CASE AUTH/3259/10/19 ***NO BREACH OF THE CODE***

COMPLAINANT v OTSUKA EUROPE

Jinarc Risk Minimisation Materials

An employee complained about Otsuka Europe in relation to risk minimisation plan (RMP) materials for Jinarc (Tolvaptan) and alleged a lack of urgency in dealing with patient safety.

The complainant alleged that the latest European RMP materials did not contain all of the necessary safety data. The affiliates had expressed concerns over the omissions. However, the RMP material remained unchanged, despite this being a centralized procedure/process. The complainant believed that vulnerable patients were being placed at risk.

The complainant was also deeply concerned regarding the lack of urgency that Otsuka had demonstrated in light of the PMCPA audit and associated actions. At the time of the complaint the several senior leaders had been away for two weeks in Japan. All major decisions had been put on hold until their return.

The complainant stated that he/she was deeply saddened that senior leaders in Otsuka had yet to understand the seriousness of the current situation. It had no standard operating procedures (SOPs), no clear direction, no clear decisions (even the 'pens down' approach to halting activity was confusing) and yet, it had focused on Mexican themed events, developing values (which were a mockery given the l*aissez-faire* attitude of the leaders) and playing table tennis.

The complainant feared that Otsuka was not putting patient safety first, instead, focusing on activities that appeared frivolous.

The complainant responded to a request for further information including what was missing from the European risk management plan materials and what was the impact on patient safety? The response included that unfortunately, the sections on pregnancy had been removed. Studies in animals had shown reproductive toxicity, the risk to humans was unknown. It was ethical to forewarn patients who were planning to have a family. Further advice from the EMA on dehydration (a significant side effect with tolvaptan) had also not been taken into consideration. Therefore, patients could be at risk of dehydration secondary to the aquaretic effects of tolvaptan, especially in cases where patients had insufficient water intake.

The complainant wanted to understand how the material was approved in the first place (what was the process of approval)? Why was such pivotal information missed? Had the RMP materials been cross checked with the advice of the EMA and summary of product characteristics (SPC)?

The detailed response from Otsuka is given below.

The Panel noted that references to pregnancy and dehydration were missing in updated centralised approved risk minimisation measures (aRMM) materials. The Panel noted Otsuka Europe's explanation that this was due to an exceptional inconsistency between the EMA approved European Tolvaptan RMP version 14.1 and the conditions to the marketing authorisation (Annex IID) with respect to the requirements pertaining to aRMMs and the inclusion of references to pregnancy and dehydration (which existed since the grant of the Jinarc marketing authorisation). The Panel noted that the issue was however identified as part of the local review process and rollout of the materials was stopped; EU affiliates had been instructed to pause the review of local aRMM materials vs the revised centralised material. The Panel noted Otsuka's submission that at no point were any aRMM materials issued by Otsuka to health professionals or patients that erroneously did not include reference to pregnancy and dehydration.

The Panel noted Otsuka's submission that the current aRMM materials available to health professionals and patients contained the required reference to pregnancy and dehydration. The Panel therefore considered, based on the very narrow allegation, that the aRMMs provided to health professionals and patients were not misleading as alleged. No breach of the Code was ruled. The Panel noted that the Code required that promotion must encourage the rational use of a medicine by presenting it objectively and without exaggerating its properties. The Panel did not consider that there was evidence that the current aRMM materials provided to health professional and patients constituted promotion and therefore ruled no breach of the Code. The feedback provided by the EU affiliates in this case was part of the review and approval of the Jinarc aRMM materials and appeared to have been actioned appropriately. Thus, the Panel did not consider that Otsuka had failed to maintain high standards in this regard and no breach of the Code was ruled. The Panel consequently ruled no breach of Clause 2. The complainant appealed all but one of the rulings of no breach of the Code. The Appeal Board upheld all the rulings of no breach appealed by the complainant.

The Panel noted that the complainant bore the burden of proof and did not consider that he/she had provided evidence to show that on the balance of probabilities Otsuka had demonstrated a lack of urgency in addressing the issues highlighted during the recent PMCPA audit, or that senior leaders in Otsuka Europe 'have yet to understand the seriousness' of Otsuka Europe's current compliance situation, or that Otsuka Europe had no processes in place, or that Otsuka was not putting patient safety first but was focussing on frivolous activities. The Panel noted Otsuka's detailed submission on these points. The Panel therefore ruled no breaches of the Code including Clause 2 in relation to each matter. The Appeal Board upheld the rulings of no breach on appeal by the complainant.

An employee complained about Otsuka Pharmaceuticals Europe Ltd in relation to risk minimisation plan (RMP) materials for Jinarc (Tolvaptan) and alleged lack of urgency in dealing with patient safety.

COMPLAINT

The complainant alleged that the latest European RMP materials did not contain all of the necessary safety data. The affiliates had expressed concerns over the omissions. However,

the RMP material remained unchanged, despite this being a centralized procedure/process. The complainant believed that vulnerable patients were being placed at risk.

The complainant was also deeply concerned regarding the lack of urgency that Otsuka had demonstrated in light of the PMCPA audit and associated actions. At the time of the complaint several senior leaders had been away for two weeks in Japan. All major decisions had been put on hold until their return.

The complainant stated that he/she was deeply saddened that senior leaders in Otsuka had yet to understand the seriousness of the current situation. It had no standard operating procedures (SOPs), no clear direction, no clear decisions (even the 'pens down' approach to halting activity was confusing) and yet, it had focused on Mexican themed events, developing values (which were a mockery given the l*aissez-faire* attitude of the leaders) and playing table tennis.

