CASE AUTH/3123/11/18

OTSUKA EMPLOYEE v OTSUKA EUROPE

Updating prescribing information

An Otsuka employee complained that Otsuka Europe was not transparent in its response to the PMCPA regarding Case AUTH/3041/6/17, which was in relation to summary of product characteristics (SPC) and prescribing information updates from 2017 for Jinarc (tolvaptan, used in chronic kidney disease), Samsca (tolvaptan, used in hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion) and Abilify (aripiprazole, used in schizophrenia). Abilify Maintena was a prolonged-release injectable formulation of aripiprazole.

The complainant stated that he/she was part of the team remediating the process for SPC and prescribing information updates and when Otsuka provided its response to the PMCPA in June 2018 it had failed to disclose audit reports (copies of which were provided) and in doing so, was not transparent.

There had been issues with the flow of SPC changes from 2016 when the initial audit reports were done. The audits highlighted the lack of oversight at a European and Global level and it was extremely worrying that very senior leaders within the European and Global organisations had been aware of this issue and had failed to correct it.

Although the response to the PMCPA was sent almost 6 months ago, the new standard operating procedure (SOP) on SPC distribution across Europe had just been released to the organisation and during this time the affiliates and distributor partners were left confused as there was no consistent, clear communication around SPC changes. This was due to the guidance document that was issued in June 2018 and the reissue of SOP 'MA002' a few weeks later; both documents did not provide clear guidance on the process.

The complainant was dismayed that the issue had been allowed to continue since 2016 and possibly longer given the audit reports. It was unacceptable that the issue was highlighted again in November 2017 and it had taken the European organisation 12 months to partly remediate.

The complainant clarified that his/her complaint was against Otsuka Europe and not Otsuka UK. Otsuka UK had initially identified the issue and had been remediating promptly and would have had no visibility of the audit reports which were driven by Global Quality Assurance.

The detailed response from Otsuka Europe is given below.

Otsuka had given a combined response to Cases AUTH/3041/6/18 (Otsuka Europe) and AUTH/3042/6/18 (Otsuka UK) which were both ongoing at the time the current complaint, which was against Otsuka Europe only, was received.

The Panel noted that Case AUTH/3041/6/18 concerned poor governance and lack of processes including the failure to communicate or update changes to the summary of product characteristics (SPC) and prescribing information from 2017 for Jinarc, Samsca and Abilify.

The Panel noted that the complainant provided two internal reports which each covered pharmacovigilance and regulatory affairs: an audit of Otsuka Pharmaceutical Development and Commercialization Inc., US, in May 2016 and an audit of Otsuka Europe Development and Commercialisation Ltd in September 2016.

The Panel noted Otsuka's submission that at the time of its response to Cases AUTH/3041/6/18 and AUTH/3042/6/18, the actions required as a result of the two internal audit reports had been closed with all corrective and preventative actions (CAPAs) completed by April 2017. The Panel noted that for these previous cases, Otsuka had been asked to respond in relation to SPC changes from 2017 onwards, the time period identified in the complaint. The Panel noted that the governance standards in place at the company prior to 1 January 2017 might, nonetheless, be relevant when deciding whether Otsuka Europe had provided a complete response. Context was important.

The Panel noted that the May 2016 internal audit of Otsuka Pharmaceutical Development and Commercialisation had, *inter alia*, a major finding related to the lack of company oversight of the global labelling process. In addition, in relation to delays and non-conformities for processes to update labelling for Tolvaptan (2013) and Abilify (2015 and 2016) the auditors noted that users of the product might not have access to the most up-to-date information and this might result in non-compliance. The September 2016 internal audit of Otsuka Europe Commercialisation and Development had, *inter alia*, a critical finding in relation to the lack of company oversight of the overall labelling process and a major finding in relation to the submission, tracking and notification of labelling changes which were not in accordance with SOPs effective at that time.

In the Panel's view, such information was directly relevant to the subject matter of the previous case in question, Case AUTH/3041/6/18; it illustrated that there were relevant recent global governance issues and it would have been helpful if such information was provided by Otsuka in its response to that case.

The September 2016 internal audit report referred to the addition of anuria to Section 4.3 of the Jinarc SPC and the fact that timelines were not set initially. This Jinarc SPC update was referred to in Otsuka's response to Cases AUTH/3041/6/18 and AUTH/3042/6/18 and the Panel considered that the provision of this additional information from the September 2016 internal audit report would have been directly relevant.

The Panel noted that the September 2016 internal audit report contained CAPAs, some of which were not closed until April 2017, relevant to the time-period that Otsuka was discussing in its response to Case AUTH/3041/6/18. The Panel further noted Otsuka Europe's submission that it did not provide information to the PMCPA about incorrect

Abilify Maintena prescribing information that was detected by the Otsuka UK medical team in April 2018 which related to SPC changes from 2014. The Panel considered that although this related to SPC changes prior to 2017, and outside the time-period at issue in Case AUTH/3041/6/18, the error was detected within the time-period relevant to that complaint and was therefore pertinent.

In the Panel's view, relevant information from the internal audit reports ought to have been disclosed. The Panel was concerned that the company's response to the previous complaint implied that the company first became aware of relevant compliance matters further to a concern raised by an employee in November 2017 stating that '*since then*', corrective and preventative measures had been put in place. This statement was misleading and not a true reflection of the company's compliance position. Noting its comments above, the Panel considered that Otsuka Europe had failed to maintain high standards by not supplying all the relevant information in its response to Case AUTH/3041/6/18 and a breach of the Code was ruled.

The Panel noted that it was clear that senior staff at Otsuka Europe were aware of the compliance difficulties; certain senior staff were named as being present during the audit. The Panel noted Otsuka Europe's submission that, despite a huge amount of work and with the best intentions, employees and third parties were confused by the inconsistent dates and timelines introduced between June and October 2018. The Panel further noted Otsuka Europe's submission that it had taken too long to update the relevant SOP and train employees on the new timelines and that it acknowledged that processes fell short of expected high standards at least as far back as 2014. The Panel considered that Otsuka Europe's lack of clear and consistent instructions to employees and third parties meant that Otsuka Europe had failed to maintain high standards as alleged and a breach of the Code was ruled.

The Panel noted that Otsuka Europe had referred to an initial concern being raised in November 2017, but it appeared to the Panel that there were issues identified in the internal audits prior to this. The Panel noted that Otsuka Europe had taken steps to attempt to remediate some of the issues identified in Cases AUTH/3041/6/18 and AUTH/3042/6/18 and noted the company's detailed submission in this regard.

