CASE AUTH/3151/1/19

ANONYMOUS EMPLOYEES v OTSUKA EUROPE

SPC changes and prescribing information

A 'group of concerned employees' complained that Otsuka Pharmaceuticals Europe Ltd (based in the UK) was unable to properly manage updates to the summary of product characteristics (SPC) and prescribing information for Jinarc (tolvaptan). Jinarc was used in certain patients with chronic kidney disease.

The complainants alleged that the latest SPC and prescribing information update for Jinarc took place on 21 December 2018, and emails sent out for action/information indicated that the process was in chaos. Senior members of the European team did not appear to understand the process.

The complainants were saddened that even after having received a complaint in June 2018 [Case AUTH/3041/6/18] and further concerns at the end of last year, Otsuka Europe seemed unable to put this critical process concerning patient safety in place.

At an EU medical meeting a senior employee stated that he/she knew that the new standard operating procedure (SOP) (MA 002) for updating SPCs and prescribing information was flawed, but it was still approved and sent out for training, as he/she wanted to 'test the affiliates'. Moreover, he/she added that Otsuka could perhaps use legal privilege to prevent the PMCPA receiving all the necessary information. The complainants queried whether the content of any response from Europe could be trusted and alleged that the European organization was compromised.

In subsequent communication, the complainants raised more concerns about Otsuka Europe and Otsuka Europe Development and Commercialisation (D&C) Ltd.

The complainants noted their concern about communication from Otsuka Europe D&C regarding information about Jinarc Type IA-IN-G (addition of wallet card blister) European Medicines Agency (EMA) favourable opinion dated 21 December 2018 and noted that global medical had been kept in the loop of such communication. The complainants queried what the Japanese global headquarters had done to rectify the situation. Members of the global quality, regulatory and safety (QRS) team were copied into the emails; were they not aware that the current situation was unacceptable?

The complainants noted that some people copied into the email had left the business. What checks had been done to ensure the appropriate staff members received this important notification if the mailing lists were not kept up-to-date?

The complainants gave key dates with regard to changes to the Jinarc package information and alleged that the date for new/updated SPC and package leaflets to be distributed was wrong. If Otsuka Europe and Otsuka Europe D&C could not calculate the dates appropriately, what were the affiliates and third parties supposed to do?
The complainants alleged that out-of-date Jinarc prescribing information (prepared December 2018) had the incorrect stages for chronic kidney disease – it should have stated stages 1 to 4 and not 1 to 3. There were also missing adverse events – the complainants provided a track change copy of the prescribing information.

The complainants stated that there was no central repository for storing up-to-date prescribing information. Moreover, there was no standard process for creating the prescribing information. This increased the risk of the incorrect document/ lack of standardized prescribing information across the brands and incorrect timelines distributed to the affiliates and third parties.

The complainants stated that the correct prescribing information was distributed on 10 January 2019 with the correct indication and safety updates.

The complainants were very concerned that the process for the distribution of SPCs and prescribing information was still not correct despite the new SOP which came into effect at the end of October 2018. The process was not fit for purpose and was currently being rewritten by medical. If the process was not ready/correct, it should not have been trained out to the entire European organization.

The complainants stated that there was a prevalent blame culture within the organization. There was a climate of fear within the European organisation and the complainants believed that senior leaders within Otsuka Europe and Otsuka Europe D&C were lining up their next sacrificial lambs as the process was still not fit for purpose.

The complainants were also saddened that the global QRS team and the Japanese headquarters had failed to take a more involved approach. This was a critical process that impacted patient safety, and it had not been given the priority it deserved.

The detailed response from Otsuka Europe is given below.

The Panel noted Otsuka Europe's submission that the SPC update in question related to the addition of blisters in wallet cards with new marketing authorization holder (MAH) numbers. The Panel noted that the communication in question, dated 21 December 2018, included several required affiliate actions including timelines for, *inter alia*, distribution of the updated SPC and package leaflet, withdrawal

of previous SPC, package leaflet and promotional materials and update of non-promotional materials. The Panel noted that the timeline for actions were given in both the number of business days and the completion date. The Panel noted that there was some confusion in that the number of business days did not appear to correlate with the completion date.

The Panel noted Otsuka Europe's submission that the timelines stipulated in the communication in question were calculated incorrectly and caused some affiliates to question the dates provided. The Panel considered, however, that the completion dates in the email in question appeared to be correct if 24 and 31 December and the public holidays were not considered to be working days. The Panel was concerned to note that these specific/ additional 'non-working days' did not appear to be either covered in the relevant SOP or to be widely communicated and, in the Panel's view, this caused confusion as had an incorrect reference to the communication in question as 'the Jinarc SmPC change regarding gout', which was not so.

The Panel noted that although a completion date was given, the confusion around how the dates were calculated (with regard to business days) and the lack of clear communication in this regard caused confusion with regard to a critical process and meant that Otsuka Europe had failed to maintain high standards. A breach was ruled.

The Panel did not consider that the email demonstrated that senior European leaders did not understand the process and no breach was ruled in this regard.

With regard to the incorrect prescribing information included in the communication in question, the Panel noted Otsuka Europe's timeline of events; the SPC was revised in July 2018 to include an extension to the indication in Section 4.1 (CKD stage 4) and the addition of abdominal pain as a common side effect to Section 4.8; the prescribing information was updated at the time to reflect these SPC changes. There was then a further SPC change regarding the addition of acute liver failure to Sections 4.4 and 4.8 which were included in the revised September 2018 prescribing information. In November 2018, the SPC due to a change of marketing authorisation holder and again in December 2018 to include the addition of wallet card blisters. Both the November 2018 and December 2018 prescribing information omitted the previously added information regarding CKD stage 4, abdominal pain and acute liver failure.