The complainant feared that Otsuka was not putting patient safety first, instead, focusing on activities that appeared frivolous.

The case preparation manager asked for more information from the complainant who was asked to provide as much detail about the material at issue as possible. What was missing from the European risk management plan materials? What was the impact on patient safety?

In response the complainant explained that advice from the EMA stated '…The educational programme is aimed at ensuring awareness about the potential risk to hepatotoxicity and providing guidance on how to manage this risk and the importance of pregnancy prevention prior to the initiation and during the treatment with Jinarc….'.

The complainant stated that unfortunately, the sections on pregnancy had been removed. Studies in animals had shown reproductive toxicity, the risk to humans was unknown. It was ethical to forewarn patients who were planning to have a family.

Advice from the EMA on dehydration (a significant side effect with tolvaptan) had also not been taken into consideration. Therefore, patients could be at risk of dehydration secondary to the aquaretic effects of tolvaptan, especially in cases where patients had insufficient water intake.

The complainant wanted to understand how the material was approved in the first place (what was the process of approval)? Why was such pivotal information missed? Had the RMP materials been cross checked with the advice of the EMA and summary of product characteristics (SPC)?

When writing to Otsuka, the Authority asked it to consider the requirements of Clauses 7.2, 7.9, 7.10, 9.1 and 2 of the Code.

RESPONSE

1 Jinarc Additional Risk Minimisation Materials.

Otsuka explained that as part of the marketing authorisation, Jinarc had a Risk Management Plan (RMP) as well as educational materials as additional Risk Minimisation Measures (aRMMs) to ensure that Jinarc was used as safely as possible in light of the risk of hepatotoxicity associated with the medicine. The aRMM materials included:

- Health professional educational guide
- Prescribing checklist
- Patient alert card
- Patient education brochure.

Over the past year, Otsuka had received feedback from multiple regulatory agencies across the EU that the Jinarc aRMM materials were too detailed. Also, the materials could be further optimised to meet the current *Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators* and its addendum.

The guidance stated the following in relation to aRMMs and the associated educational materials.

Module XVI Section B.2.1 Educational Programme:

'The content of [nay] educational material should be fully aligned with the currently approved product information for a medicinal product, such as the SmPC and PL, and should add rather than duplicate SmPC and PL information. […] the focus of the educational material should be on the risk(s) related to the product and the management of those risk(s) requiring additional risk minimisation.'

Module XVI Section B.2.1.1. Educational Tools:

> *'This information should focus on clearly defined actions related to specific safety concerns described in the RMP and should not be diluted by including information that is not relevant to the safety concern and that is already adequately presented in the SmPC or package leaflet.'*

Module XVI Addendum 1 Section 1.2. Principles of Educational Materials:

> *'- Any educational material should be specifically designed to fulfil the risk minimisation objectives.*
> *- It should focus on the specific safety concern(s) and provide clear statements and concise messages describing actions to be taken in order to prevent and minimise these risks.'*

Further, additional guidance in *Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems* was relevant.

Module V Section C.3. Assessment of the risk management plan within the EU regulatory network:

> *'For centrally authorised medicinal products, only risk minimisation measures recommended by the PRAC and subsequently agreed by the CHMP should be included in the risk minimisation plan as additional risk minimisation activities. Additional risk minimisation measures are conditions to the marketing in authorisation; key elements are detailed in annex II to the Commission decision.'*

Based on the guidance quoted above, the RMP and the conditions of the marketing authorisation were expected to be aligned on the aspect of additional risk minimisation measures. Thus, the reference documents used to better align the aRMM materials with the guidance was the European Medicines Agency (EMA) approved European Tolvaptan RMP version 14.1 which contained the safety concerns and the risk minimisation plan for Jinarc, and the EU Jinarc summary of product characteristics (SPC).

In August 2019, Otsuka Global Pharmacovigilance initiated the review of central aRMM material. This review was conducted as required by the Otsuka Global Standard Operating Procedure (GSOP) PV-3401-GSOP "Risk Management Plan Production and Tracking" and the related Working Practice PV-3401-WP-005. It involved the GPV Medical Safety Product Leader, Senior Manager Regulatory Affairs Region Europe and Associate Director PV Europe (acting as the Regional aRMM lead). This procedure ensured a cross-functional discussion and involvement of global and local stakeholders. The process also ensured that local aRMM leads were involved in development and revision of the materials at a local level, based on the finalized aRMM.

On this basis, on 21 August an email was sent by the regional aRMM lead to the Otsuka EU affiliates notifying them that the centralised aRMM materials were being revised and once received by the affiliates they '*will then need to review against your local materials and any local requirements you may have*'.

The central aRMM materials completed the first internal review and approval on 23 August 2019 within the Otsuka regulatory electronic document management system (CREDO) by the same functions that had reviewed the aRMM materials in August. Subsequently, on 4 September, the regional aRMM lead provided these materials to the local aRMM leads with the request to review and to report the results back.

On 4 October, the UK affiliate (Otsuka Pharmaceuticals (UK) Ltd) verbally raised with the Regional aRMM lead a concern about the removal of reference to pregnancy and dehydration from aRMM materials. On 7 October, an email was received by the Regional aRMM lead from the Otsuka affiliate for Scandinavia and BeNeLux informing the Regional aRMM lead that the new education materials, in contrast to the existing materials, did not contain the measures related to pregnancy and dehydration, although such was mandated as per Annex IID to the EC decision. The email stated that certain aRMM materials should include reference to the importance of pregnancy prevention prior to the initiation of, and during the treatment with, Jinarc and the patient alert card should include the signs and symptoms severe dehydration.

