CASE AUTH/2939/2/17 and AUTH/2940/2/17

# VOLUNTARY ADMISSION BY ASTELLAS UK AND ASTELLAS EUROPE

## Failure to provide accurate prescribing information

**Astellas UK and Astellas Europe respectively voluntarily admitted breaches of the Code with regard to the content of prescribing information for seven medicines promoted by Astellas in the UK.**

**Whilst the voluntary admission was made under the self-regulatory system, given the potential impact on patient safety, the companies informed the Medicines and Healthcare products Regulatory Agency (MHRA) which was advised that the PMCPA was dealing with the matter as a complaint under the Code.**

**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. In addition to the clauses cited by Astellas, (Clauses 4.2, 9.1 and 2) the companies were also asked to consider the requirements of Clauses 4.1, 4.10 and 26.3 of the Code.**

**Astellas stated that the issues highlighted did not relate to the content of any summaries of product characteristics (SPC) or patient information leaflets (PIL).**

**Astellas UK provided detailed background information. In late November 2016, the copy approval system raised an alert that the prescribing information for Flomaxtra XL (tamsulosin hydrochloride) was due for routine re-approval. During the review process a signatory noticed that at least one adverse reaction contained within the Flomaxtra XL SPC (Stevens–Johnson syndrome) which should be categorised as serious had not thus far been included in the prescribing information.**

**The issue was initially thought to be isolated to the prescribing information for one medicine, omitting three serious adverse reactions (Stevens-Johnson syndrome, syncope and priapism).**

**However, a thorough investigation (as detailed below) identified the breadth of the issue, including the impact on Astellas Europe. Astellas Europe was informed of the issue in February 2017, and then began its own review (see below).**

**The review was conducted on all medicines currently promoted by Astellas UK, namely Advagraf, Betmiga, Dificlir, Modigraf, Mycamine, Prograf, Qutenza, Vesicare and Xtandi. The review also revealed that in addition to the inconsistent categorisation around seriousness, there were a number of incidences of common adverse reactions, as well as warnings and precautions, which had not been included in the prescribing information.**

**There had been inconsistency in ownership of the construction of the original prescribing information in Astellas UK. Where Astellas UK had documented the development of the original prescribing information through the Zinc approval system, these products (Betmiga, Xtandi, Dificlir and Qutenza) had been unaffected by the omissions described. For the affected products, it was unclear as to whether the original prescribing information was developed by Astellas UK.**

**However, the process for the approval of revised prescribing information had been erroneously confined to the review of the information that had been revised, rather than a full review of the prescribing information every time. Thus, if the prescribing information was incomplete from the outset, this was not picked up at subsequent revisions.**

**As an immediate action, the prescribing information and all promotional items for the Astellas medicines promoted that had incomplete prescribing information (Flomaxtra, Vesomni, Vesicare, Advagraf, Prograf, Modigraf and Mycamine) had been withdrawn. As an interim measure, the SPC would be used in the UK supplemented with the legal classification and the cost. This interim solution would remain in place until a revised process was in place.**

**Astellas Europe was the regional headquarters for Europe, Middle East and Africa (EMEA), based in the UK, and therefore operated differently to Astellas UK with regard to the creation of promotional material and use of prescribing information. Astellas Europe created regional template promotional materials for adaption according to local law or codes of practice ie materials would be reviewed and adapted for local use by the relevant affiliate.**

**There were some materials and activities that were produced and implemented by Astellas Europe directly. These generally used Astellas Europe generated/adapted prescribing information.**

**Under the current process for development and revision of UK prescribing information Astellas Europe, medical affairs had assumed responsibility for updating prescribing information when it became aware of SPC updates. Historically each brand team had taken a slightly different approach, and had either used the UK prescribing information as a basis and adapted that, together with a supplementary adverse event reporting statement, or prepared their own European/EMEA version of prescribing information.**

**Subsequent to the Astellas UK investigation, a review of prescribing information and promotional materials generated by Astellas Europe had been initiated.**

**Astellas Europe was notified of this issue in February 2017. It had no formal written process around the development and revision of prescribing information and had not routinely been notified about prescribing information updates. The same lack of guidance around categorisation of seriousness applied equally to Astellas Europe.**