The Panel noted the requirements for prescribing information (defined by Clause 4.2) including that it must be up-to-date and must be consistent with the SPC for the medicine. The Panel noted Otsuka Europe's submission that, although certified and distributed to affiliates, neither the November 2018 nor the December 2018 prescribing information was used in external materials. The Panel was unclear with regard to what Jinarc promotional material, if any, was in circulation during November and December. Otsuka Europe made no submission in this regard. The Panel noted that the complaint concerned the internal distribution of the Jinarc prescribing information dated December 2018 as an attachment to the email dated 21 December 2018; the complainant made no reference to its use on materials. The Panel considered that it had no evidence before it in this case that incorrect or out-of-date prescribing information was actually used and considered that there was no allegation concerning its use on materials and in that regard, ruled no breach. The Panel noted that the use of incorrect Jinarc prescribing information on materials was the subject of another complaint (Case AUTH/3041/6/18).

Although it appeared that the errors in the December 2018 prescribing information had been identified internally prior to the Authority's receipt of the complaint and remedial action taken, the Panel considered that Otsuka Europe had failed to maintain high standards by certifying and distributing incorrect prescribing information which omitted important safety information and a change to the licensed indication and which had the potential to be used in multiple affiliates. A breach of the Code was ruled.

The Panel noted Otsuka's submission that it was developing a repository and a process for authoring/ updating prescribing information, however, this was not currently in place. The Panel was concerned that there appeared to be a general lack of oversight and guidance with regard to prescribing information creation and revision and noted the errors that had occurred in the November and December 2018 Jinarc prescribing information. Prescribing information was critical information required in all promotional materials and had the potential to impact patient safety. The Panel noted that Otsuka acknowledged that the relevant SOP still needed to be improved in relation to both SPC and prescribing information updates. The Panel considered that the lack of a clear process for both the creation and revision of prescribing information and SPC updates meant that Otsuka Europe had failed to maintain high standards and a breach was ruled.

The Panel noted that the complainants had provided no evidence that individuals who should have received the communication in question had been omitted from the distribution list. That the email in question had been sent to individuals who had left the company was not in itself a breach of the Code so long as individuals who should have received it had done so. In the Panel's view, the complainants had not discharged their burden of proof to show that a breach of the Code had occurred in this regard and no breach was ruled.

The Panel noted the complainants' allegations that a senior member of the Otsuka Europe medical team stated that the SOP for SPC and prescribing information updates was flawed but was still approved and trained out in order to 'test the affiliates'; and that he/she stated that Otsuka Europe could use legal privilege to prevent the PMCPA receiving all the necessary information. The Panel noted that Otsuka Europe found no evidence that these statements were made. It appeared that there had been an acknowledgement at the meeting in question that the SOP required improvement. One

person recalled use of the word 'flawed'. Otsuka Europe acknowledged that the SOP required improvement. The Panel considered that this was a serious allegation; self-regulation relied upon, *inter alia*, full transparency from companies. The parties' accounts differed. It was difficult to determine where the truth lay. The Panel noted, however, that the complainants bore the burden of proof and considered, on balance, that the burden of proof had not been discharged and it therefore ruled no breach.

With regard to the allegations about the Japanese parent company, global quality, regulatory and safety team, global medical and pharmacovigilance, the complainants had provided no detail and, in the Panel's view, the complainants had not discharged their burden of proof. No breach was ruled in this regard.

With regard to the allegation that there was a prevalent blame culture within the organisation and a climate of fear, the Panel considered that comments about the culture of an organisation might fall within the scope of the Code if that culture directly or indirectly contributed to a breach of the Code. The Panel noted Otsuka's submission that Otsuka Europe had a whistleblowing procedure and an incident response procedure which specifically stated that employees would be protected from retaliation. The complainants had provided no detail with regard to this allegation and, in the Panel's view, the complainants had not discharged their burden of proof. No breach was ruled in this regard.

The Panel noted its comments and rulings above. The Panel noted that Clause 2 was a sign of particular censure and reserved for such use. On balance, the Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 and ruled no breach accordingly. This ruling was appealed by the complainants.

The Appeal Board noted from the Panel's rulings above that there was a lack of clear process for both the creation and revision of prescribing information and SPC updates; that Otsuka Europe had certified and internally distributed to multiple affiliates incorrect prescribing information which omitted important safety information and a change to the licensed indication; and that the lack of clear communication about completion dates for an SPC update caused confusion with regard to a critical process had meant that Otsuka Europe failed to maintain high standards and three separate breaches of the Code were ruled.

The Appeal Board noted that Otsuka Europe agreed with the complainants' appeal that the cumulative effect of the issues warranted a breach of Clause 2. The company apologised for its inability to effectively remediate the issues highlighted in Case AUTH/3041/6/18, and its continued failure to address the issues with regard to SPC updates and prescribing information. Otsuka Europe submitted that these failings had reduced confidence in the pharmaceutical industry. The Appeal Board was very concerned about how long it was taking Otsuka Europe to address these issues. Otsuka Europe stated that this delay was due to the company failing to understand the role of prescribing information in relation to patient safety.

The Appeal Board considered that the cumulative effect of Otsuka Europe's failings in this case reduced confidence in the pharmaceutical industry and ruled a breach of Clause 2. The appeal on this point was successful.

