ABPI Board noted the comments from both the Appeal Board and Astellas. The ABPI Board noted the limited information provided about matters raised in Case AUTH/2984/10/17. This was still to be considered by the PMCPA and the Appeal Board and was not before the ABPI Board for consideration.

The view of the Appeal Board was clear. The ABPI Board agreed with the Appeal Board's views and assessment of the re-audits and concluded that meaningful progress had now been made.

The ABPI Board believed that the culture in the companies had improved and noted that much of this had been led by the General Manager of Astellas UK. However, the Board recognised the importance of an ongoing commitment to ensure sustained culture change. On reviewing all the material, the ABPI Board had concerns about the sustainability of the changes made given that there had already been five audits/re-audits, and especially as further types of activity were still to be fully re-introduced across the companies.

The ABPI Board therefore decided that it wanted to see the report of the 2019 re-audits and be informed of major developments including the outcome of Case AUTH/2984/10/17.

In the circumstances, there was no need for the ABPI Board to consider expelling Astellas UK from membership of the ABPI. The suspension would end on 24 June 2018 and Astellas would revert to full membership of the ABPI.

Astellas should be cognisant of this ongoing sustainability requirement and monitoring (particularly in light of the matters still to be concluded in Case AUTH/2984/10/17) when communicating about the Board's decision.

The ABPI Board also decided that the MHRA should be advised of the position and that EFPIA should be updated and asked to ensure that the EFPIA Board was informed of the position.

APPEAL BOARD FURTHER CONSIDERATION

Astellas UK and Astellas Europe were re-audited in April 2019 and the report of the re-audits was considered in May 2019.

The Appeal Board noted the detailed response from Astellas Europe and Astellas UK to the report of the April 2019 re-audits.

The Appeal Board noted two new senior appointments; a new President EMEA Operations who joined Astellas in July 2018 and a new General Manager, Astellas UK who was appointed from April 2019.

The Appeal Board noted from the report of the April 2019 re-audits that it appeared that a more compliant culture was embedded within Astellas with improved communication. It was essential that this was maintained.

The Appeal Board considered that Astellas UK must ensure a proper professional approach to investigating and responding to any complaint under the Code such that the shortcomings in Case AUTH/2984/10/17 were not repeated. The Appeal Board noted that an audit had not been required in Case AUTH/2984/10/17. The case had, in accordance with established practice, been discussed as part of an examination of the company's culture at the re-audits.

The Appeal Board noted that these were the sixth audits/re-audits of each company and that the first audits were in December 2015. The Appeal Board considered that, on the information provided in the report of the April 2019 re-audits, it appeared that the companies had made further improvements, that this would be maintained and broadly the companies were where they should be. The Appeal Board, however, remained very concerned about the amount of time it had taken Astellas to reach this point. The Appeal Board noted that Astellas stated that it would follow up on the issues identified in the report of the April 2019 re-audits and it was committed to maintaining its approach to embedding a sustainable compliance culture. The Appeal Board noted a number of activities/actions were due to be undertaken. On the understanding that this work was completed, that the progress shown to date was continued and a company-wide commitment to compliance was maintained, the Appeal Board decided that, on the basis of the information in the report of April 2019 re-audits, no further action

was required in relation to Case AUTH/2780/7/15, Case AUTH/2883/10/16, Cases AUTH/2939/2/17 and AUTH/2940/2/17.

The Appeal Board noted that the audit/re-audits in these four cases had been required by the Appeal Board. They had not been required by the ABPI Board. Nonetheless, the Appeal Board noted the ABPI Board's request to see the report of the April 2019 re-audits.

At the re-audits in April 2019 it was noted that the MHRA decided that Astellas advertising materials should be submitted for review. This was introduced for all new materials issued since 1 December 2018.

ABPI BOARD UPDATE

In June 2019 the ABPI Board received an update as requested. It noted the comments from both the Appeal Board and Astellas and the improvements made.

Voluntary admission received	**20 October 2016**
Undertaking received	**15 February 2017**
Appeal Board consideration	**16 March 2017, 25 May, 16 November, 7 December, 17 May 2018, 22 May 2019**
ABPI Board consideration	**6 June 2017, 5 December, 5 June 2018**
ABPI Board update	**4 June 2019**
Interim case report first published	**3 May 2017**
Case completed	**22 May 2019**