**There had been no consistent approach to the approval process across brands and the process was not well defined. Astellas recognized that this needed to be, and was working to ensure that the process was, robust and consistent.**

**A review was undertaken of serious and common adverse events, contraindications, warnings and precautions in the active Astellas Europe prescribing information for Advagraf, Betmiga, Dificlir, Modigraf, Prograf, Qutenza, Vesomni, Vesicare and Xtandi. This review had identified omissions in the Astellas Europe prescribing information for Vesomni and Vesicare. An analysis of these omissions was provided.**

**There was no active Astellas Europe prescribing information for Mycamine.**

**A full retrospective analysis of Astellas Europe prescribing information was completed at the end of February. This showed omissions for previous versions of the prescribing information for Mycamine and Qutenza.**

**A review had been undertaken of all the active Astellas Europe promotional material for Advagraf, Betmiga, Dificlir, Modigraf, Mycamine, Prograf, Qutenza, Vesomni, Vesicare and Xtandi to identify if any materials needed to be recalled, the results of which were provided.**

**As an immediate action the active prescribing information for Vesomni and Vesicare and the identified promotional materials were recalled.**

**Astellas UK and Astellas Europe stated that it was clear that Astellas required a robust, consistent and reproducible process for the generation of prescribing information. A discussion with global colleagues had started and a cross-functional task force formed to work on a revised process.**

**The companies submitted that there were issues with the prescribing information for seven medicines. In addition, Astellas UK and Astellas Europe acknowledged that the deficiencies in their processes which related to the consistent inclusion of the relevant safety information in the prescribing information of these products represented a failure to maintain high standards. Given that such omissions had the potential to impact on patient safety, the companies considered the issues uncovered were contrary to the requirements of Clause 2 and in that regard they had sent a copy of the voluntary admission to the MHRA.**

**The companies submitted that they were treating this issue with the utmost seriousness; they recognized the gravity of the situation and were addressing it as a priority.**

**The detailed response from Astellas UK and Astellas Europe appears below.**

**The Panel was extremely concerned that incomplete prescribing information had been used by the companies for a number of years on large numbers of materials. It noted the companies' submissions that the omissions from the Astellas UK prescribing information included serious adverse reactions as well as common adverse reactions, warnings and precautions. The omissions from the Astellas Europe prescribing information included inconsistent categorisation around seriousness as well as common adverse reactions, warnings and precautions. The Panel was also very concerned that the systems at both companies had not picked up the errors sooner.**

**The Panel noted that both Astellas UK and Astellas Europe had withdrawn current materials with incomplete prescribing information. These being Astellas UK materials for Flomaxtra, Vesomni, Vesicare, Advagraf, Prograf, Modigraf and Mycamine. The Astellas Europe materials related to Vesomni and Vesicare. In addition Astellas Europe had identified omissions in previous versions of the prescribing information for Mycamine and Qutenza.**

**The Panel ruled breaches of the Code in relation to each of the seven Astellas UK products with incomplete prescribing information and in relation to each of the four Astellas Europe products with incomplete prescribing information. High standards had not been maintained and breaches of the Code were ruled. The Panel considered that the failures brought discredit upon and reduced confidence in the pharmaceutical industry. It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about their medicines. Breaches of Clause 2 of the Code were ruled.**

**With regard to the use of the black triangle, the Panel accepted Astellas UK and Astellas Europe's submissions that the black triangle was not required to be included in the prescribing information and thus ruled no breaches of the Code.**

**The Panel was extremely concerned about its rulings and comments above. Some of the matters raised went to the heart of self-regulation and patient safety. Astellas' oversight of the prescribing information had been very poor. 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 both Astellas UK and Astellas Europe to the Appeal Board for it to consider whether further sanctions were appropriate in these cases.**

**The Appeal Board noted that these cases had arisen from a voluntary admission by Astellas UK and Astellas Europe and that the companies had**

**accepted all the rulings of breaches of the Code including Clause 2. The Appeal Board also noted that Astellas sincerely apologised for the failings.**