In the Panel's view, inadequacies in the process had been present since at least as far back as 2014 and had still not been fully corrected despite internal audits, concerns being raised internally and a complaint to the PMCPA. Otsuka Europe had failed to timely and robustly address inadequacies in a critical process that had the potential to impact patient safety. That it had failed to do so brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

The Panel noted that the compliance messages and behaviours of global and European functions would directly impact local compliance behaviours. That the internal audits of global and European functions had uncovered serious compliance failings that had the potential to impact patient safety was a serious matter. Although it appeared that Otsuka Europe was now trying to address the issues in question, the Panel considered that the further information disclosed in this case highlighted that the magnitude of the compliance issues at Otsuka Europe, and that impacted on Otsuka Europe, were greater than apparent in Case AUTH/3041/6/18. For all the reasons outlined above, the Panel considered that this Case warranted reporting Otsuka Europe to the Appeal Board under

Paragraph 8.2 of the Constitution and Procedure for the Appeal Board to consider in relation to Paragraph 11.3 of the Constitution and Procedure.

The Appeal Board noted the Panel's comments and rulings of breaches of the Code in Case AUTH/3123/11/18, including its decision to report Otsuka Europe to the Appeal Board. The Appeal Board noted that Otsuka Europe had provided detailed information about its compliance difficulties and it had apologised.

The Appeal Board noted the timelines provided showing European remediation to date from March 2018. It appeared from questioning the company representatives that little activity had taken place following the internal audit in September 2016 and when the issue was raised internally in November 2017. It was only after the complaint was made to the PMCPA in June 2018 that action was taken. This raised concerns about how seriously the company took the issue, its impact on patient safety and the culture at Otsuka. The company representatives stated that the delay was due to a lack of understanding of the seriousness and importance of the process. There was a lack of communication across the company. Senior leaders had apologised to employees. Speak-up processes had been introduced and more was shared about reporting incidents.

The Appeal Board noted the company's submission that it recently had another internal audit of its end-to-end processes and it was awaiting that report. The company representatives referred to the CORE programme which started in February 2019 led by the UK. The CORE programme had 4 elements; culture and compliance, one organisation, ready for audit and everybody was responsible for compliance. The company representatives also referred briefly to other issues identified mentioning meetings and congresses. These would be prioritised. Otsuka UK referred to a new meetings process.

The Appeal Board was also concerned that Otsuka Europe had neither referred to nor provided the relevant internal audits of global and European functions in its response to Case AUTH/3041/6/18.

The Appeal Board was very concerned that an overall failure of governance in relation to Otsuka Europe's processes in implementing SPC changes, updating prescribing information and updating and withdrawing promotional materials in a timely manner had potential patient safety implications. It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about its medicines. The Appeal Board noted Otsuka Europe's submission that it was now putting systems and processes in place to address these issues. The Appeal Board noted the scale of the task but queried whether this was being done sufficiently quickly given the seriousness of the matter.

The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Otsuka Europe should be publicly reprimanded for the failures to implement SPC changes and update impacted materials in a timely manner which had potential to impact patient safety. The Appeal Board also decided to require an audit of Otsuka Europe's procedures in relation to the Code in the present case to take place by mid July 2019. This audit would take place at the same time as those required in Cases AUTH/3041/6/18 (Otsuka Europe) and Case AUTH/3042/6/18 (Otsuka UK). On receipt of

the report of the audit the Appeal Board would consider whether further sanctions were necessary.

On receipt of the report for the July 2019 audits the Appeal Board was very concerned to note the extent of the companies' failings including that there was a systemic lack of governance shown by the failure to take action in these cases. Leadership and communication needed to be improved urgently. The governance from Japan to Europe and from Europe to UK needed huge improvement. There appeared to be longstanding failures in this regard, particularly in relation to holding senior individuals to account.

The Appeal Board noted that the report of the audits highlighted a number of concerns including that existing senior staff needed to improve their knowledge and leadership on compliance matters, engage with and ensure that all staff understood its importance. Staff should be helped and encouraged to improve their skills in relation to matters covered by the Code. Significant commitment was required to address the issues.

The Appeal Board noted from the report of the audits that Otsuka Europe had not provided accurate information about the training of the SOPs to the Appeal Board in March 2019 when the reports from the Panel were considered. The Appeal Board noted that self-regulation relied upon, *inter alia*, the provision of complete and accurate information from pharmaceutical companies. The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Otsuka Europe should be publicly reprimanded for providing inaccurate information to the Appeal Board.

The Appeal Board noted Otsuka's compliance plan and decided that Otsuka should provide a detailed written account of its progress by the end of November 2019. It was vital that swift comprehensive action was taken and noting the failure to take appropriate action over a long period of time, the Appeal Board considered that given the exceptional circumstances of this matter, including the scale and seriousness of the difficulties at Otsuka, it would be helpful if Otsuka representatives attended the December 2019 meeting of the Appeal Board to discuss the progress and future plans. The Appeal Board noted that both Otsuka Europe and Otsuka UK had set themselves a number of compliance objectives and considered that sufficient time would be needed for these to be completed in order for any meaningful progress to be assessed. The Appeal Board decided that both Otsuka Europe and Otsuka UK should be re-audited in early 2020. At its meeting in December the Appeal Board would decide the timing of the re-audits and on receipt of the report for the re-audits it would decide whether further sanctions were necessary.

At its meeting in December 2019 representatives from Otsuka Europe and Otsuka UK attended to discuss the progress and future plans. The companies welcomed the opportunity to provide the Appeal Board and PMCPA with a written account of the activities conducted and progress made since receipt of the report of the audits. The Appeal Board noted that whilst there was a lot of work to be done, a number of activities and actions were completed, planned and/or in process. On the information before it the Appeal Board decided that the re-audits should take place in April 2020 at which point it expected substantial improvements. On receipt of the report for the re-audits it would decide whether further sanctions were necessary.

On receipt of the report for the April 2020 re-audits the Appeal Board noted the difficulties of conducting audits remotely and that there was little new activity due to the continuation of the 'pencils down'/'deprioritisation' policies. The Appeal Board considered that there had been some progress and it appeared that things were now heading in the right direction. There had been changes with new staff and new members of the Otsuka Board as well as additional resource for compliance and compliance objectives had been introduced. Key senior staff still needed to continue to develop their leadership on compliance. The Appeal Board noted that whilst most staff understood the reasons for the re-audits; it was concerned that some staff still did not. Otsuka UK and Otsuka Europe needed to continue to improve working relationships, including in and between the medical departments. It appeared that communication with Japan had improved. There was to be a staff survey in late 2020.

The Appeal Board noted that further improvement was required, the report of the re-audits highlighted a number of areas on which to focus.