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COMPLAINT

The complainants stated that during the recent EU medical meeting, they were informed that Otsuka had received a further complaint about the update of SPCs and prescribing information at the end of 2018.

The complainants submitted that the latest SPC and prescribing information update for Jinarc took place on 21 December 2018, and emails sent out for action/information indicated that the process was in chaos. Communication from senior members of the European team demonstrated that they did not understand the process.

The complainants were saddened that even after having received a complaint in June 2018 [Case AUTH/3041/6/18] and further concerns at the end of last year, Otsuka Europe seemed unable to put this critical process concerning patient safety in place.

At the EU medical meeting referred to above, a senior employee stated that he/she knew that the new standard operating procedure (SOP) (MA 002) for updating SPCs and prescribing information was flawed, but it was still approved and sent out for training, as he/she wanted to 'test the affiliates'. Moreover, he/she added that Otsuka could perhaps use legal privilege to prevent the PMCPA receiving all the necessary information. The complainants queried whether the content of any response from Europe could be trusted if this was the view of a senior member of the team. The complainants considered that the European organization was compromised.

In subsequent communication, the complainants raised more concerns about Otsuka Europe and Otsuka Europe Development and Commercialisation (D&C) Ltd.

The complainants noted their concern about communication from Otsuka Europe D&C regarding information about Jinarc Type IA-IN-G (addition of wallet card blister) European Medicines Agency (EMA) favourable opinion dated 21 December 2018 and noted that global medical had been kept in the loop of such communication. The complainants queried what the Japanese global headquarters had

done to rectify the situation, especially as it must be aware of the numerous failings in the process (especially since June 2018). If Otsuka Europe and Otsuka Europe D&C had failed to distribute SPC and prescribing information appropriately, did Japan not take note and act accordingly? What actions, if any, did Japan take to help or rectify the situation? The complainants stated that they could not ask such questions in their organization for fear of retribution. Members of the global quality, regulatory and safety (QRS) team were copied into the emails; were they not aware that the current situation was unacceptable? The complainants had heard that the global QRS team had been kept updated by senior leaders in Otsuka Europe and was satisfied with the progress – surely this could not be the case. This made a mockery of patient safety if the global QRS team had done little or nothing to correct the European processes.

The complainants noted that some people (names provided) copied into the email left the business in the summer of 2018; they had been part of the team that was supposed to rewrite the process for SPC and prescribing information distribution. What checks had been done to ensure the appropriate staff members received this important notification if the mailing lists were not kept up-to-date?

The complainants gave key dates with regard to changes to the Jinarc package information and alleged that the date for new/updated SPC and package leaflets to be distributed was wrong – within 2 business days due 28 December 2018, but if the start date for implementation was 19 December 2018 (as stated on page 1 of the relevant document) 2 business days was 21 December 2018, or if the start date for implementation was 21 December 2018, 2 business days was 24 December 2018. The implementation dates for withdrawal of the SPC were also alleged to be wrong – 5 business days, due by 4 January 2019 but if the start date for implementation was 19 December 2018, 5 business days was 27 December 2018 and if the start date for implementation was 21 December 2018, 5 business days was 31 January [sic].

The complainants stated that it was very confusing as there seemed to be additional days that had not been counted, apart from the public holiday. If Otsuka Europe and Otsuka Europe D&C could not calculate the dates appropriately, what were the affiliates and third parties supposed to do?

The complainants alleged that out-of-date Jinarc prescribing information (prepared December 2018) had the incorrect stages for chronic kidney disease – it should have stated stages 1 to 4 and not 1 to 3. There were also missing adverse events – the complainants provided a track change copy of the prescribing information to illustrate the point.

The complainants stated that there was no central repository for storing up-to-date prescribing information. Moreover, there was no standard process for creating the prescribing information. The complainants considered that this increased the risk of the incorrect document/lack of standardized prescribing information across the brands and incorrect timelines distributed to the affiliates and third parties.

The complainants stated that the correct prescribing information was distributed on 10 January 2019 with the correct indication and safety updates (copy provided).

The complainants were very concerned that the process for the distribution of SPCs and prescribing information was still not correct despite the new SOP which came into effect at the end of October 2018. The process was not fit for purpose, as stated above and was currently being rewritten by medical from scratch. If the process was not ready/correct, it should not have been trained out to the entire European organization.

The complainants stated that there was a prevalent blame culture within the organization. A senior employee was removed from the business because he/she was blamed for not correcting the SOP in time. There was a climate of fear within the European organisation and the complainants believed that senior leaders within Otsuka Europe and Otsuka Europe D&C were lining up their next sacrificial lambs as the process was still not fit for purpose.

The complainants were also saddened that the global QRS team and the Japanese headquarters had failed to take a more involved approach. This was a critical process that impacted patient safety, and it had not been given the priority it deserved.

When writing to Otsuka Europe, the Authority asked it to consider the requirements of Clauses 4.1, 4.2, 9.1 and 2 of the 2016 Code.

RESPONSE

Otsuka Europe noted that the complainants referred to the update to the Jinarc SPC and prescribing information that it sent out on 21 December 2018 for the addition of blisters in wallet cards with new Marketing Authorization Holder (MAH) numbers. The complainants specifically alleged that:

- the emails sent out for action indicated that the process (EU-SOP-MA-002) was in chaos;
- emails from senior European leaders demonstrated a lack of understanding of the process; and
- the prescribing information communicated on 21 December 2018 was incorrect as it did not have all the necessary safety information.