On the same day, the Regional aRMM lead forwarded the email from the affiliate for Scandinavia and BeNeLux to the Medical Safety Product Leader and the responsible Associate Director, Aggregate Report Team, stating that reference to pregnancy and dehydration might have to be added back in to the central aRMM materials and asking for feedback on this. The reginal aRMM lead also replied to the email from the affiliate for Scandinavia and BeNeLux to confirm agreement with their assessment, that Global colleagues had been informed and stating that no changes were required for the aRMM materials in the meantime. On 9 October, the Regional aRMM lead also confirmed in agreement with OPUK that reference to pregnancy and dehydration should remain in materials.

An investigation into this matter has confirmed that:

- Annex IID ‘Conditions or Restrictions with Regard to the Safe and Effective Use of the Medicinal Product’. Under the section ‘Additional Risk Minimisation Measures’, contained requirements for the aRMM materials with respect to the importance of pregnancy prevention and signs of severe dehydration.
- The aRMM materials had always included this information. The materials were included in the RMP as an Annex since receipt of the marketing authorisation.
- In contrast, ever since marketing authorisation in 2015, the approved EU RMP indicated that no aRMMs were required for either the Important Identified Risk ‘Volume depletion, dehydration and associated sequelae’ or the Missing Information ‘Pregnancy Outcome Data’.

The approach of using the RMP as reference document was based on the assumption that, as per GVP guidance, the requirements of the Annex IID would follow the risk minimisation plan in the RMP. Hence, in this exceptional situation where there was an inconsistency between these documents, the concerned aRMM requirements in Annex IID were missed and thus were not included in the updated central aRMM materials. However, it was during the next process step, the local review, that the issue was discovered.

The issue was discovered and action was taken before any materials obtained health authority approval and hence no materials were used with, or provided to, health professionals (HCPs) or patients. Given that the current aRMM materials (ie those available to health professionals and patients) contained all the required educational and informational elements, the EU affiliates had now been instructed to pause the review of local aRMM materials v the revised centralised material until further clarity had been obtained on how to address the existing inconsistency in the RMP.

After initial investigation a deviation has been raised to document the process of root cause analysis and corrective preventative actions:

- The marketing authorisation holder will be requesting further guidance from the EMA in order to address the existing inconsistency between the RMP and the Annex IID.
- The PV-3401-GSOP ‘Risk Management Plan Production and Tracking’ will be further strengthened in order to be more robust in avoiding exceptional situations like these. This should ensure that any new or updated EU RMP is checked against Annex II before approval. In case any inconsistencies are found these should be resolved in collaboration with the EMA. The RMP, SPC and the conditions to the marketing authorisation, Annex II, will be used as references for the development and update of EU aRMM materials.

In summary, due to an exceptional inconsistency between approved RMP and the conditions to the marketing authorisation (Annex IID) with respect to the requirements pertaining to aRMMs, existing ever since the marketing authorisation of Jinarc, the mentioned aRMMs were missing in updated central aRMM materials. The issue was identified as part of the standard review activities as per GSOP, during local review. Subsequently, the issue was raised and actioned appropriately, including halting the rollout of the materials, investigating and raising a deviation to create corrective and preventative actions. At no point had there been any aRMM materials issued by Otsuka to health professionals or patients that erroneously did not include reference to pregnancy and dehydration.

As there was never material provided to either patients or health professionals that was misleading, Otsuka did not consider that there had been any breach of Clause 7.2. Similarly, all information provided in aRMM materials reflected the available evidence in relation to adverse events and Otsuka did not consider that there had been any breach of Clause 7.9. Information provided was presented objectively and thus there had been no breach of Clause 7.10. The feedback provided by the EU affiliates in this case was part of the review and approval of the Jinarc aRMM materials and actioned appropriately. Thus, Otsuka did not consider that there had been any failure to maintain high standards and refuted any breach of Clauses 9.1 and consequently Clause 2.

2 Lack of a sense of urgency.

The complainant raised concerns that Otsuka had demonstrated a lack of urgency in addressing the issues highlighted during the recent PMCPA audit and referred to a number of matters, which Otsuka grouped into categories and addressed below:

a) Senior leadership and direction

The complainant was concerned that senior leaders in Otsuka Europe 'have yet to understand the seriousness' of Otsuka Europe's current compliance situation. Otsuka Europe would like to reassure the complainant and the PMCPA that each member of the European Pharmaceutical Leadership Team (EPLT) was fully aware of the gravity of the situation that Otsuka faced. Senior leaders had met on a regular basis since February 2019 as part of the CORE project (the Otsuka compliance -improvement programme) to assess the progress and challenges in relation to the organisation's overall improvement plans and activities.

The complainant was correct in that three members of the EPLT, travelled to Japan for business purposes, however it was incorrect that during this time 'all major decisions' were put on hold.

Otsuka Europe was working towards building a compliance framework that was sustainable and not reliant on individuals. As part of this, during the time that certain senior leaders were out of the country, the compliance team, worked on the following activities:

- Restructuring the compliance department, gaining additional senior headcount and successfully recruiting compliance staff in late 2019.
- Developing a comprehensive breakdown of the recommendations made throughout the report of the audit conducted by the PMCPA in July 2019 in order to develop a plan to detail and track the improvement activities required of Otsuka Europe, Europe Development and Commercialisation Ltd (OEDC) and Otsuka UK.
- Continuing to develop detailed and simplified SOPs for Otsuka Europe which have been drafted by Otsuka Europe staff earlier in the year, in addition to planning face-to-face training to implement these processes.
- Developing training materials in order to communicate the issues and learnings from the various audits conducted in Otsuka Europe in face-to-face workshops.
- Finalising documentation to use a third party to provide comprehensive training for Otsuka Europe signatories, reviewers and originators of Otsuka Europe materials and activities.