The Appeal Board decided that Otsuka UK and Otsuka Europe should be re-audited in April 2021 at which point it also expected the companies to demonstrate continued progress and improvement. On receipt of the of the report for the re-audits the Appeal Board would decide whether further sanctions were necessary.

On receipt of the report for the April 2021 re-audits the Appeal Board noted that there had been some further progress and it appeared that matters were continuing to head in the right direction. However, the Appeal Board considered that the pace of improvement needed to accelerate. Otsuka UK and Otsuka Europe needed to continue to improve working relationships, including in and between the medical departments. Senior staff needed to work together to continue to improve their knowledge and leadership on compliance. The Appeal Board noted that further improvement was required, the report of the re-audits highlighted a number of areas on which to focus. The Appeal Board decided that Otsuka UK and Otsuka Europe should be re-audited in December 2021/January2022 at which point it expected the companies to demonstrate continued progress and embedded improvement. On receipt of the report for the re-audits the Appeal Board would decide whether further sanctions were necessary.

On receipt of the report for the January 2022 re-audits the Appeal Board noted that Otsuka had continued to build on the improvements described in the report of the 27 and 28 April 2021 re-audits. It was important that progress on company culture continued such that there was a team approach both within each company and between each company.

The Appeal Board noted that the report of the January 2022 re-audits still highlighted work to be done and it was important that these were addressed.

The Appeal Board considered that from the report of the January 2022 re-audits it appeared that there had been further progress. The Appeal Board was concerned that it had taken 4 audits/re-audits to get to this stage.

The Appeal Board noted that Otsuka had a compliance CORE tracker to address recommendations from the re-audits. On the basis that this work was completed, the

progress shown to date was continued and commitment to compliance was maintained, the Appeal Board decided that no further action was required.

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COMPLAINT

The complainant stated that he/she was part of the team remediating the process for SPC and prescribing information updates and when Otsuka provided its response to the PMCPA in June 2018 it had failed to disclose audit reports (copies of which were provided) and in doing so, was not transparent.

There had been issues with the flow of SPC changes from 2016 when the initial audit reports were done. The audits highlighted the lack of oversight at a European and Global level and it was extremely worrying that very senior leaders within the European and Global organisations had been aware of this issue and had failed to correct it.

Although the response to the PMCPA was sent almost 6 months ago, the new standard operating procedure (SOP) on SPC distribution across Europe had just been released to the organisation and during this time the affiliates and distributor partners were left confused as there was no consistent, clear communication around SPC changes. This was due to the guidance document that was issued in June 2018 and the reissue of 'MA002' a few weeks later; both documents did not provide clear guidance on the process.

The complainant was dismayed that the issue had been allowed to continue since 2016 and possibly longer given the audit reports. It was unacceptable that the issue was highlighted again in November 2017 and it had taken the European organisation 12 months to partly remediate.

The complainant clarified that his/her complaint was against Otsuka Europe and not Otsuka UK. Otsuka UK had initially identified the issue and had been remediating promptly and would have had no visibility of the audit reports which were driven by Global Quality Assurance.

When writing to Otsuka Europe the Authority asked it to consider the requirements of Clauses 9.1 and 2 of the Code.

RESPONSE

Otsuka Europe stated that there appeared to be four main concerns to address:

1 That Otsuka was 'not transparent in its actions' in response to Case AUTH/3042/6/18 in that it failed to disclose two internal audit reports.
2 Senior leaders within the Global and European organisations were aware of 'the issue with the flow of the SmPC changes' and had failed to correct it.

3 It took too long to revise the SOP on 'SmPC distribution across Europe'.
4 There was a period of confusion for affiliate and distributor partners due to 'no consistent, clear communication around SmPC changes'.

Since November 2017 when this issue was originally identified, Otsuka Europe had been engaged in a remediation program as originally described in its response to Case AUTH/3042/6/18. Otsuka Europe was assessing and continuously improving its controls. Otsuka Europe stated that although it fully respected employees' choices to raise concerns through external channels, it also encouraged them to raise the concerns through its SpeakUp! Line or other internal mechanisms to provide the company an opportunity to look into and address them.

Otsuka Europe submitted that the internal audit reports the PMCPA received were incomplete and therefore inaccurate as they did not contain the Corrective and Preventive Actions (CAPA) records.

Otsuka Europe responded to each of the complainant's concerns.

1 Otsuka was 'not transparent in its actions' in response to Case AUTH/3042/6/18, specifically related to two internal audit reports.

When Otsuka prepared its response, the actions required as a result of the two internal audit reports referred to by the complainant had been closed with all CAPAs complete in December 2016 and April 2017. The response given in Case AUTH/3042/6/18 focused on the period requested, January 2017 to June 2018, and the issue identified by the complainant, that being that the processes for clear and consistent communication of updates to summaries of product characteristics (SPCs) to affiliates and third parties fell short of expected high standards as acknowledged in the company's response.

Otsuka Europe stated that the two internal audit reports provided by the complainant to the PMCPA were incomplete. During the joint Otsuka Europe/Otsuka UK preparation for its response in Case AUTH/3042/6/18, these audits were discussed at a high level, but no member of the response team stated that they believed it was important to include the reports in its response. Therefore, a discussion to include or not include these reports did not take place. It was not customary practice to provide internal audit reports outside the company, as they were confidential documents. However, due to the nature of this complaint, it provided the complete audit reports including all investigations, root cause analyses and CAPAs to facilitate the Panel's review. Additionally, Otsuka Global Regulatory Affairs was recently re-audited by the same auditor that conducted the internal audits in 2016 (complete 2016 reports and the 2018 report provided).

Otsuka Europe submitted that, for additional transparency, its prior response in Case AUTH/3042/6/18 focused only on the period from 1 January 2017 to June 2018; and analysed the timing and flow of changes to prescribing information, materials and electronic medicines compendium (eMC) resulting from the SPC changes made during this period. The previous response therefore did not include the SPCs and the prescribing information for Abilify Maintena during prior periods. During the preparation of the response to Case AUTH/3042/6/18 the below further issues were raised by Otsuka UK, which related to SPC changes made prior to 1 January 2017 and outside the period of the request.

In its response to Case AUTH/3042/6/18, Otsuka did not explicitly state that Abilify Maintena prescribing information was incorrect prior to January 2017, as demonstrated in the Master Abilify v3 document created as part of the June 2018 response effort (copy provided). In April 2018 a member of the UK medical team detected two earlier changes to the SPC which had not been incorporated into the UK prescribing information: the addition of diplopia as an uncommon adverse event which was communicated on 30 October 2014; and a warning statement advising against the use of Abilify Maintena in case of severe attacks of psychosis requiring immediate symptom control which was communicated on 3 February 2016.