Otsuka Europe disagreed that the communication sent indicated that the process was in chaos or demonstrated a lack of understanding of the process, despite demonstrating opportunities to improve the process. However, the complainants were correct in their more important claim; the prescribing information sent out on 21 December 2018 was inconsistent with the revised SPC as it did not have all the necessary safety information. This prescribing information, however, was not used and in that regard the company denied a breach of Clauses 4.1 and 4.2.

Otsuka Europe submitted that, additionally, on 21 February 2019 it identified discrepancies between the January 2019 version of the Jinarc prescribing information and the current SPC, some of which were present at least as far back as 30 July 2018 (corresponding SPC and prescribing information revisions were provided). On 21 February 2019, out of an abundance of caution, an employee recalled the February 2019 prescribing information which included these same discrepancies. These discrepancies were escalated through the Otsuka governance process documented in PV-3101-GSOP 'Safety Governance' to the medical safety review team, which evaluated the potential for a risk to patient safety. This team was the main global governance body responsible for the overall management of safety issues related to all Otsuka pharmaceutical products (both marketed and in development). Over the course of two meetings, held on 22 and 23 February 2019, the medical safety review team reviewed the January Jinarc prescribing information and determined that the discrepancies noted with the approved SPC did not pose a risk to patient safety. In particular, the evaluation of the phrasing 'should' vs 'must' in relation to having access to, and being able to drink sufficient amounts of water, was reviewed. The review team concluded that there was no inconsistency between the SPC and the January prescribing information on that point.

Otsuka Europe submitted that, based on the conclusion of the medical safety review team, it had considered these discrepancies against the requirements of Clauses 4.1 and 4.2 of the Code. Although the version of the prescribing information that was distributed contained discrepancies with the latest approved SPC, it remained consistent as a condensed version of the SPC. Specifically, common adverse reactions and serious adverse reactions likely to be encountered in clinical practice as well as precautions and contra-indications were appropriately described. Therefore, Otsuka Europe concluded that these discrepancies were not in breach of Clauses 4.1 or 4.2 (Otsuka Europe provided a timeline of relevant events).

Otsuka Europe submitted that, in both the November and December prescribing information revisions, the overall process did not prevent prescribing information which was inconsistent with the SPC from being certified and communicated to affiliates. Additionally, the overall process did not detect and resolve differences in opinion related to discrepancies between the SPC and prescribing information as identified on 21 February 2019. Therefore, despite efforts to remediate the issues highlighted in Case AUTH/3041/6/18, the company was not effective in doing so. As this was a continued failure to address the issues originally described in Case AUTH/3041/6/18, Otsuka Europe acknowledged a breach of Clauses 9.1 and 2. As EU-SOP-MA-002 had not effectively achieved a key objective, ie to ensure that up-to-date prescribing information was provided when performing promotional activities, the company acknowledged a further breach of Clauses 9.1 and 2.

Otsuka submitted that it had assessed these failings and identified contributing factors, with their associated remediations which it would address as a matter of urgency (details provided).

Otsuka Europe submitted that it regretted and apologised for the slow progress it had made in this regard. The remediations identified were under way. Additionally, an independent audit, to be conducted from 25 February to 1 March 2019, would assess the entire end-to-end product labelling process including the medical affairs segment. Any findings which were identified would be included in the remediation programme.

Otsuka Europe noted that there had been successes in its remediations: notifications of changes to SPC and prescribing information were sent to all affiliates via general mailbox addresses; tracking the implementation of prescribing information changes (including withdrawal of promotional material) was in place and the company had shortened its windows to withdraw promotional material.

Otsuka Europe noted that the complainants had also referred to a recent EU medical meeting at which it was alleged that a senior employee commented on the current version (version 5) of EU-SOP-MA-002 and also on the provision of information to the PMCPA. Given the date of the complainants' letter and its receipt by the PMCPA, it was possible that the complainants had referred to one of two meetings that took place in January 2019; details were provided.

Otsuka submitted that attendees of both meetings had been interviewed. Otsuka Europe had interviewed relevant individuals and the interview notes were provided.

A number of those interviewed recalled a general agreement that the current version of EU-SOP-MA-002 could be improved but there was no evidence that a senior employee stated that, in general, the SOP was flawed or that it was being trained out to test affiliates. One interviewee recalled the word 'flawed' being used, but only in the context of the need to remove the requirement and timelines for the reintroduction of revised promotional material. The senior employee might have referred to improving the SOP once it had been used in practice, but, given that processes should be regularly reviewed with a view to continuous quality improvement, the company did not consider that this was inappropriate or in breach of the Code. There was no evidence that any comment was made at either meeting about using legal privilege to prevent information being received by the PMCPA and Otsuka Europe denied any breach of the Code in that regard.

Otsuka Europe noted that the complainants had raised a number of other concerns:

- Oversight from the global organisation and distribution of information as well as maintenance of the email lists used to notify affiliates of SPC and prescribing information changes;
- Confusion in relation to timelines;

- Out-of-date prescribing information (addressed above);
- Distribution of correct prescribing information (addressed above); and
- Concern about the relevant process and blame culture.

Otsuka Europe refuted the complainants' allegations that it did not provide information or receive oversight from the global organisation; while the company could improve its email list maintenance, the existing process to update mailing lists did not constitute a breach of the Code. Otsuka Europe recognized that despite its best efforts to remediate, EU-SOP-MA-002 still needed to be improved as there continued to be inconsistencies between the SPC and prescribing information. Otsuka Europe also recognized that while many employees used internal reporting mechanisms to raise matters of concern, some at least felt uncomfortable doing so.