In addition, remotely from Japan, two members of the senior team dialled in to and participated in the regular Audit and Risk Committee meeting, at which a significant proportion of time was dedicated to discussing Core.

The complainant also referred to 'pens down', which appeared to be reference to the initiative whereby Otsuka Europe had significantly reduced (details given) the activities that it was conducting, by only commencing those which related to a contractual, regulatory or legal obligation; Otsuka Europe referred to this as 'pencils down'. As previously communicated to the PMCPA, this was put in place in April 2019 in order to allow Otsuka Europe to focus on improvement activities. There had been some questions as to what this meant for day-to-day activities for the organisation and it recently developed and circulated a Q & A document to address these. Whilst the organisation required further clarity on a number of questions in relation to 'pencils down' Otsuka Europe did not consider that this amounted to 'no clear direction, no decisions*'.*

In relation to the allegation that Otsuka Europe had no processes, Otsuka noted that there were a number of European processes in place. Otsuka Europe submitted it would shortly be implementing a number of updated European SOPs as well as Otsuka Europe specific SOPs but in the interim the current European processes were being followed.

b) Social Activities

Finally, the complainant appeared to be concerned about a number of social activities that had been organised for Otsuka Europe and Otsuka UK over the summer months. Otsuka had a number of ongoing compliance issues and complaints that it must address, and this had understandably, impacted on morale within the organisation. In order to address this and to fully engage the organisation in the improvement activities, the first step was to create a team spirit amongst staff and a positive working atmosphere, and such social activities were part of this and important for employee's wellbeing. Otsuka Europe submitted that it would continue to arrange these at appropriate times, not least to show appreciation for the considerable time and effort that employees had and continued to, put into the vital improvement activities that Otsuka must carry out. Indeed, feedback from staff about these activities had been very positive.

With all of the above in mind, Otsuka Europe did not consider that Otsuka Europe's actions in this regard had failed to maintain high standards or brought the industry in to disrepute, and it therefore refuted that there had been any breach of Clauses 9.1 and 2.

PANEL RULING

The Panel noted that references to pregnancy and dehydration were missing in updated centralised aRMM materials. The Panel noted Otsuka Europe's explanation that this was due to an exceptional inconsistency between the EMA approved European Tolvaptan RMP version 14.1 and the conditions to the marketing authorisation (Annex IID) with respect to the requirements pertaining to aRMMs and the inclusion of references to pregnancy and dehydration (which existed since the grant of the Jinarc marketing authorisation). The Panel noted that the issue was however identified as part of the local review process and rollout of the materials was stopped; EU affiliates had been instructed to pause the review of local aRMM materials vs the revised centralised material. The Panel noted Otsuka's submission that at no point were any aRMM materials issued by Otsuka to health professionals or patients that erroneously did not include reference to pregnancy and dehydration.

The Panel noted Otsuka's submission that the current aRMM materials available to health professionals and patients contained the required reference to pregnancy and dehydration. The Panel therefore considered, based on the very narrow allegation, that the aRMMs provided to health professionals and patients were not misleading as alleged. No breach of Clause 7.2 was ruled. The Panel similarly and for the same reasons ruled no breach of Clause 7.9. The Panel noted that Clause 7.10 required that promotion must encourage the rational use of a medicine by presenting it objectively and without exaggerating its properties. The Panel did not consider that there was evidence that the current aRMM materials provided to health professional and patients constituted promotion and therefore Clause 7.10 was not relevant and the Panel therefore ruled no breach of Clause 7.10. The feedback provided by the EU affiliates in this case was part of the review and approval of the Jinarc aRMM materials and appeared to have been actioned appropriately. Thus, the Panel did not consider that Otsuka had failed to maintain high standards in this regard and no breach of Clauses 9.1 was ruled. The Panel consequently ruled no breach of Clause 2.

The Panel noted that the complainant bore the burden of proof and did not consider that he/she had provided evidence to show that on the balance of probabilities Otsuka had demonstrated a lack of urgency in addressing the issues highlighted during the recent PMCPA audit, or that senior leaders in Otsuka Europe 'have yet to understand the seriousness' of Otsuka Europe's current compliance situation, or that Otsuka Europe had no processes in place, or that Otsuka was not putting patient safety first but was focussing on frivolous activities. The Panel noted Otsuka's detailed submission on these points. The Panel therefore ruled no breach of Clauses 9.1 and 2 in relation to each matter alleged and described above.

APPEAL BY THE COMPLAINANT

The complainant wanted the Appeal Board to focus on, Clauses 9.1 and 2. The complainant noted that as per his/her original complaint, the areas of concerns were based on two facts:

1 the Risk Management Materials for Tolvaptan
2 lack of urgency with dealing with patient safety.

The complainant stated that the reasons for the appeal were based on the following:

A Otsuka Europe had failed to learn and amend the necessary documents/processes as per cases AUTH/3041/6/18 and AUTH/3042/6/18

The complainant alleged that Otsuka Europe had admitted that in August 2019, global pharmacovigilance initiated a central review of aRMM material, this was despite Otsuka UK and Otsuka Europe being invited to the Appeal Board in March 2019 (in light of previous failings as indicated in the above cases). Various staff were said by the complainant to have admitted that the RMP process was not robust enough (as evidenced by the slides presented to the Appeal Board and shared within the organisation). The gaps within the RMP process were identified in the summer of 2018 (AUTH/3041/6/18 and AUTH/3042/6/18). If senior leaders were serious in remediating the gaps, why had it taken:

- 14 months (from original PMCPA re: patient safety related issues) before the Global Otsuka SOP PV-3401-GSOP Risk Management Plan Production and Tracking was introduced?