Otsuka Europe submitted that it was raised during its response in Case AUTH/3042/6/18 that there were two versions of prescribing information for Abilify Maintena from April 2016 to no later than 31 August 2018, when a single prescribing information for Abilify Maintena was used in support of its 5-year renewal. Otsuka Europe's version of the prescribing information included the 3 February 2016 warnings on the use of Abilify Maintena in case of severe psychotic attacks while Otsuka UK's version did not. Otsuka Europe and Otsuka UK reached different conclusions regarding the medical necessity of including the SPC change in the prescribing information (a copy of the Otsuka Europe prescribing information from April 2016 and the four versions of the Otsuka UK prescribing information during the period August 2014 to December 2018 were provided). The Otsuka Europe version of the prescribing information did not contain a job bag number and Otsuka Europe could not locate it in Zinc therefore it could not be demonstrated to have been independently approved until 31 August 2018.

Otsuka Europe submitted that the process described in EU-SOP-MA-002 in effect at this time did not meet high standards, and in this specific case clearly did not provide guidance on the process to generate, review, and approve prescribing information using a consistent, repeatable process across Europe. As explained in its response to Case AUTH/3042/6/18, the creation of a common European prescribing information was now handled centrally under the responsibility of Otsuka Europe, which certified and then distributed prescribing information to affiliates, such as Otsuka UK, for local implementation.

2 Senior leaders within the Global and European organisations were aware of 'the issue with the flow of the SmPC changes' and have failed to correct it

Otsuka Europe submitted that the complainant was referring to senior leaders being aware of the issues identified in the two 2016 internal audits and failed to address them; Otsuka Europe refuted the allegation that issues were known but not corrected. Both audits and for all findings, root cause analyses were performed and CAPAs implemented and closed by April 2017.

3 It took some time to revise the SOP on 'SmPC distribution across Europe'

Otsuka Europe agreed that it had taken too long to update EU-SOP-MA-002 'Notification by OPEL of Changes to SPC and PIL to the OPEL Affiliates'. As indicated in the response in Case AUTH/3042/6/18, an internal concern was raised in November 2017 by Otsuka UK and in response a task force was formed in February 2018 with cross-functional representation from senior management. Subsequent to its response in Case AUTH/3042/6/18, the team had endeavoured to improve oversight of the implementation of changes to an SPC on all levels. A summary of the steps taken following its response in Case AUTH/3042/6/18 was provided:

- The Guidance Document 'Process and timelines for OPEL[Otsuka Europe] and affiliates to implement updates to Summary of Product Characteristics (SmPC) and Patient

Information Leaflets (PL/ PIL)' V2 (which was put in place in June 2018 as an interim solution until EU-SOP-MA-002 was revised) was updated on 10 July 2018 as a controlled document, and re-communicated to Otsuka Europe and in all affiliates. It superseded the previous (uncontrolled) version. Training was assigned to all relevant employees. In preparing this response, Otsuka Europe identified a limitation of its Electronic Learning Management System (ELMS) in that it could not report on any training which might have been incomplete at the time a controlled document was withdrawn. However, it did find a way to generate a report which provided a reasonable estimate of those employees who were not trained. Therefore, while Otsuka Europe could not provide exact completion rates for this training due to employees leaving and joining the organization, it estimated it was 91%. In addition, a single affiliate determined that they would not assign training to their employees on this Guidance Document and instead waited to train in the revised EU-SOP-MA-002. At the time this decision was made (shortly after 10 July 2018), the date EU-SOP-MA-002 v5 would be revised was communicated as 15 August 2018.

- The revised EU-SOP-MA-002 v5 was made effective on 23 October 2018 after extensive cross functional consultation. Online training was assigned before the effective date of the SOP for Otsuka Europe employees and some affiliates; some affiliates were assigned training after the effective date of the SOP. A root cause analysis was done and indicated a communication error had resulted in affiliates being confused about when the training was required. Training was followed up and the company currently had a 100% completion rate for all employees. Face-to-face training was also conducted with all Medical Affairs Europe and Regulatory Affairs Europe employees on 2 and 22 of November 2018. This version of the SOP contained specific timelines for the withdrawal of outdated prescribing information and promotional material. To provide further clarity, the timelines were included in a flowchart, which had been used in the training of all responsible staff in medical affairs and regulatory affairs. This flowchart was included in the materials used to conduct face-to-face training on EU-SOP-MA-002 v5 for critical staff (copy provided).

- Otsuka Europe revised the two SOPs which described the process to approve and to withdraw promotional and non-promotional material, as these processes were directly downstream from EU-SOP-MA-002 and critical to ensure the use of up-to-date materials at all times. These documents were approved on 22 November 2018 and trained via face-to-face sessions (69% completion) between 23 November 2018 and 3 December 2018. Any employees who could not attend would be assigned online training; and follow-up face-to-face sessions have been scheduled for January 2019. The SOPs would be made effective on 31 January 2019 following completion of training.

A detailed table of the key steps taken in the company's remediation was provided.

Otsuka Europe stated that as it would take some time to complete the revisions to the European SOP, tracking of the implementation of all SPC and prescribing information updates across all affiliates was put in place, beginning after the 10 July 2018 version of the Guidance Document and accompanying training. The Guidance Document provided instruction on how to communicate prescribing information changes to affiliates, including instructions to follow country codes and regulations if stricter, and confirm the receipt of the updated prescribing information. This, combined with the action to replace individual email contacts with mailboxes,

was intended to address the key process issues identified in Otsuka Europe's earlier investigation and documented in its response.

Two SPC updates occurred between its response to the PMCPA and 10 July 2018, for Jinarc and Samsca. These were tracked to a 1 to 2-month timeline; thereafter, Otsuka Europe decided to track to a 1-month timeline across all affiliates except for one change which needed to follow a packaging change timeline. The following table provided the results of these SPC updates:

Communication of SPC Changes through 14 December 2018:

Update	EMA Decision	Communication to Affiliates	Deadline to Withdraw Promotional Material /Prescribing Information sent to Affiliates	Expected Timelines for Withdrawal	Dates Against Which Otsuka Europe Tracked	Date of Withdrawal (UK)
Jinarc – Contraindication benzazepine	29 June 2018	3 July 2018 5 July 2018 13 July 2018	13 July 2018 29 Dec 2018 13 July 2018[1]	6 months	26 Aug 2018	4 July 2018 (RMP approved by MHRA 14 November 2018)[2]
Samsca - Contraindication benzazepine	29 June 2018	6 July 2018 13 July 2018	29 Dec 2018 29 Dec 2018	6 months	23 Aug 2018	9 July 2018
Samsca acute liver failure	23 July 2018	23 July 2018	23 Aug 2018	30 days	23 Aug 2018	24 July 2018