Oversight from the global organisation and distribution of information

Otsuka Europe noted the complainants' concern that global medical and the global QRS team might not have been kept fully informed in relation to the issues faced by Otsuka Europe to communicate to affiliates changes to SPCs or might not have taken any action in relation to such issues. Otsuka Europe confirmed that there had been significant communication within Otsuka in relation to the issues via a number of channels:

1 Updates on remediation progress by members of Otsuka Europe senior leadership and compliance to the Otsuka Europe Board on a quarterly basis.
2 At least a dozen updates including both remediation progress and complaint response updates to the global QRS team, as PMCPA complaints had been received and responses drafted by Otsuka Europe.
3 Ad hoc updates via the emergency compliance risk reporting route to Otsuka Pharmaceutical Company Compliance, as PMCPA complaints had been received and responses drafted by Otsuka Europe.
4 Monthly remediation progress updates from senior Europe employees. This was implemented as a recommendation of the Otsuka Europe Board.

Details about vanity roles were provided including that the global QRS team was the overarching global governance, decision-making and oversight body for significant quality, regulatory, and safety issues. The team had been quite involved in providing recommendations and suggestions to Otsuka Europe during a dozen planned and ad-hoc meetings since June 2018. In addition, on 31 January 2019, it approved an independent audit to provide a comprehensive and objective assessment of the entire end-to-end labelling process, with a plan for accelerated remediation of all findings and observations. This audit planned to identify and holistically address the gaps in the process and took place from 25 February through to 1 March 2019.

The Otsuka Europe board had told Otsuka Europe that the remediation was moving too slowly and it asked Otsuka Europe to work with global regulatory affairs, global pharmacovigilance and global quality through Otsuka Europe D&C to speed up the corrective actions. Additionally, the Otsuka Europe board recommended monthly updates from a named employee at Otsuka Europe to a very senior employee in medical, safety, regulatory and quality.

Otsuka Europe noted that regardless of the recommendations and advice received from global, it was ultimately responsible for the successful execution of the plans to improve the processes that required remediation, in addition to communicating up-to-date and appropriate information on its marketed products to prescribers.

In summary, Otsuka Europe refuted the allegation that the global organisations had failed to take a more involved approach over issues related to the SPC implementation process. There had been consistent oversight, communication and provision of advice where considered appropriate as noted above. However, not all employees would know of these interactions and the slow pace of remediation had left some with the incorrect perception that these issues had not been taken seriously. Otsuka Europe stated that it would enhance communication to employees around this issue and had implemented a series of weekly Town Hall style updates.

Otsuka Europe noted the complainants' concern that distribution lists for the communication of SPC and prescribing information revisions were not kept up-to-date. but noted that in that regard it had taken two important steps to address this issue.

In Case AUTH/3041/6/18, Otsuka Europe acknowledged that emails notifying affiliates of SPC or prescribing information changes had not reached their destinations due to poorly maintained mailing lists. The company standardized its process to use generic email inboxes in each affiliate, implementing them where they did not exist. This substituted for the named individuals and reduced the need to maintain the mailing list. Additionally, as previously explained in Case AUTH/3123/11/18, tracking the implementation of SPC/prescribing information revisions in each affiliate was a remediation Otsuka Europe took to address these communication issues.

Specifically, the first step in this tracking was an acknowledgement that the communication on changes to SPC and prescribing information had been received by the affiliate or third party; failure to respond in a very short timeframe would be noted and appropriate action taken. This check was put in place specifically after noting the failures in Cases AUTH/3041/6/18 and AUTH/3042/6/18; it ensured that communication was received by the affiliates and third parties, and thereby mitigated the risk that an email address change would be overlooked and not correctly added to the mailing list.

As the complainants noted, Otsuka Europe needed to continue to improve the process to remove incorrect

or outdated emails from the mailing list. In the new version of EU-SOP-MA-002, the mailing list would be simplified to remove all named individuals.

Otsuka Europe denied any breach of the Code with regard to this allegation.

Confusion in relation to timelines

Otsuka Europe noted the complainants' references to the timelines included in the communication of a prescribing information revision sent out on 21 December 2018. These timelines were calculated incorrectly and caused some affiliates to question the provided dates. Otsuka Europe acknowledged that the current version had caused some confusion in relation to timelines for implementation of the SPC updates. As noted above, EU-SOP-MA-002 was being revised. Whilst Otsuka Europe admitted breaches of the Code with regard to the overall process, it did not believe that an incorrectly calculated timeline was a breach of the Code.

Concern about EU-SOP-MA-002 and 'blame culture

Otsuka Europe noted that the complainants referred to EU-SOP-MA-002 being updated 'from scratch'. As noted above, the relevant SOP was being rewritten; there continued to be failings in the relevant process and the company was addressing that as a matter of urgency. Otsuka Europe acknowledged breaches in this regard as stated above.

In relation to the allegation of a 'blame culture' at Otsuka Europe, and a 'climate of fear' where employees expressed concerns about retaliation, it was important to recognize that individuals' perceptions were their realities. Otsuka Europe recognized that the very nature of these complaints indicated at least one or more employees had this concern about the company's culture.

Otsuka Europe noted that its whistleblowing policy and its incident response procedure both specifically stated that employees would be protected from retaliation. A SpeakUp programme was re-launched in 2017. Employees could elevate concerns to the SpeakUp line or website via their direct manager, or through authorized recipients in the organization. During 2018, the company discovered that due to a firewall misconfiguration, 6 contacts to the SpeakUp line were not routed correctly. When identified, the issue was fixed and incidents were promptly acted upon. Other reporting mechanisms were not affected.