- 16 months (from original PMCPA re: patient safety related issues) affiliates were having to point out the materials issued from Otsuka Europe were still missing important safety information?
- another complaint to the PMCPA before Otsuka Europe realised that there were inconsistencies of safety related matters of the RMP material since Jinarc obtained its marketing authorisation since 2015?

B Otsuka Europe had not provided the PMCPA with full and frank disclosure

The complainant alleged that affiliates were not trained on the Global Otsuka SOP PV-3401-GSOP Risk Management Plan Production and Tracking SOP. Therefore, Otsuka Europe's assertion that the affiliates provided feedback (as part of the process) once the materials were approved was not accurate. Otsuka Europe failed to disclose that during the time of the complaint, Otsuka Europe and Otsuka UK were in disagreement, to the point that the complainant's Otsuka UK colleagues had telephone conferences at nine o'clock at night to resolve ongoing issues. Both organisations were attempting to avoid another Clause 2, and Otsuka UK was trying to meet its original commitment to the PMCPA to update its RMP materials. Having spoken to his/her Otsuka UK colleagues – Otsuka Europe was attempting to blame the UK. The complainant stated that with such disarray, how could there be a process that provided clarity on roles and responsibilities (between regional and affiliates)? The complainant alleged that there was no process, especially given the recent history of poor governance within the organisation. If it was a true process, why

- was there no formal training of the process for the affiliates (Otsuka UK colleagues were not even aware of the SOP)?
- were mistakes still present in the RMP materials (sent to affiliates if a thorough review had taken place?
- were the materials in questions not approved by a medical signatory?

The complainant stated that in his/her understanding of the Otsuka Europe process for dissemination of material, was that all materials must be certified/ approved by a medical signatory before sending to the affiliates (this too the complainant believed was part of Otsuka Europe's commitment to the PMCPA). After having spoken to a member of the medical staff for Otsuka Europe, he/she was not aware that RMP materials were being updated or distributed to the affiliates. The complainant stated that this did not sound like a proper, robust process.

The complainant alleged that in his/her understanding that it was an Otsuka Europe undertaking that employees would not be engaging in activities, as its processes and personnel were not able to deal with the current compliance crisis. The complainant noted that this was an undertaking by a senior leader on behalf of Otsuka. The undertaking was supposed to be effective from April 2019, and although leaders provided verbal updates during the weekly meetings, there was significant confusion with Otsuka Europe. The complainant and his/her colleagues were instructed to carry on as usual especially when it came to delivering partner related projects, despite not having appropriate medical signatories or processes to ensure compliance with the Code/ EFPIA. The complainant was surprised that a named person did not seem to remember the numerous questions with respect to the 'pens down' approach. Why did it take until the end of October 2019 before the first formal written communication was sent out to the organisation? This was not an indicator that senior leaders were not 'keeping their fingers on the pulse' and remediating effectively, nor ensuring that all gaps related to patient safety were resolved.

C Otsuka Europe's rationale for missing relevant safety material and rationale for not breaching the Code was that patients and health professionals were not exposed to the materials

The complainant alleged that the Code had its specificities concerning the cases it oversaw. However, it did seem that Otsuka Europe benefited from this perpetual 'get out of jail card' – the ultimate responsibility lay with affiliates, even though Otsuka Europe had failed in ensuring that materials were of good quality or having appropriate governance for matters relating to patient safety.

The complainant did not believe that Otsuka Europe had admitted that due to exceptional inconsistency between the approved RMP and the conditions to the marketing authorisation (Annex IID) with respect to requirements pertaining to aRMMs, ever since the marketing authorisation of Jinarc, the mentioned aRMMs were missing in the updated central aRMM materials – the organisation did not breach any codes of practice. The complainant alleged that his/her employers had admitted to the PMCPA that they did not do a thorough check (when receiving feedback from competent authorities or when the gaps were initially identified in summer of 2018), hence the missing information on safety. This was not good enough during the regular business, more so when an organisation was in between PMCPA audits. The lack of accountability within the organisation was genuinely appalling.

D Other allegations/Summary

The complainant alleged that Otsuka Europe had admitted that the RMP materials had not been accurate since 2015; there were no words to describe the complainant's disappointment. The complainant stated that he/she was embarrassed to be an Otsuka Europe employee. The complainant stated that Otsuka Europe had significantly more resources than the affiliates (the number of individuals that oversaw the management of the RMP materials, for instance), and yet the affiliates bore all of the responsibility. The frustration with senior management (based in the UK, Germany, USA and Japan) stemmed for the reluctance to admit mistakes and hold individuals accountable. Senior leaders had been busy with international trips that involved rugby world cup matches (what impression did it leave for the rest of the organisation that was struggling to remediate gaps?), attempting to carry favour with Japan instead of fixing problems closer to home.

The complainant alleged that that providing 'supporting emails' by employees was a desperate ploy by Otsuka Europe. Did the Otsuka leaders believe that their systemic ills had been resolved by a couple of themed events? No other pharmaceutical company had accrued as many breaches over the space of 2 years, and Otsuka Europe leaders should reflect on the learnings and act appropriately.