**The Appeal Board considered that these cases raised serious concerns about multiple failings and a complete lack of control. The lack of processes with regard to updating prescribing information was shocking. The Appeal Board considered the companies' failure to ensure that prescribing information was accurate and complete was totally unacceptable and that such failings raised very serious concerns with regard to patient safety. The Appeal Board considered that given the importance of patient safety, this issue should have been an absolute priority. The amount of time that had elapsed between Astellas UK discovering the problem (late November 2016) and completing a cross-check of SPCs against prescribing information (27 January 2017) was totally unacceptable. It appeared that Astellas Europe was not informed until late January and in early February Astellas Europe was updated with a list of products with prescribing information issues. The voluntary admissions were made in February. The Appeal Board did not consider that the explanation from Astellas including that neither Flomaxtra or Vesomni were actively promoted and therefore staff had not initially realised the seriousness of the situation and the difficulty of arranging meetings in December/ January justified the delay in taking appropriate action. In addition given the heightened focus on compliance arising from other issues faced by the companies, the Appeal Board considered that much greater priority should have been given to reviewing the materials and understanding the scale of the problems.**

**The Appeal Board noted that Astellas UK was currently suspended from membership of the ABPI in relation to matters arising in Case AUTH/2780/7/15. Astellas UK and Astellas Europe had each been audited in December 2015 and September 2016 and more recently in April 2017 which also covered the audit required in Case AUTH/2883/10/11.**
**The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, both companies should be publicly reprimanded for a lamentable lack of concern for patient safety and wholly inadequate oversight and control. The Appeal Board also decided to require an audit of both Astellas UK and Astellas Europe procedures in relation to the Code. The audits would take place in October 2017 and on receipt of the report, the Appeal Board would consider whether further sanctions were necessary.**

**The Appeal Board considered that these cases raised very serious matters due to the total failure of the companies' systems in relation to the control of prescribing information, the potential consequences for patient safety and the continuing nature of the failures over many years. In addition, given the level of scrutiny the companies were already under in relation to compliance, the Appeal Board was very concerned about the initial lack of urgency in conducting a full review and addressing any issues as set out above. Consequently, the Appeal Board decided that in accordance with Paragraph 12.1 of the Constitution and Procedure, both companies should be reported to the ABPI Board.**

**The ABPI Board noted the rulings of breaches of the Code in each case, the decisions of the Appeal Board regarding audits, and public reprimands in each case and that each case had been reported separately to the ABPI Board.**

**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 the number of job bags, the overall numbers 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.**

In Cases AUTH/2939/2/17 and AUTH/2940/2/17 Astellas UK and Astellas Europe respectively voluntarily admitted breaches of the Code with regard to the content of prescribing information for seven medicines promoted by Astellas in the UK. Astellas UK stated that the issue had the potential to impact certain Astellas Europe activities hence the joint voluntary admission.

Whilst the voluntary admission was made under the self-regulatory system, given the potential impact on patient safety, the companies had copied the letter to the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA was informed that the PMCPA was dealing with the matter as a complaint under the Code.

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. In addition to the clauses cited by Astellas, (Clauses 4.2, 9.1 and 2) the companies were also asked to consider the requirements of Clauses 4.1, 4.10 and 26.3 of the Code.

**VOLUNTARY ADMISSION**

Astellas stated that the issues highlighted related to prescribing information only, and not to the content of any summaries of product characteristics (SPC) or patient information leaflets (PIL) for any Astellas medicine.

**Astellas UK**

**Background**

Astellas UK stated that in late November 2016, the Zinc copy approval system raised an alert that the prescribing information for Flomaxtra XL (tamsulosin hydrochloride) was due for routine re-approval. During the review process, and taking account of the requirements of Clause 4.2 of the Code (which required 'a succinct statement of common adverse reactions….serious adverse reactions…'), one of Astellas UK's medical signatories noticed that at least one adverse reaction contained within the Flomaxtra XL SPC (Stevens–Johnson syndrome) which should be categorised as serious had not thus far been included in the prescribing information.