Update	EMA Decision	Communication to Affiliates	Deadline to Withdraw Promotional Material /Prescribing Information sent to Affiliates	Expected Timelines for Withdrawal	Dates Against Which Otsuka Europe Tracked	Date of Withdrawal (UK)
Jinarc REPRISE CKD stage 4 license extension	26 July 2018	30 July 2018	26 Aug 2018	30 days	26 Aug 2018	31 July 2018
Samsca new pack size blister	23 Aug 2018	5 Oct 2018	23 Feb 2019	Custom due to packaging	23 Feb 2019	Update to prescribing information was required once pack change was implemented
Abilify Maintena 5 - year renewal	27 Aug 2018	31 Aug 2018	27 Sept 2018	30 days	27 Sept 2018	N/A (determined no need to withdraw material)
Jinarc acute liver failure	15 Oct 2018	15 Oct 2018	15 Nov 2018	30 days	15 Nov 2018	16 October 2018 (RMP updated 14 November 2018)

[1] Otsuka Europe acknowledged that these changing timelines did not represent a controlled process. It did not have an explanation for the changing dates and regretted the impression this created.

[2] The update for the Jinarc RMP material was delayed at the request of MHRA to include the acute liver failure SPC change.

After the revision to EU-SOP-MA-002 v5, Otsuka Europe implemented a process that tracked to a deadline of five working days to withdraw all outdated SPCs, prescribing information and promotional material from the date of communication from Otsuka Europe Medical and Otsuka Europe Development and Commercialisation Regulatory to all affiliates. This deadline was introduced in order to track to the strictest timelines.

Additionally, it had some unusual situations arise with the transfer of the marketing authorisation holder (MAH) from Otsuka Europe to Otsuka Pharmaceutical Netherlands B.V. as part of its strategy for Brexit. This sort of SPC update was very unusual in that it was between two separate entities within the same company. When the transition occurs, both companies might release product through the transition period. As the SPC update was planned and did not have updates related to safety, there was a wider timeframe provided for these updates. Otsuka Europe identified these updates and provided details.

The task force formed in February 2018 also took a broader approach to address not just these issues, but to also identify and address any other potential gaps related to the ABPI Code within the company's processes. Since June 2018, Otsuka Europe had:

- Reviewed 22 compliance-related policies, SOPs, guidance documents and other working practices; 15 policies and SOPs were in the process of being restructured, with two SOPs not requiring revision.
- Conducted face to face training on 9 high-priority revised SOPs for all key employees, with completion rates between 60-69%; any employees who could not attend in person would be assigned online training and would attend face-to-face training in January 2019.

In addition to the above:

- an external compliance consultancy conducted an audit of promotional and non-promotional materials in August 2018. The scope was to understand the general quality of materials, the quality of job bag set up, and compliance with the relevant internal processes and ABPI Code. Identified issues were remediated through mandatory ABPI baseline training and training for signatories which accompanied the implementation of EU-SOP-MA-009 and EU-SOP-MA-010, which together described the process to review, approve, withdraw, or recall promotional and non-promotional material. Email was sent to signatories by Otsuka Europe summarizing the findings and assigning key actions.
- a new Head of Medical, Europe was appointed in September 2018 (during the interim, the Medical leadership team reported directly to the President and CEO).
- the compliance team had been enhanced with two senior appointments and Compliance Champions in all relevant functions and disease areas had been appointed.

Otsuka Europe recognized that it had taken too long to implement a revised version of EU-SOP-MA-002 as this issue was identified and raised in November 2017 and corrected on 23 October 2018. Additionally, Otsuka Europe acknowledged that it failed to follow the process described in EU-SOP-ALL-001v4, Preparation and Change Management of Otsuka Region Europe Standard Operating Procedures (SOPs) in not reviewing this document for update at least three times in the 6-year period, as required.

While it was making progress in the remediation of its processes, it regretted that it was not as far advanced as it had planned.

4 There was a period of confusion for affiliate and distributor partners due to 'no consistent, clear communication around SPC changes'.

EU-SOP-MA-002 v4 and the Guidance Document v2 were effective at the same time from 19 June 2018 to 23 October 2018. EU-SOP-MA-002 v4 contained timelines for updating material to reference a revised SPC which were too long. The Guidance Document v2, which was updated on 10 July 2018 post Otsuka Europe's response in Case AUTH/3042/6/18, introduced a statement that the prescribing information, once released to affiliates by Otsuka Europe '… must be implemented immediately'. Online training was provided for both EU-SOP-MA-002 v4 and the Guidance Document v2, but unfortunately this training did not clarify which timelines should be followed, and employees found this confusing. In addition, joint communication from Otsuka Europe and Otsuka Europe Development & Commercialisation on each SPC change did not always clarify these timelines consistently.

During the period between Otsuka's response in Case AUTH/3042/6/18 and 23 October 2018, employee concerns and a lack of comprehension of the new process were being addressed and followed up appropriately. Additionally, Otsuka Europe tracked every SPC and prescribing information update across affiliates to evaluate compliance with the communicated timelines. During this tracking it realised that in some circumstances the originally communicated timelines were incorrect; when this was detected it rapidly communicated corrected timelines and continued tracking.

Otsuka Europe realised that despite a huge amount of work and with the best of intentions, employees were confused by the inconsistent dates and timelines introduced between June and October 2018, and by its attempts to clarify and correct these timelines.

Third parties were also confused. As previously disclosed, Otsuka Europe submitted that its process to update third parties was insufficient. In prioritising its remediation, Otsuka Europe focused first on the gaps identified in EU-SOP-MA-002; next on other regional and Otsuka Europe policies and SOPs; followed by remediation with its third parties.

Prior to and throughout its remediation, SPC changes were communicated to Third Party A in the same emails sent to its affiliates. These emails were sent to recipients as identified by Third Party A and on 19 November 2018 Third Party A confirmed Regulatory and Medical as the recipients of these communications. For Third Party B, only one SPC change required notification for the transfer of MAH between Otsuka Europe and Otsuka Pharmaceutical Netherlands B.V. This change was communicated to a particular individual in Third Party B identified on 31 October 2018. Otsuka Europe manually followed up with this communication as it was aware that the process was not yet robust enough. Additionally, Third Party A exclusively marketed Otsuka products in territories where local codes and regulations provided different timelines for the implementation of updated prescribing information and withdrawal of prior promotional material. As a result, Otsuka was in the process of implementing a mechanism which accommodated Third Party A's different timelines.