The complainant alleged that there was still a fair amount of finger-pointing between the organisations (Otsuka Europe v Otsuka UK). A senior leader had been replaced, and hopefully, things would start to improve. CORE seemed to be dysfunctional, as there were serious gaps remaining, as demonstrated by this complaint. The members of CORE also seemed to change regularly without rhyme or reason, thus losing continuity and confidence that things would improve quickly.

The complainant stated that he/she would like the Appeal Board to consider the seriousness of the above especially in light of an organisation that had failed to take patient safety seriously, even though its activities were under the PMCPA's spotlight and had been found not to have disclosed information in a full and frank manner.

The complaint stated that Otsuka Europe had breached Clauses 9.1 and 2 for

1 Not maintaining high standards (not realising that Jinarc RMP materials were out of date for four years) and
2 Bringing disrepute to the pharmaceutical industry (the numerous complaints surrounding material and risk to patient safety had not been successfully addressed, despite multiple complaints to the PMCPA).

* * * * *

In response to a request for clarification which rulings were being appealed the complainant stated that he/she was appealing the rulings of no breach of Clauses 7.2, 7.9, 9.1 and 2 The complainant I did not believe Otsuka Europe had breached Clause 7.10.

Clause 7.2

The complainant alleged that given that the material, and thus information produced by Otsuka Europe was not accurate, not up to date – the RMP material was in breach of Clause 7.2.

Clause 7.9

The complainant alleged that as Otsuka Europe had already admitted that – In summary, due to an exceptional inconsistency between approved RMP and the conditions to the marketing authorisation (Annex IID) with respect to the requirements pertaining to aRMMs, existing ever since the marketing authorisation of Jinarc, the mentioned aRMMs were missing in updated central aRMM materials', by not having all pertinent information about risks, Otsuka Europe had breached Clause 7.9.

Summary

The complainant disputed the Panel's ruling that 'based on the very narrow allegation' (the complainant did not understand, how the Panel had come to this conclusion), Otsuka Europe were not found in breach of the clauses mentioned above. It was a matter of opinion.

The complainant alleged that the Panel had not grasped the two fundamental concerns:

1 the Risk Management Materials for Tolvaptan that Otsuka Europe produced had been inconsistent since 2015, despite having complaints that had necessitated Appeal Board invitations and audits by the PMCPA for Otsuka

2 lack of urgency with dealing with patient safety - the organisation was confused (the only formal written briefing to the organisation regarding 'pens down' was sent 29 October 2019, despite senior leaders being aware that employees were not clear on the messaging) due to the lack of leadership by senior managers in Otsuka Europe

> and processes such as the updating of RMP materials did not take priority (trips to Japan/ rugby world cup events/ themed events).

The complainant stated that he/she was not a Code expert, and hoped that he/she had been able to convey his/her points. It was a difficult task, especially given the nature of the case.

COMMENTS FROM OTSUKA EUROPE

Otsuka Europe noted that the complainant's concerns fell into four categories and addressed each of these in turn below.

A Revision of certain documents and processes

Otsuka Europe noted that the complainant referred to 'gaps within the RMP [risk management plan] process' that were 'identified in the summer of 2018'. Otsuka Europe assumed that this was a reference to the fact that at that time certain Jinarc additional Risk Minimisation Measures (aRMM) material used in the UK had not been updated following revisions to the Jinarc summary of product characteristics (SPC). This matter formed part of the issues in Case AUTH/3042/6/18.

Otsuka Europe submitted that the root cause of the issue at that time was a lack of process to ensure that aRMM materials were updated if required following an SPC update. The issue was addressed in the revision of the relevant SOP (PV-3401-GSOP 'Risk Management Plan Production and Tracking') which became effective on 29 March 2019. This required in Section 3.1.4 that the relevant Otsuka personnel:

> 'Throughout the product lifecycle, review and identify safety information that impact the safety risk profile of the product. Such information can include, but is not limited to, significant changes to Pharmacovigilance (PV) or Risk Management (RM) activities and other relevant input, signaling information, safety information provided by the HA, and updates to reference safety information/labeling.'

It also stated that the same personnel must 'Request new or updated RMP as required' (Section 3.1.5 refers).

Otsuka Europe submitted that this update to PV-3401-GSOP also included a new global working practice (PV-3401-WP- 005 'Local Management of aRMM Materials') which detailed the management of local aRMM materials. Section 2.3 of this working practice indicated that updates to the aRMM materials might be required for several reasons including but not limited to an update of the RMP, update of the Company Core Data Sheet (CCDS) or SPC or a direct health authority request.

Otsuka Europe submitted that in addition, the SOP directing the notification across Europe of changes to SPCs (EU-SOP-MA-002 v6.0 'Notification of changes to SPC PL and PI by OPEL/OPNL/ONPG to OPEL affiliates and relevant third parties' were also subsequently revised to include a reference to update of aRMM materials in line with SPC changes.

Otsuka Europe submitted that as previously noted that it had initiated a review of the central EU aRMM materials in order to optimise the material in line with current Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of

tools and effectiveness indicators and its addendum. Broadly speaking, these guidelines directed that aRMM material must focus on the risk that needs to be managed, rather than just repeating all of the information in the medicine's SPC.

This review of the central EU aRMM materials was not initiated because the aRMM material omitted certain safety information; they did contain, and always had contained, reference to the signs of dehydration and the need to avoid pregnancy. The review of aRMM that started in August 2019 was therefore in no way related to the issue identified in the Summer 2018.