There had been a significant increase in incidents reported in January/February 2019. In 2018, 47 incidents were raised internally, 19 were specifically related to Otsuka Europe; in 2019 there had been 27 incidents recorded, 21 of which were specifically related to Otsuka Europe. Each of these incidents had been recorded; each complainant had been contacted; and each was being investigated according to priority.

Otsuka Europe recognized that these concerns and individual perceptions required it to make concerted efforts to address its culture and in February the company had set up a team to address culture head on. The team would engage employees via surveys, the weekly Town Hall style meetings and other mechanisms to positively change culture.

With regard to the complainants' comment about why an employee had left the organisation, Otsuka Europe stated that it did not comment on management discussions with individual employees, consistent with privacy and employment law requirements.

Regardless of the accuracy of the complainants' claims, Otsuka Europe did not believe that cultural issues were breaches of the Code.

Summary

Otsuka Europe considered that the mistakes made in the revision of the Jinarc prescribing information were regrettable and it acknowledged breaches of Clauses 9.1 and 2 of the Code in that regard.

The company did not consider that any of the additional information provided by the complainants amounted to a breach of the Code apart from those acknowledged. Otsuka Europe stated that it was addressing the five priority remediations as soon as possible. In the meantime, it would continue to track the implementation of SPC revisions in all European affiliates.

PANEL RULING

The Panel noted that Otsuka Europe's headquarters were based in the UK. Otsuka Europe was a member of the ABPI and thus obliged to comply with the Code.

The Panel noted the complainants' allegation that a communication sent by Otsuka Europe dated 21 December 2018 in relation to a change in the Jinarc summary of product characteristics (SPC) in December 2018 included incorrect implementation dates and was confusing and included out-of-date Jinarc prescribing information. The complainants also alleged that there was no central repository for prescribing information and no process for its creation; the process for updating the prescribing information and SPC were not correct; and the email distribution list for SPC/prescribing information revisions was not up-to-date. In addition, the complainants made allegations about what was said by a senior member of the European medical team and about oversight by Otsuka's global teams.

The Panel noted Otsuka Europe's submission that the SPC update in question related to the addition of blisters in wallet cards with new Marketing Authorization Holder (MAH) numbers. The Panel noted that the communication in question, dated 21 December 2018, included several required affiliate actions including timelines for, *inter alia*, distribution of the updated SPC and package leaflet, withdrawal of previous SPC, package leaflet and promotional materials and update of non-promotional materials. The timeline for actions were given in both the number of business days and the completion date.

The Panel noted that there was some confusion in that the number of business days did not appear to correlate with the completion date. The Panel noted that when the dates were queried by an Otsuka UK employee, the response was that for the purpose of calculating working days for implementation dates taking into account the Christmas and New Year period; 24 and 31 December were considered as 'non-working' days in addition to the national public holidays (25, 26 December and 1 January). It was not clear if this was communicated to all of the original email recipients or just the individual who had queried it.

The Panel noted Otsuka Europe's submission that the timelines stipulated in the communication in question were calculated incorrectly and caused some affiliates to question the dates provided. The Panel considered, however, that the completion dates in the email in question appeared to be correct if 24 and 31 December and the public holidays were not considered to be working days. The Panel was concerned to note that these specific/additional 'non-working days' did not appear to be either covered in the relevant SOP or to be widely communicated and in the Panel's view this caused confusion. The Panel noted that further confusion was caused by a senior member of Otsuka Europe incorrectly referring to the communication in question as 'the Jinarc SmPC change regarding gout', which was not so.

The Panel had no information with regard to the dates of actual implementation performed by the recipients of the email in question. Otsuka Europe made no submission in this regard and there was no allegation on this point.

The Panel noted that although a completion date was given, the confusion around how the dates were calculated (with regard to business days) and the lack of clear communication in this regard caused confusion with regard to a critical process and meant that Otsuka Europe had failed to maintain high standards in this regard. A breach of Clause 9.1 was ruled.

The Panel did not consider that the email demonstrated that senior European leaders did not understand the process and no breach of Clause 9.1 was ruled in this regard.

With regard to the incorrect prescribing information included in the communication in question, the Panel noted Otsuka Europe's timeline of events; the SPC was revised in July 2018 to include an extension to the indication in Section 4.1 (CKD stage 4) and the addition of abdominal pain as a common side effect to section 4.8; the prescribing information was updated at the time to reflect these SPC changes. There was then a further SPC change regarding the addition of acute liver failure to sections 4.4 and 4.8 and these changes were included in the revised September 2018 prescribing information. In November 2018, the SPC was revised due to a change of marketing authorisation holder and was revised again in December 2018 to include the addition of wallet card blisters; however, both the November 2018 and December 2018 prescribing information omitted the previously added information regarding CKD stage 4, abdominal pain and acute liver failure.
The Panel noted the general principle that prescribing information (defined by Clause 4.2) must be up-to-date and must comply with Clauses 4.1 and 4.2 of the Code. The prescribing information must be consistent with the SPC for the medicine. The Panel noted Otsuka Europe's submission that, although certified and distributed to affiliates, neither the November 2018 nor the December 2018 prescribing information was used in external materials. The Panel was unclear with regard to what Jinarc promotional material, if any, was in circulation during November and December. Otsuka Europe made no submission in this regard. The Panel noted that the complaint concerned the internal distribution of the Jinarc prescribing information dated December 2018 as an attachment to the email dated 21 December 2018; the complainant made no reference to its use on materials. The Panel considered that it had no evidence before it in this case that incorrect or out-of-date prescribing information was actually used and considered that there was no allegation concerning its use on materials and in that regard, ruled no breach of Clause 4.1. The Panel noted that the use of incorrect Jinarc prescribing information on materials was the subject of another complaint (Case AUTH/3041/6/18).