The issue was initially thought to be isolated to the prescribing information for one medicine, omitting three serious adverse reactions (Stevens-Johnson syndrome, syncope and priapism).

However, a thorough investigation conducted in December 2016 and January 2017 (as detailed below) identified the breadth of the issue, including the impact on Astellas Europe. Astellas Europe was informed of the issue in February 2017, at which point it began its own review (see below).

**Current process for development and revision of UK prescribing information**

Astellas UK standard operating procedure (SOP) 1000, Control of New and Changed Products, covered the process up to and including the circulation of an approved SPC following a new product launch or update of the SPC following a variation. Once the approved SPC had been circulated by the Astellas UK regulatory team, the Astellas UK medical information department was responsible for constructing or revising the prescribing information and submitting this to the relevant Astellas UK medical affairs and/or commercial teams for review and approval in Zinc.

The MedInfo Manual entitled 'How to write Prescribing Information M16' (effective February 2014) was used to support the development and updating of prescribing information. Prior to this, there was no formal guidance on how to develop prescribing information, other than the requirements listed in Clause 4.2. The MedInfo Manual M16 did not provide guidance on how to categorise adverse reactions as serious.

**Investigation**

The companies stated that the SPCs listed side effects in accordance with their reported frequency and not with regard to their seriousness. For the purposes of this investigation, and in order to carry out a wider look at seriousness categorisation for adverse reactions in the SPCs, and hence their inclusion in the prescribing information, it was agreed with Astellas Global Pharmacovigilance colleagues that the EudraVigilance Expert Working Group publication entitled Important Medical Event Terms List (IME list), based on MedDRA version 19.1 would be the reference document. The review was conducted on all Astellas medicines currently promoted by Astellas UK, namely Advagraf, Betmiga, Dificlir, Modigraf, Mycamine, Prograf, Qutenza, Vesicare and Xtandi. The review also revealed that in addition to the inconsistent categorisation around seriousness, there were a number of incidences of common adverse reactions, as well as warnings and precautions, which had not been included in the prescribing information.

It became clear during the review that there had been inconsistency in ownership of the construction of the original prescribing information in Astellas UK. In those circumstances where Astellas UK had documented the development of the original prescribing information through the Zinc approval system, these products (Betmiga, Xtandi, Dificlir and Qutenza) had been unaffected by the omissions described. For the affected products, it was unclear as to whether the original prescribing information was developed by Astellas UK.

However, the process for the approval of revised prescribing information had been erroneously

confined to the review of the information that had been revised, rather than incorporating a full review of the prescribing information every time. Thus, if the prescribing information was incomplete from the outset, this was not picked up at subsequent revisions.

**Corrective action**

As an immediate action, the prescribing information and all promotional items for the Astellas medicines promoted that had incomplete prescribing information (Flomaxtra, Vesomni, Vesicare, Advagraf, Prograf, Modigraf and Mycamine) had been withdrawn. As an interim measure, the SPC would be used in the UK in lieu of Clause 4.2 (i) to (viii), supplemented with the legal classification and the cost. This interim solution would remain in place until a revised process for the development, approval and subsequent revision of prescribing information was drafted and implemented, to include a thorough review of prescribing information from the outset as well as at every revision; guidance on categorisation of adverse reactions would also be included.

**Astellas Europe**

**Background**

Astellas Europe was the regional headquarters for Europe, Middle East and Africa (EMEA), based in the UK, and therefore operated differently to Astellas UK with regards to the creation of promotional material and use of prescribing information. Astellas Europe created regional template promotional materials for adaption according to local law or codes of practice ie materials would be reviewed and adapted for local use by the relevant affiliate eg Astellas UK in the UK.

There were some materials and activities that were produced and implemented by Astellas Europe directly ie not executed locally by affiliates. These included congress symposia, congress booths, pan-European stand-alone meetings and journal advertisements/supplements. These used Astellas Europe generated/adapted prescribing information as outlined below, unless local rules necessitated otherwise eg stricter rules might apply in a country where a congress was held, or where a journal advertisement or supplement was published.