<u>Summary</u>

Otsuka Europe's process implemented immediately after the first response had been used for SPC updates and demonstrated that prescribing information created and certified centrally within Otsuka Europe had been communicated to the affiliates; and that there had been active confirmations back to Otsuka Europe with confirmation that the prescribing information and communication had been received. The central prescribing information had been implemented across all affiliates and third parties where prescribing information was used. Further, the UK which had the strictest timeline, had implemented this immediately and consistently within 5 days of communication from Otsuka Europe.

Otsuka Europe had provided the PMCPA with complete and accurate copies of the two internal audit reports provided by the complainant, which demonstrated that a process of detecting, assessing and remediating issues within its control environment was operating effectively and with appropriate oversight and governance from senior management. Otsuka took a literal approach to the period 1 January 2017 to June 2018 in responding to Case AUTH/3042/6/18.

Otsuka Europe had taken too long to update EU-SOP-MA-002 and train its employees on the new timelines. Additionally, its attempts to remediate the originally detected issue did introduce confusion for its employees and partners, although its actions demonstrated a concerted effort to improve its process. Since this was a critical process, this amounted to a failure to maintain high standards and therefore Otsuka Europe acknowledged that this was a breach of Clause 9.1.

As acknowledged in its response to Case AUTH/3042/6/18, Otsuka's processes for implementation of updates to SPCs fell short of expected high standards regarding clear and consistent communication of the actions required regarding updates to prescribing information; the processes were not always consistently followed; and that some of the historical prescribing information and materials in Otsuka Europe and Otsuka UK did not meet the highest standards. The company acknowledged that these processes fell short of expected high standards at least as far back as 2014.

Otsuka Europe sincerely apologised for and understood that failing to timely and robustly address inadequacies in a critical process that had the potential to impact patient safety, and the confusion of those expected to follow the process caused by its actions and omissions, brought the industry into disrepute and acknowledged that this was a breach of Clause 2.

While Otsuka Europe had implemented EU-SOP-MA-002 v5 and trained its employees, its first opportunity to evaluate the execution of this improved process occurred with SPC changes for Jinarc in December and January. Subsequently, it will continue to improve and revise its processes. Most importantly, it will monitor and track the implementation of SPC changes including measures that reduce the dependency on communication via emails; and creating a central repository of prescribing information that can be directly accessed by the affiliates.

PANEL RULING

The Panel noted that in its response to the current case, Otsuka Europe referred to a previous case, Case AUTH/3042/6/18, which was against Otsuka UK. However, the relevant previous case against Otsuka Europe was Case AUTH/3041/6/18. Otsuka had given a combined response to Cases AUTH/3041/6/18 and AUTH/3042/6/18 which were both ongoing at the time the current complaint, which was against Otsuka Europe only, was received.

The Panel noted that the complainant alleged that Otsuka failed to disclose internal audit reports and in so doing was not transparent in its response to the PMCPA in June 2018 in relation to Case AUTH/3041/6/18. The Panel noted that Case AUTH/3041/6/18 concerned poor governance and lack of processes including the failure to communicate or update changes to the summary of product characteristics (SPC) and prescribing information from 2017 for Jinarc, Samsca and Abilify.

The Panel noted that the complainant provided two internal reports which each covered pharmacovigilance and regulatory affairs: an audit of Otsuka Pharmaceutical Development and Commercialization Inc., US, in May 2016; and an audit of Otsuka Europe Development and Commercialisation Ltd in September 2016. The Panel noted Otsuka Europe's submission that the internal audit reports provided to the PMCPA by the complainant were incomplete and therefore inaccurate as they did not contain the Corrective and Preventative Actions (CAPA) records.

The Panel noted Otsuka's submission that at the time of its response to Cases AUTH/3041/6/18 and AUTH/3042/6/18, the actions required as a result of the two internal audit reports had been closed with all CAPAs completed by April 2017. The Panel noted that for these previous cases, Otsuka had been asked to respond in relation to SPC changes from 2017 onwards, the time period identified in the complaint. The Panel noted that the governance standards in place at the company prior to 1 January 2017 might, nonetheless, be relevant when deciding whether Otsuka Europe had provided a complete response. Context was important.

The Panel noted that the May 2016 internal audit of Otsuka Pharmaceutical Development and Commercialisation had, *inter alia*, a major finding related to the lack of company oversight of the global labelling process. In addition, in relation to delays and non-conformities for processes to update labelling for Tolvaptan (2013) and Abilify (2015 and 2016) the auditors noted that users of the product might not have access to the most up-to-date information and this might result in non-compliance. The September 2016 internal audit of Otsuka Europe Commercialisation and Development had, *inter alia*, a critical finding in relation to the lack of company oversight of the overall labelling process and a major finding in relation to the submission, tracking and notification of labelling changes which were not in accordance with SOPs effective at that time.

In the Panel's view, such information was directly relevant to the subject matter of the previous case in question, Case AUTH/3041/6/18; it illustrated that there were relevant recent global governance issues and it would have been helpful if such information was provided by Otsuka in its response to that case.

The Panel particularly noted matters raised in the September 2016 internal audit report. That report referred to the addition of anuria to Section 4.3 of the Jinarc SPC and the fact that timelines were not set initially. This Jinarc SPC update was referred to in Otsuka's response to Cases AUTH/3041/6/18 and AUTH/3042/6/18 and the Panel considered that the provision of this additional information from the September 2016 internal audit report would have been directly relevant.

The Panel noted that the September 2016 audit report contained CAPAs, some of which were not closed until April 2017, relevant to the time-period that Otsuka was discussing in its response to Case AUTH/3041/6/18. The Panel further noted Otsuka Europe's submission that it did not provide information to the PMCPA about incorrect Abilify Maintena prescribing information that was detected by the Otsuka UK medical team in April 2018 which related to

SPC changes from 2014. The Panel considered that although this related to SPC changes prior to 2017, and outside the time-period at issue in Case AUTH/3041/6/18, the error was detected within the time-period relevant to that complaint and was therefore pertinent.

In the Panel's view, relevant information from the internal audit reports ought to have been disclosed. The Panel was concerned that the company's response to the previous complaint implied that the company first became aware of relevant compliance matters further to a concern raised by an employee in November 2017 stating that '*since then*', corrective and preventative measures had been put in place. This statement was misleading and not a true reflection of the company's compliance position. Noting its comments above, the Panel considered that Otsuka Europe had failed to maintain high standards by not supplying all the relevant information in its response to Case AUTH/3041/6/18 and a breach of Clause 9.1 was ruled.

The Panel noted the complainant's allegation that senior leaders within the Global and European organisations had been aware of the issues related to the SPC update process but had failed to correct it. The Panel further noted the allegation that the new relevant SOP had only just been released to the organisation, despite Otsuka's response to the PMCPA almost 6 months ago; and in the interim, affiliates and distributor partners had been left confused as there was no consistent, clear communication around SPC changes.