Although it appeared to the Panel, from information provided by both parties, that the errors in the December 2018 prescribing information had been identified internally prior to the Authority's receipt of the complaint and remedial action taken, the Panel considered that Otsuka Europe had failed to maintain high standards by certifying and widely distributing incorrect prescribing information which omitted important safety information and a change to the licensed indication and which had the potential to be used in multiple affiliates. The Panel therefore ruled a breach of Clause 9.1.

The Panel noted the allegation that there was no central repository for storing up-to-date prescribing information, no standard process for the creation of prescribing information and the process for updating the prescribing information and SPC was not correct despite the latest SOP. The Panel noted Otsuka's submission that it was developing a repository and a process for authoring/updating prescribing information, however, this was not currently in place. The Panel was concerned that there appeared to be a general lack of oversight and guidance with regard to prescribing information creation and revision and noted the errors that had occurred in the November and December 2018 Jinarc prescribing information. The Panel considered that prescribing information was critical information required in all promotional materials and had the potential to impact patient safety.
The Panel noted that Otsuka acknowledged that the relevant SOP, SOP-MA-002, still needed to be improved in relation to both SPC and prescribing information updates. The Panel considered that the lack of a clear process for both the creation and revision of prescribing information and SPC updates meant that Otsuka Europe had failed to

maintain high standards and a breach of Clause 9.1 was ruled.

With regard to the allegation that the email distribution list for the communication of SPC and prescribing information revisions contained individuals who had left the company and mailing lists were not kept up-to-date, the Panel noted that the complainants had provided no evidence that individuals who should have received the communication in question had been omitted from the distribution list. The Panel noted Otsuka Europe's submission that it used generic email inboxes in each affiliate, and it intended to simplify the mailing list in its new version of the relevant SOP to remove all named individuals. In the Panel's view, that the email in question had been sent to individuals who had left the company was not in itself a breach of the Code so long as individuals who should have received it had done so. In the Panel's view, the complainants had not discharged their burden of proof to show that a breach of the Code had occurred in this regard and no breach of Clause 9.1 was ruled.

The Panel noted the complainants' allegations that a senior member of the Otsuka Europe medical team stated that the SOP for SPC and prescribing information updates (EU-SOP-MA-002) was flawed but was still approved and trained out in order to 'test the affiliates'; and that he/she stated that Otsuka Europe could use legal privilege to prevent the PMCPA receiving all the necessary information. The Panel noted Otsuka Europe's submission that its investigation into the alleged comments found no evidence that these statements were made. The Panel noted that, nonetheless, it appeared that there had been an acknowledgement at the meeting in question that the SOP required improvement. One interviewee recalled use of the word 'flawed'. Otsuka Europe acknowledged that the SOP required improvement. The Panel considered that this was a serious allegation; self-regulation relied upon, *inter alia*, full transparency from companies. The parties' accounts differed. It was difficult to determine where the truth lay. The Panel noted, however, that the complainants bore the burden of proof and considered, on balance, that the burden of proof had not been discharged and it therefore ruled no breach of Clause 9.1.

The Panel noted the complainants' allegations with regard to its Japanese parent company, global quality, regulatory and safety team, global medical and pharmacovigilance. The Panel noted Otsuka's submission that there had been consistent oversight, communication and provision of advice where considered appropriate from the above mentioned groups and that it refuted the allegation that Otsuka's global organisations had failed to take a more involved approach with respect to the issues related to the SPC implementation process. The Panel noted that rulings were made based on the evidence provided by both parties and that the complainants bore the burden of proof. The extent to which these allegations came within the scope of the Code in relation to global was unclear. Otsuka had made no submission on this point. The complainants had provided no detail with regard to this allegation and, in the Panel's view, the complainants had not discharged their burden of proof. No breach of

Clause 9.1 was ruled in this regard.

With regard to the allegation that there was a prevalent blame culture within the organisation and a climate of fear. The Panel considered that comments about the culture of an organisation might fall within the scope of the Code if that culture directly or indirectly contributed to a breach of the Code. The Panel noted Otsuka's submission that Otsuka Europe had a whistleblowing procedure and an incident response procedure which specifically stated that employees would be protected from retaliation. The complainants had provided no detail with regard to this allegation and, in the Panel's view, the complainants had not discharged their burden of proof. No breach of Clause 9.1 was ruled in this regard.

The Panel noted its comments and rulings above. The Panel noted that Clause 2 was a sign of particular censure and reserved for such use. On balance, the Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 and ruled no breach accordingly. The complainants appealed this ruling.

APPEAL BY THE COMPLAINANT

The complainants appealed against the Panel's ruling of no breach of Clause 2.

The complainant's alleged that Otsuka had reduced confidence in the pharmaceutical industry for the following reasons:

- Unclear communication for the update of materials for new prescribing information – (a breach of Clause 9.1).
- Failed to maintain high standards by certifying and widely distributing incorrect prescribing information which omitted important safety information and a change to the licensed indication (breach of Clause 9.1).
- Unable to remediate a critical process (distribution of updated SPC and prescribing information) despite an initial PMCPA complaint in June 2018.