**Current process for development and revision of UK prescribing information**

Astellas Europe, medical affairs had assumed responsibility for updating prescribing information when it became aware of SPC updates. Historically each brand team had taken a slightly different approach, and had either used the UK prescribing information as a basis and adapted that, together with a supplementary adverse event reporting statement, or prepared their own European/EMEA version of prescribing information.

Subsequent to the Astellas UK investigation, a review of prescribing information and promotional materials generated by Astellas Europe had been initiated (see below).

Astellas Europe was notified of this issue in February 2017. It had a supportive tool (STL-1793 and parent document SOP 256 Review and Approval of Materials or Activities (Zinc)), which outlined the requirements for prescribing information at an EMEA regional headquarters level.

Astellas Europe had no formal written process around the development and revision of prescribing information and had not routinely been notified about prescribing information updates. The same lack of guidance around categorisation of seriousness applied equally to Astellas Europe.

There had been no consistent approach to the approval process across brands and the process was not well defined. Astellas recognized that this needed to be, and was working to ensure that the process was, robust and consistent.

**Investigation**

A review was undertaken of serious and common adverse events, contraindications, warnings and precautions in the active Astellas Europe prescribing information for Advagraf, Betmiga, Dificlir, Modigraf, Prograf, Qutenza, Vesomni, Vesicare and Xtandi. This review had identified omissions in the Astellas Europe prescribing information for Vesomni and Vesicare. An analysis of these omissions was provided.

There was no active Astellas Europe prescribing information for Mycamine. There were no omissions with respect to serious and common adverse events, contraindications, warnings and precautions in the active Astellas Europe prescribing information for Advagraf, Betmiga, Dificlir, Modigraf, Prograf, Qutenza, and Xtandi.

For completeness, a full retrospective analysis of Astellas Europe prescribing information was underway to be completed by the end of February.

A review had been undertaken of all the active Astellas Europe promotional material for Advagraf, Betmiga, Dificlir, Modigraf, Mycamine, Prograf, Qutenza, Vesomni, Vesicare and Xtandi to identify if any materials needed to be recalled, the results of which were provided.

As an immediate action the active prescribing information for Vesomni and Vesicare and the identified promotional materials were recalled (initiated on 20 February 2017 completed by 24 February 2017).

**Astellas UK and Astellas Europe**

**Preventative action**

The companies submitted that it was clear that Astellas required a robust, consistent and reproducible process for the generation of prescribing information in accordance with the Code. This involved a collaborative approach with global colleagues. This discussion had already started and a cross-functional task force formed to work on a revised process.

**Code Clauses**

The companies submitted that there had been seven breaches of Clause 4.2 (there were issues with the prescribing information for seven medicines). In addition, Astellas UK and Astellas Europe acknowledged that the deficiencies in their processes which related to the consistent inclusion of the relevant safety information in the prescribing information of these products represented a failure to maintain high standards, in breach of Clause 9.1. Given that such omissions had the potential to impact patient safety, the companies considered the issues uncovered were contrary to the requirements of Clause 2 and in that regard they had sent a copy of the voluntary admission to the MHRA.

The companies submitted that they were treating this issue with the utmost seriousness; they recognized the gravity of the situation that had been uncovered by the investigation and were addressing it as a priority.

**RESPONSE ASTELLAS UK**

Astellas UK pointed out that it only implemented the use of Zinc for approval of material in 2009, therefore the lists of the revisions to prescribing information and certificates and the lists of materials effected and withdrawn only went back as far as that date.

In relation to the products that were unaffected by the issue of incomplete prescribing information (Betmiga, Xtandi, Dificlir and Qutenza), Astellas UK submitted it was confident that there were no serious or common adverse events missing from the relevant prescribing information and that precautions and warnings reflected the substance of the relevant SPC. Although Qutenza was approved on 15 May 2009, its first marketing/commercial launch occurred only on 15 June 2010 and thus no prescribing information was produced in 2009.