The Panel noted that it was clear that senior staff at Otsuka Europe were aware of the compliance difficulties; certain senior staff were named as being present during the audit. The Panel noted Otsuka Europe's submission that, despite a huge amount of work and with the best intentions, employees and third parties were confused by the inconsistent dates and timelines introduced between June and October 2018. The Panel further noted Otsuka Europe's submission that it had taken too long to update the relevant SOP and train employees on the new timelines and that it acknowledged that processes fell short of expected high standards at least as far back as 2014. The Panel considered that Otsuka Europe's lack of clear and consistent instructions to employees and third parties meant that Otsuka Europe had failed to maintain high standards as alleged and a breach of Clause 9.1 was ruled.

The Panel noted Otsuka Europe's submission that it failed to timely and robustly address inadequacies in a critical process that had the potential to impact patient safety and the confusion of those expected to follow the process caused by its actions and omissions brought the industry into disrepute. The Panel noted that Otsuka Europe had referred to an initial concern being raised in November 2017, but it appeared to the Panel that there were issues identified in the internal audits prior to this. The Panel noted that Otsuka Europe had taken steps to attempt to remediate some of the issues identified in Cases AUTH/3041/6/18 and AUTH/3042/6/18 and noted the company's detailed submission in this regard.

In the Panel's view, inadequacies in the process had been present since at least as far back as 2014 and had still not been fully corrected despite internal audits, concerns being raised internally and a complaint to the PMCPA. Otsuka Europe had failed to timely and robustly address inadequacies in a critical process that had the potential to impact patient safety. That it had failed to do so brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

The Panel noted that the compliance messages and behaviours of global and European functions would directly impact local compliance behaviours. That the internal audits of global

and European functions had uncovered serious compliance failings that had the potential to impact patient safety was a serious matter. Although it appeared that Otsuka Europe was now trying to address the issues in question, the Panel considered that the further information disclosed in this case highlighted that the magnitude of the compliance issues at Otsuka Europe, and that impacted on Otsuka Europe, were greater than apparent in Case AUTH/3041/6/18. For all the reasons outlined above, the Panel considered that this Case warranted reporting Otsuka Europe to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for the Appeal Board to consider in relation to Paragraph 11.3 of the Constitution and Procedure.

COMMENTS FROM OTSUKA EUROPE ON THE REPORT FROM THE PANEL

Otsuka Europe provided the requisite undertaking and assurance in respect of the Panel's rulings of breaches of Clauses 2 and 9.1 in Case AUTH/3123/11/18.

Otsuka Europe regretted the actions and inactions that had brought it to this point and was hopeful that it would have the opportunity to demonstrate its commitment to improve. Otsuka Europe stated that since June 2018 it had embarked on an ambitious continuous improvement programme, some of which had already been communicated in its response above. Otsuka Europe acknowledged that its progress had been slower than anticipated, and that the additional issues raised to the PMCPA in January 2019 indicated it had a long road ahead.

The company submitted, however, that it was important to recognise that compliance programmes were not rebuilt over a short time; they required dedicated effort over the long term. To that end, Otsuka Europe would:

- continue to commit resources to face-to-face interactive training to enhance employees' understanding and would continue to improve its compliance training programme;
- continue to strengthen European regional and Otsuka Europe-specific procedures, including the SOPs which described the process to communicate SPC changes;
- Improve its monitoring capabilities once training was completed and SOPs were embedded in order to measure compliance and ensure continuous improvement;
- enhance its ability to correctly identify prescribing information versions through a central repository;
- invest in new tools to help certify materials and events, as well as manage incident reporting and investigations and
- recruit an experienced compliance professional to join an already expanded compliance team and assist Otsuka Europe in implementing an enhanced compliance programme.

Otsuka Europe stated that both Otsuka Europe and Otsuka UK were one company and were committed to self-regulation and high ethical standards. Otsuka Europe recognised the severity of the issues and accepted the Panel's rulings. Otsuka Europe stated it must, and would, continue to do better.

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At the consideration of the three reports at the same Appeal Board meeting, Otsuka's presentation concerning Otsuka Europe in relation to Case AUTH/3123/11/18 was covered by

its presentation in Cases AUTH/3041/6/18 (Otsuka Europe) and AUTH/3042/6/18 (Otsuka UK). The following comments were made in relation to all three cases.

The company representatives from both Otsuka UK and Europe accepted accountability and agreed that Otsuka had not met the required standards and it had let down patients, customers, partners, employees and the industry. Otsuka noted that the speed of remediation of these issues had not been fast enough.

Otsuka noted that it was making fundamental changes in relation to people/culture, process and structure/governance. Moving forward, there would be a continuous improvement programme (CORE) across Otsuka which was being led by the managing director from Otsuka UK. There was a new head of compliance and medical at Otsuka Europe. The senior leadership team at Otsuka UK had been in place since November 2017.

In relation to the Jinarc Risk Management Plan (RMP), Otsuka submitted that materials at launch contained an error and there had been no consistent update of RMP materials since launch in 2015. There was no oversight of this material and no process for its update. Furthermore, communication of RMP updates was not consistent. Otsuka submitted that the process for the update of RMP materials in relation to SPC updates would become effective at the end of March 2019 and that all current materials were approved by the MHRA in November 2018 and up-to-date. Otsuka UK would update RMP materials should a change in SPC necessitate a safety-related change.

An internal audit carried out by an external consultant was due to report shortly. Headquarters in Japan had been kept up-to-date throughout the process.

Individually and collectively Otsuka committed to conducting its business with integrity and transparency, to the highest ethical standards and to place patients and customers at the heart of its business. Otsuka anticipated that the Appeal Board would require an audit of its procedures and it looked forward to demonstrating its improvements.

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board noted the Panel's comments and rulings of breaches of Clauses 2 and 9.1 of the Code in Case AUTH/3123/11/18, including its decision to report Otsuka Europe to the Appeal Board. The Appeal Board noted that Otsuka Europe had provided detailed information about its compliance difficulties and it had apologised.

The Appeal Board noted the timelines provided showing European remediation to date from March 2018. It appeared from questioning the company representatives that little activity had taken place following the internal audit in September 2016 and when the issue was raised internally in November 2017. It was only after the complaint was made to the PMCPA in June 2018 that action was taken. This raised concerns about how seriously the company took the issue, its impact on patient safety and the culture at Otsuka. The company representatives stated that the delay was due to a lack of understanding of the seriousness and importance of the process. There was a lack of communication across the company. Senior leaders had apologised to employees. Speak-up processes had been introduced and more was shared about reporting incidents.