RESPONSE TO APPEAL

Otsuka Europe submitted that as acknowledged in its initial response, it had admitted to two breaches of Clause 2 due to:

- Otsuka Europe's inability to effectively remediate the issues highlighted in Case AUTH/3041/6/18 and the continued failure to address the issues.
- Not effectively achieving one of the key objectives of EU-SOP-MA-002 v6.0 'Notification of Changes to SPC, PL and prescribing information by OPEL/OPNL/ONPG to the OPEL affiliates and relevant Third Parties', to ensure that up-to-date information was provided when performing promotional activities via the prescribing information.

Thus, Otsuka Europe agreed with the complainants in this case that the cumulative effect of the issues reduced confidence in and brought the industry in to disrepute.
Whilst Otsuka Europe acknowledged the above, it considered it was vital that the Appeal Board understood the significant actions that had been taken in order to address these and other issues faced:

- Otsuka Europe confirmed that EU-SOP-MA-002 v6.0 the European process which included the creation and communication of prescribing information had been comprehensively reviewed and clarified and had been effective since 30 April 2019.
- Otsuka Europe submitted that as part of its response to Case AUTH/3151/1/19 it committed to reviewing all of the prescribing information and as a result of this review it submitted a voluntary admission (24 June 2019), detailing the outcome of the review including the identified discrepancies between the prescribing information and the relevant SPC. All prescribing information was comprehensive and fully consistent with the SPC. Although not a Code requirement Otsuka Europe had taken and implemented the decision to include all adverse events in the prescribing information in order to remove the element of subjectivity as to which adverse events should be included (in particular in relation to serious side effects), to avoid further issues in the future.
- Details of various staff changes and appointments were provided.
- As communicated to the PMCPA on 6 April 2019, Otsuka Europe had ceased initiating promotional and non-promotional activities unless such activities were required for legal, regulatory (eg, prescribing information and risk minimisation materials) or contractual reasons. The latter included work done jointly with Alliance partners. From June 2019, any Otsuka Europe signatories had to have completed comprehensive third party validation.
- A cross-functional project team had developed Otsuka Europe specific procedures for all Code-related activities conducted by Otsuka Europe, in order to provide the depth of detail required by the organisation. These had been extensively reviewed and were currently being cross-checked to ensure that they were robust. These would then be rolled out with comprehensive face-to-face training and knowledge and would then be validated via Otsuka's learning management system.
- The July meeting of the newly formed European Pharmaceutical Leadership Team (EPLT) included an assessment of the current challenges faced by Otsuka Europe, what the future held for the organisation and what the leadership team wanted, and how the leadership team intended to achieve their goals. Details were provided. These included:

    - Creation of a Vision and Roadmap to 2024.
    - Strategy to achieve Roadmap to 2024.
    - Continue to strengthen Culture & Engagement.
    - Continue CORE activities.
    - Get the 'Basics' right on business processes.

The above goals were presented at a town hall meeting in July 2019.

- A European Code of Conduct for all employees that would set out the ethical standards for employees to adhere to was being developed.
- Otsuka Europe was committed to transparent communication within the organisation and expected the same from its leadership team. In addition to the weekly town hall meetings, Otsuka Europe had instituted weekly 'Ask EPLT' sessions where any staff member might ask questions as part of a small group in a more informal setting.

Otsuka Europe hoped that the above demonstrated the approach that Otsuka Europe was taking to address the significant issues that it faced.

FINAL COMMENTS FROM THE COMPLAINANT

The complainants acknowledged that Otsuka Europe accepted a breach of Clause 2. However, the complainants were unclear as to why it had taken nearly eight months to review all associated prescribing information, especially as Otsuka Europe had committed to do so at the beginning of the year.

Could Otsuka claim to take patient safety seriously if the prescribing information did not have all the relevant safety information? What was the duration of the inconsistencies, and was the Pharmacovigilance/Global made aware of the risk to patient safety? If Pharmacovigilance/ Global was aware, what were their actions? The complainants did not understand the claim that the European process which included the creation and communication of prescribing information had been comprehensively reviewed and clarified and had been effective since 30 April 2019, if this was true, why was the voluntary submission made on 24 June 2019? Did this indicate that the process had failed, especially concerning the latest SPC change?

The complainants stated that Otsuka's current leadership needed more tangible outputs and they had not seen a significant difference between the past and present leadership.

APPEAL BOARD RULING

The Appeal Board noted from the Panel's rulings above that there was a lack of clear process for both the creation and revision of prescribing information and SPC updates; that Otsuka Europe had certified and internally distributed to multiple affiliates incorrect prescribing information which omitted important safety information and a change to the licensed indication; and that the lack of clear communication about completion dates for an SPC update caused confusion with regard to a critical process had meant that Otsuka Europe failed to maintain high standards and three separate breaches of Clause 9.1 were ruled.

The Appeal Board noted that Otsuka Europe agreed with the complainants' appeal that the cumulative effect of the issues warranted a breach of Clause 2. The company apologised for its inability to

effectively remediate the issues highlighted in Case AUTH/3041/6/18, and its continued failure to address the issues with regard to SPC updates and prescribing information. Otsuka Europe submitted that these failings had reduced confidence in the pharmaceutical industry. The Appeal Board was very concerned about how long it was taking Otsuka Europe to address these issues. The representatives from Otsuka Europe stated that this delay was due to the company failing to understand the role of prescribing information in relation to patient safety.

The Appeal Board considered that the cumulative effect of Otsuka Europe's failings in this case reduced confidence in the pharmaceutical industry and ruled a breach of Clause 2. The appeal on this point was successful.

Complaint received	**24 January 2019**
Case completed	**16 October 2019**