Otsuka Europe submitted that the central EU materials provided to affiliates for review against their locally approved aRMM materials as a result of this exercise did omit reference to dehydration and pregnancy for the exceptional reason explained in Otsuka Europe's initial response to this case (and described again in more detail in Section C below). However, as part of the review process required by the relevant SOP and associated working practice, this omission was picked up and addressed before any materials were provided to MHRA or made available to health professionals or patients within the UK or EU.

Otsuka Europe submitted that at no point were any aRMM materials used by it with, or provided to, health professionals or patients that erroneously did not include reference to pregnancy and dehydration. Otsuka Europe did not consider that there had been any breach of Clauses 7.2 or 7.9.

Otsuka Europe submitted that it had acknowledged in previous cases that there had been failings in relation to process and governance, but it denied the complainant's allegation that these failings had not been taken seriously by all staff, including senior management; issues had been examined and addressed appropriately. Thus, Otsuka Europe denied any failure to maintain high standards or that any of our actions had reduced confidence in, or brought into disrepute, the industry, and denied any breach of Clauses 9.1 and 2.

B Provision of information to the PMCPA

Otsuka Europe noted that the complainant was not clear as to what information he/she was referring to in relation to his/her allegation that Otsuka Europe had not made a full and frank disclosure to the PMCPA; however there was reference to training on PV-3401-GSOP 'Risk Management Plan Production and Tracking'. The complainant alleged that staff in Otsuka Pharmaceuticals UK had not been trained on this process so omissions in draft aRMM material could not have been detected as part of this process.

Otsuka Europe confirmed that the relevant member of staff who received the draft aRMM material for review in September 2019 was trained on PV-3401-WP-005 in April 2019 on the version of the process effective at that time.

Otsuka Europenoted that the complainant also referred to the review and approval of the draft central EU aRMM materials before they were sent to the affiliates and whether this was conducted by a signatory. As previously communicated in its initial response to this case, the central EU aRMM materials were reviewed and approved in August 2019 within the Otsuka Regulatory electronic document management system (CREDO) and details were provided. This was a thorough review compared to the RMP for Jinarc. There was no requirement in Otsuka Europe's safety processes (or indeed to the Code) for aRMM materials to be certified

before dissemination to affiliates. Review and update of aRMM materials was then performed locally as required in line with all local regulatory and Code requirements.

Otsuka Europe noted that the complainant in addition made reference to 'Otsuka Europe undertaking that employees would not be engaging in activities' and that he/she and his/her colleagues were 'instructed to carry on as usual especially when it came to delivering partner related projects…'. Otsuka Europe assumed this was a reference to 'pencils down', the initiative whereby Otsuka Europe significantly reduced the activities that it conducted, by only commencing those which related to a contractual, regulatory or legal obligation. The partner projects that the complainant referred to would fall into the category of contractual obligations. At that time Otsuka Europe used external support for certification purposes.

Otsuka Europe submitted that as previously communicated there had been some questions as to what "pencils down" meant for day-to-day activities for the organisation and Otsuka Europe developed and circulated a Q&A document. Whilst the organisation required further clarity on a number of questions in relation to 'pencils down' Otsuka Europe submitted that this did not amount to senior leaders 'not keeping their fingers on the pulse and remediating effectively'.

Otsuka Europe submitted that the 'pencils down' approach did not apply to activities required and covered under regulatory requirements such as review of the aRMM materials in line with GVP Module XVI.

Otsuka Europe noted that the complainant also referred to an apparent disagreement between Otsuka Europe and Otsuka UK and 'telephone conferences at nine o'clock at night to resolve ongoing issues. Both organisations were attempting to avoid another Clause 2, and Otsuka UK was trying to meet its original commitment to the PMCPA to update its RMP materials". Again, Otsuka Europe was not entirely sure what the complainant was referring to, but it assumed that this was reference to revision of aRMM material after the audit conducted by the PMCPA in July 2019. Otsuka UK had communicated to the PMCPA that aRMM material would be revised by 1 November 2019, however global safety colleagues required sufficient time to review the changes made to the materials in detail. At the time consideration was being given to amending the central EU materials so global colleagues wanted to understand the timelines and whether the revisions Otsuka UK planned could wait, which involved a number of international calls. This was not 'to avoid a Clause 2' as the complainant alleged but merely to co-ordinate several planned updates and to meet the commitment made the PMCPA.

C Removal of information from additional risk minimization measures material

Otsuka Europe submitted that due to an exceptional inconsistency between the approved RMP and the conditions to the marketing authorisation (Annex IID) with respect to the content of aRMM materials, certain aRMMs were missed in the update of central aRMM materials. Investigation into this matter had identified that the inconsistency was introduced during the marketing authorisation application (MAA) process. The outcome of that process was a RMP approved by the regulatory authority that did not mandate aRMMs for dehydration and pregnancy. However, at the same time conditions were included in the marketing authorisation (as per Annex IID) that did mandate aRMM materials to include reference to pregnancy and dehydration.

As a result of detecting this inconsistency, Otsuka Europe had updated the relevant SOP (PV-3401- GSOP 'Risk Management Plan Production and Tracking') and associated working

practice (PV-3401-WP-001 'Risk Management Plan (RMP) Preparation, Maintenance and Tracking') to ensure that the annexes to the marketing authorisation were reviewed when a RMP was developed or updated. (Step 2.2.14 of the working practice stated: 'Utilize product information such as Summary of Product Characteristics (SPC), patient leaflet and annexes, to ensure alignment and relevant information is included in RMP').