As outlined above, Astellas UK submitted that there had been seven breaches of Clause 4.2 (there were issues with the prescribing information for seven medicines). The company understood that if prescribing information failed to meet the requirements of Clause 4.2 it was ruled in breach of Clause 4.1. Therefore Astellas UK considered there had been multiple breaches of Clause 4.1. In addition, the company acknowledged that the deficiencies in its process which related to the consistent inclusion of the relevant safety information in the prescribing information of its products represented a failure to maintain high standards, in breach of Clause 9.1. Given that such omissions had the potential to impact on patient safety, the issues uncovered were contrary to the requirements of Clause 2. Astellas UK had no further comment with regard to Clauses 4.2, 9.1 and 2, to add to those above.

With regard to Clauses 4.10 and 26.3 and the Authority's view that these clauses were relevant as the Astellas UK review of prescribing information noted a failure to include an inverted black triangle, Astellas UK routinely placed the black triangle on the prescribing information for products where additional monitoring was required. However, the inverted black triangle was also placed adjacent to the most prominent display of the product name. Therefore Astellas UK submitted there was no breach of either Clauses 4.10 or 26.3 if the black triangle was omitted from the prescribing information.

**RESPONSE ASTELLAS EUROPE**

The initial review undertaken by Astellas Europe focused on serious and common adverse events, contraindications, warnings and precautions in the active Astellas Europe prescribing information for Advagraf, Betmiga, Dificlir, Modigraf, Prograf, Qutenza, Vesomni, Vesicare and Xtandi. This review identified omissions in the Astellas Europe prescribing information for Vesomni and Vesicare. An analysis of these two products was then expanded retrospectively and provided previously.

A wider retrospective analysis had now been conducted by Astellas Europe on the UK licensed products promoted by Astellas Europe, namely Advagraf, Betmiga, Dificlir, Modigraf, Mycamine, Prograf, Qutenza, Vesicare and Xtandi. The review of prescribing information focused on serious and common adverse events, contraindications and warnings and precautions, but not the inclusion of the black triangle. The presence of an inverted black triangle on prescribing information was not a requirement of the Code *per se* (the Code required that promotional material and product related material for patients contained a black triangle).

The result of the Astellas Europe retrospective review was provided. The prescribing information was mainly generated on a needs basis as it was usually used for one-off congress items. The retrospective analysis for each product was conducted by the individual brand teams to ensure the history behind each update could be included in the spreadsheet.

The review revealed that in addition to the inconsistent categorisation around seriousness, there were a number of incidences of common adverse reactions, as well as warnings and precautions, which had not been included in the prescribing information.

This retrospective review identified omissions in the Astellas Europe prescribing information for Vesomni, Vesicare, Mycamine and Qutenza at various stages of their lifecycle:

- An analysis of the omissions for Vesomni and Vesicare was provided previously and was included as part of the full analysis below.
- There was no active Astellas Europe prescribing information for Mycamine but retrospective review showed there were earlier omissions in the prescribing information.
- Whilst no omissions were seen in the active Astellas Europe prescribing information for Qutenza, the retrospective review showed earlier omissions in the prescribing information.
- There were no omissions with respect to serious and common adverse events, contraindications,

warnings and precautions in the active and retrospective Astellas Europe prescribing information for Advagraf, Betmiga, Dificlir, Modigraf, Prograf, and Xtandi.

As an immediate action the active prescribing information for Vesomni and Vesicare was recalled as notified in the voluntary admission.

Astellas Europe noted that it only implemented the use of Zinc for approval of material in 2010, therefore the revisions to the prescribing information, lists of material effected (those produced by Astellas Europe directly ie, not executed locally by affiliates) and the lists of Astellas Europe materials withdrawn only went back as far as then.

As outlined above, Astellas Europe submitted that there had been four breaches of Clause 4.2 (there were issues with the prescribing information for four medicines). The company understood that if prescribing information failed to meet the requirements of Clause 4.2 it was ruled in breach of Clause 4.1. Therefore, Astellas Europe considered that there had been multiple breaches of Clause 4.1. In addition, the company acknowledged that the deficiencies in its process which related to the consistent inclusion of the relevant safety information in the prescribing information of the products represented a failure to maintain high standards, in breach of Clause 9.1. Given that such omissions had the potential to impact on patient safety, the issues uncovered were contrary to the requirements of Clause 2.