The Appeal Board noted the company's submission that it recently had another internal audit of its end-to-end processes and it was awaiting that report. The company representatives referred to the CORE programme which started in February 2019 led by the UK. The CORE programme had 4 elements; culture and compliance, one organisation, ready for audit and everybody was responsible for compliance. The company representatives also referred briefly to other issues identified mentioning meetings and congresses. These would be prioritised. Otsuka UK referred to a new meetings process.

The Appeal Board was also concerned that Otsuka Europe had neither referred to nor provided the relevant internal audits of global and European functions in its response to Case AUTH/3041/6/18.

The Appeal Board was very concerned that an overall failure of governance in relation to Otsuka Europe's processes in implementing SPC changes, updating prescribing information and updating and withdrawing promotional materials in a timely manner had potential patient safety implications. It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about its medicines. The Appeal Board noted Otsuka Europe's submission that it was now putting systems and processes in place to address these issues. The Appeal Board noted the scale of the task but queried whether this was being done sufficiently quickly given the seriousness of the matter.

The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Otsuka Europe should be publicly reprimanded for the failures to implement SPC changes and update impacted materials in a timely manner which had potential to impact patient safety. The Appeal Board also decided to require an audit of Otsuka Europe's procedures in relation to the Code in the present case to take place by mid July 2019. This audit would take place at the same time as those required in Cases AUTH/3041/6/18 (Otsuka Europe) and Case AUTH/3042/6/18 (Otsuka UK). On receipt of the report of the audit the Appeal Board would consider whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

On receipt of the report for the July 2019 audits the Appeal Board was very concerned to note the extent of the companies' failings including that there was a systemic lack of governance shown by the failure to take action in these cases. Leadership and communication needed to be improved urgently. The governance from Japan to Europe and from Europe to UK needed huge improvement. There appeared to be longstanding failures in this regard, particularly in relation to holding senior individuals to account.

The Appeal Board noted that the report of the audits highlighted a number of concerns including that existing senior staff needed to improve their knowledge and leadership on compliance matters, engage with and ensure that all staff understood its importance. Staff should be helped and encouraged to improve their skills in relation to matters covered by the Code. Significant commitment was required to address the issues.

The Appeal Board noted from the report of the audits that Otsuka Europe had not provided accurate information about the training of the SOPs to the Appeal Board in March 2019 when the reports from the Panel were considered. The Appeal Board noted that self-regulation relied upon, *inter alia*, the provision of complete and accurate information from pharmaceutical companies. The Appeal Board decided that in accordance with Paragraph 11.3 of the

Constitution and Procedure, Otsuka Europe should be publicly reprimanded for providing inaccurate information to the Appeal Board.

The Appeal Board noted Otsuka's compliance plan and decided that Otsuka should provide a detailed written account of its progress by the end of November 2019. It was vital that swift comprehensive action was taken and noting the failure to take appropriate action over a long period of time, the Appeal Board considered that given the exceptional circumstances of this matter, including the scale and seriousness of the difficulties at Otsuka, it would be helpful if Otsuka representatives attended the December 2019 meeting of the Appeal Board to discuss the progress and future plans. The Appeal Board noted that both Otsuka Europe and Otsuka UK had set themselves a number of compliance objectives and considered that sufficient time would be needed for these to be completed in order for any meaningful progress to be assessed. The Appeal Board decided that both Otsuka Europe and Otsuka UK should be re-audited in early 2020. At its meeting in December the Appeal Board would decide the timing of the re-audits and on receipt of the report for the re-audits it would decide whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

At its meeting in December 2019 representatives from Otsuka Europe and Otsuka UK attended to discuss the progress and future plans. The companies welcomed the opportunity to provide the Appeal Board and PMCPA with a written account of the activities conducted and progress made since receipt of the report of the audits. The Appeal Board noted that whilst there was a lot of work to be done, a number of activities and actions were completed, planned and/or in process. On the information before it the Appeal Board decided that the re-audits should take place in April 2020 at which point it expected substantial improvements. On receipt of the report for the re-audits it would decide whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

On receipt of the report for the April 2020 re-audits the Appeal Board noted the difficulties of conducting audits remotely and that there was little new activity due to the continuation of the 'pencils down'/'deprioritisation' policies. The Appeal Board considered that there had been some progress and it appeared that things were now heading in the right direction. There had been changes with new staff and new members of the Otsuka Board as well as additional resource for compliance and compliance objectives had been introduced. Key senior staff still needed to continue to develop their leadership on compliance. The Appeal Board noted that whilst most staff understood the reasons for the re-audits; it was concerned that some staff still did not. Otsuka UK and Otsuka Europe needed to continue to improve working relationships, including in and between the medical departments. It appeared that communication with Japan had improved. There was to be a staff survey in late 2020.

The Appeal Board noted that further improvement was required, the report of the re-audits highlighted a number of areas on which to focus.

The Appeal Board decided that Otsuka UK and Otsuka Europe should be re-audited in April 2021 at which point it also expected the companies to demonstrate continued progress and improvement. On receipt of the of the report for the re-audits the Appeal Board would decide whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

On receipt of the report for the April 2021 re-audits the Appeal Board the Appeal Board considered that there had been some further progress and it appeared that matters were continuing to head in the right direction. However, the Appeal Board considered that the pace of improvement needed to accelerate. Otsuka UK and Otsuka Europe needed to continue to improve working relationships, including in and between the medical departments. Senior staff needed to work together to continue to improve their knowledge and leadership on compliance. There was currently no permanent medical lead for Otsuka Europe and there had been some restructuring. The Appeal Board considered it important that a medical lead for Otsuka Europe was appointed.

The Appeal Board noted that further improvement was required, the report of the re-audits highlighted a number of areas on which to focus.

The Appeal Board decided that Otsuka UK and Otsuka Europe should be re-audited in December 2021/January 2022 at which point it expected the companies to demonstrate continued progress and embedded improvement. On receipt of the report for the re-audits the Appeal Board would decide whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

On receipt of the report for the January 2022 re-audits the Appeal Board noted that Otsuka had continued to build on the improvements described in the report of the 27 and 28 April 2021 re-audits. It was important that progress on company culture continued such that there was a team approach both within each company and between each company.

The Appeal Board noted that the report of the January 2022 re-audits still highlighted work to be done and it was important that these were addressed.

The Appeal Board considered that from the report of the January 2022 re-audits it appeared that there had been further progress. The Appeal Board was concerned that it had taken 4 audits/re-audits to get to this stage.

The Appeal Board noted that Otsuka had a compliance CORE tracker to address recommendations from the re-audits. On the basis that this work was completed, the progress shown to date was continued and commitment to compliance was maintained, the Appeal Board decided that no further action was required.

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