With regard to Clauses 4.10 and 26.3 and the Authority's view that these clauses were relevant as the Astellas Europe review of prescribing information noted a failure to include an inverted black triangle, Astellas Europe stated it was aware of the requirement to place it adjacent to the most prominent display of the product name. Therefore Astellas Europe submitted there was no breach of either Clause 4.10 or 26.3 if the black triangle was omitted from the prescribing information.

**PANEL RULING**

The Panel was extremely concerned that incomplete prescribing information had been used by the companies for a number of years. It noted the companies' submissions that the omissions from the Astellas UK prescribing information included serious adverse reactions as well as common adverse reactions, warnings and precautions. The omissions from the Astellas Europe prescribing information included inconsistent categorisation around seriousness as well as common adverse reactions, warnings and precautions. The Panel was also very concerned that the systems at both companies had not picked up the errors sooner.

The Panel noted that both Astellas UK and Astellas Europe had withdrawn current materials with incomplete prescribing information. These being Astellas UK materials for Flomaxtra, Vesomni, Vesicare, Advagraf, Prograf, Modigraf and Mycamine. The Astellas Europe materials related to Vesomni and Vesicare. In addition Astellas Europe had identified omissions in previous versions of the prescribing information for Mycamine and Qutenza.

The Panel was also concerned that large numbers of materials with incomplete prescribing information had been used for a number of years.

**Case AUTH/2939/2/17 Astellas UK**

The Panel ruled breaches of Clause 4.1 in relation to each of the seven Astellas UK products with incomplete prescribing information. High standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel considered that the failures brought discredit upon and reduced confidence in the pharmaceutical industry. It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about their medicines. A breach of Clause 2 was ruled.

With regard to the use of the black triangle, the Panel noted Astellas UK's submission that in addition to the requirements of the Code regarding the placing of the black triangle on promotional material (Clause 4.10) and information to the public (Clause 26.3) it routinely placed the black triangle on the prescribing information for products where additional monitoring was required. The company submitted that it was the additional black triangle on the prescribing information that had been omitted and which was highlighted in the company's review. The Panel noted that Astellas UK denied a breach of Clauses 4.10 and 26.3. The Panel accepted Astellas UK's submission in relation to the omission and thus ruled no breach of Clauses 4.10 and 26.3.

**Case AUTH/2940/2/17 Astellas Europe**

The Panel ruled breaches of Clause 4.1 in relation to each of the four Astellas Europe products with incomplete prescribing information. High standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel considered that the failures brought discredit upon and reduced confidence in the pharmaceutical industry. It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about their medicines. A breach of Clause 2 was ruled.

The Panel noted that Astellas Europe pointed out that it was not a breach of Clauses 4.10 and 26.3 if the black triangle was omitted from the prescribing information. The Panel accepted Astellas Europe's submission and thus ruled no breach of Clauses 4.10 and 26.3.

The Panel was extremely concerned about its 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 prescribing information had been very poor. 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 both Astellas UK and Astellas Europe to the Appeal Board for it to consider whether further sanctions were appropriate.

**COMMENTS FROM ASTELLAS UK AND ASTELLAS EUROPE ON THE REPORT FROM THE PANEL**

Astellas UK and Astellas Europe fully accepted and agreed with all of the Panel's rulings. The companies were extremely disappointed to be in such a position. This was the second time in a short period of time that Astellas had been found in breach of the Code in relation to issues that might impact patient safety. The companies sincerely apologised for the failures highlighted. The companies noted the Panel's comments that their oversight of prescribing information had been poor and that some of the matters in this case went to the heart of self-regulation and patient safety. Both companies were committed to take all necessary action to raise their standards to address these matters.

Astellas had now initiated an assessment of processes relevant to the updating of prescribing information following the issue of, or change to, an SPC in all affiliates across the EMEA region.

Astellas Pharma Europe provided a report by its solicitors who carried out investigations into the recent voluntary admissions.

At the consideration of the report the representatives from Astellas UK and Astellas Europe stated that they sincerely apologised for the issues that led to these cases. The companies were extremely disappointed to be in this position; both organisations had worked very hard to address issues in relation to the companies' culture and processes during the last 12 months but clearly these cases had set them back significantly.

Astellas submitted that patient safety was a priority and it recognised that it was completely unacceptable to put this at risk. Astellas had initiated a review and validation of all processes relevant to the updating of prescribing information following the issue of, or change to, an SPC. In addition, Astellas had started new projects to improve 'third party vendor management' as well as 'patient support programmes' within its existing corrective and preventative action (CAPA) work streams. The objective was to put in place a robust and consistent process to ensure compliance with all relevant internal and external standards. Astellas was committed to achieve this as its first priority.

**APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL**

The Appeal Board noted that these cases had arisen from a voluntary admission by Astellas UK and Astellas Europe and that the companies had accepted all the rulings of breaches of the Code including Clause 2. The Appeal Board also noted that Astellas sincerely apologised for the failings. However, the Appeal Board noted the Panel's comments and rulings above.

The Appeal Board considered that these cases raised serious concerns about multiple failings and a complete lack of control. The lack of processes with regard to updating prescribing information was shocking. The Appeal Board considered the companies' failure to ensure that prescribing information was accurate and complete was totally unacceptable and that such failings raised very serious concerns with regard to patient safety. The Appeal Board considered that given the importance of patient safety, this issue should have been an absolute priority. The amount of time that had elapsed between Astellas UK discovering the problem (which according to the solicitor's report was late November 2016) and completing a cross-check of SPCs against prescribing information (27 January 2017) was totally unacceptable. It appeared that Astellas Europe was not informed until late January and in early February Astellas Europe was updated with a list of products with prescribing information issues. The voluntary admissions were made in February. The Appeal Board did not consider that the explanation from the Astellas representatives including that neither Flomaxtra or Vesomni were actively promoted and therefore staff had not initially realised the seriousness of the situation and the difficulty of arranging meetings in December/January justified the delay in taking appropriate action. In addition given the heightened focus on compliance arising from other issues faced by the companies, the Appeal Board considered that much greater priority should have been given to reviewing the materials and understanding the scale of the problems.

The Appeal Board noted that Astellas UK was currently suspended from membership of the ABPI in relation to matters arising in Case AUTH/2780/7/15. Astellas UK and Astellas Europe had each been audited in December 2015 and September 2016 and more recently in April 2017 which also covered the audit required in Case AUTH/2883/10/11.

The Appeal Board noted that it had to consider the reports and whether to impose additional sanctions in Cases AUTH/2939/2/17 and AUTH/2940/2/17, on the evidence before it and independently of the other matters involving Astellas. The report of the April 2017 re-audits was to be considered by the Appeal Board shortly and by the ABPI Board in June 2017 when it would review the suspension of Astellas UK from membership of the ABPI.

The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, both companies should be publicly reprimanded for a lamentable lack of concern for patient safety and wholly inadequate oversight and control. The Appeal Board also decided to require an audit of both Astellas UK and Astellas Europe procedures in relation to the Code. The audits would take place in October 2017 and on receipt of the report, the Appeal Board would consider whether further sanctions were necessary.

The Appeal Board considered that these cases raised very serious matters due to the total failure of the companies' systems in relation to the control of prescribing information, the potential consequences for patient safety and the continuing nature of the failures over many years. In addition, given the

level of scrutiny the companies were already under in relation to compliance, the Appeal Board was very concerned about the initial lack of urgency in conducting a full review and addressing any issues as set out above. Consequently, the Appeal Board decided that in accordance with Paragraph 12.1 of the Constitution and Procedure, both companies should be reported to the ABPI Board.

**ABPI BOARD CONSIDERATION OF THE REPORT FROM THE APPEAL BOARD**

The ABPI Board noted the rulings of breaches of the Code in each case, the decisions of the Appeal Board regarding audits, and public reprimands in each case and that each case had been reported separately to the ABPI Board.

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 the number of job bags, the overall numbers 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.

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| **Voluntary Admission received** | **22 February 2017** |
| **Undertaking received** | **25 April 2017** |
| **Appeal Board Consideration** | **25 May 2017, 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** | **23 June 2017** |
| **Case completed** | **22 May 2019** |