Otsuka Europe submitted in addition, the quality check of the RMP required in Step 2.2.26 of the same working practice required an end to end consistency review of the draft RMP to be conducted using a check list which stated in the 'General' section that the checker must ensure that 'all references to reference safety information (RSI) are in the agreement with attached RSI'.

Otsuka Europe submitted that in order to address the inconsistency between the RMP and Annex IID it had a meeting with the EMA on 6 December 2019, where it was agreed with the EMA that Otsuka should align the RMP to the Annex IID additional aRMM requirements and a due submission date Type II variation was set. The variation was subsequently submitted on 28 March 2020 and was ongoing.

Otsuka Europe submitted that given the actions that it had taken in relation to this it did not consider that there had been a failure by Otsuka Europe to maintain high standards or that any actions by Otsuka Europe had brought in to disrepute, or reduced confidence in, the industry, and it denied any breach of Clauses 9.1 and 2 in that regard.

D Other concerns

Otsuka Europe submitted that the complainant expressed disappointment that the RMP materials had not been accurate since 2015 and Otsuka must reiterate that at no point had any aRMM materials been issued by Otsuka to health professionals or patients that erroneously did not include reference to pregnancy and dehydration. Omissions in draft central EU materials were detected and addressed as part of the formally approved safety processes and at no point were these draft central EU materials used or available to health professionals or patients.

In addition, at no point was the update of the central EU or local aRMM materials nor Otsuka's commitment to patient safety deprioritised due to senior managers attending a business trip in Japan or by any themed events held to enhance the working atmosphere within the organisation.

Otsuka Europe submitted that CORE (its compliance improvement programme) had made significant and meaningful progress towards achieving a sustainable compliance framework, as recognised by the Appeal Board in December 2019 and as Otsuka Europe submitted was demonstrated in the re-audits conducted by the PMCPA in April 2020, despite the restrictions that lock-down imposed. There had been some changes to CORE leadership to reflect the recruitment of further senior leaders in both Otsuka Europe and Otsuka UK and details were provided.

Otsuka Europe submitted considered that this only enhanced the leadership of the programme. In addition, the overall leadership of CORE by a a senior leader had remained consistently strongan, as previously communicated, Otsuka's aim was to achieve a compliance framework that was sustainable and not reliant on individuals. Otsuka stated that it did not consider that that there had been a failure by Otsuka Europe to maintain high standards or that any actions

by Otsuka Europe had brought in to disrepute, or reduced confidence in, the industry, and it denied any breach of Clauses 9.1 and 2 in that regard.

FINAL COMMENTS FROM THE COMPLAINANT

A Revision of certain documents and processes

The complainant alleged that despite the gaps relating to the updating of RMP materials identified at both Otsuka Europe and Otsuka UK level in June 2018 – the RMP materials in question still lacked important safety information. Why were there still gaps despite the focus on remediation?

The complainant alleged that Otsuka Europe had provided a significant explanation of the many processes and documents that supported the RMP material. However, despite all the reassurances, the RMP material that was disseminated to the affiliates did not have all the necessary safety information. This was admitted by Otsuka Europe.

B Provision of information to the PMCPA

The complainant alleged that if Otsuka UK had received training on the RMP process as evidenced, the complainant was happy to withdraw the previous allegation on the lack of training. The complainant stated he/she had conferred with Otsuka UK colleagues.

The complainant alleged that if the 'pencils down' approach was straightforward, why did Otsuka Europe feel the need to clarify the position nearly six months after the original verbal communication? If it was that important, why did it take six months to send out an official memo to all employees? In addition to that, the majority of Otsuka Europe's work (certification of material, etc.…) concerned Abilify Maintena which was promoted with Lundbeck (presuming this also applied to other co-promotions and similar arrangements). If Otsuka Europe was stating that this fell outside the 'pencils down' approach, was it admitting that it was business as usual for the majority of its personnel? What were the percentage of job bags/projects that were done on an alliance basis vs projects/job bags that were actually stopped because of 'pencils down'?

The complainant alleged that the late-night calls, as advised by Otsuka UK colleagues were to 'avoid a Clause 2', as (and as stated by Otsuka Europe) Otsuka UK was attempting to make a commitment to the PMCPA. Otsuka Europe had felt like if it did not meet the deadline for updating the material in question, the organization would be in breach of Clause 2.

The complainant was surprised that Otsuka Europe was stating that RMP material fell outside the scope of the PMCPA and disagreed with that view.

C Removal of information from additional risk minimization measures material

The complainant referred to the comments in section A and in his/her previous letter of appeal. Ultimately, Otsuka Europe was not aware of the inconsistencies and did not do a thorough review despite admitting that there were gaps in the RMP process in 2018. If Otsuka Europe took patient safety seriously, all aspects of patient safety concerning RMP and updating of material following SPC revisions should have been remediated effectively. By its admission, Otsuka Europe did not pay attention to its documentation as part of the marketing authorization application process.

D Other concerns

The complainant alleged senior management had its view on what enhanced the leadership of CORE. However, it was an everchanging scene – all original members of CORE from early 2019 had been replaced (in some cases more than twice). If senior leaders believed that this enhanced compliance, they were not aligned with the rest of the organisation. There was little consistency in messages and actions. Having spoken to some senior leaders, even PMCPA complaints were not shared within the group. How could this encourage an open and transparent working environment, when senior leaders themselves did not trust each other.

APPEAL BOARD RULING

The Appeal Board noted that the complainant was concerned that the latest European RMP materials issued by Otsuka Europe to the affiliates did not contain all of the necessary safety data and that vulnerable patients were being placed at risk.

The Appeal Board noted the company's explanation about the exceptional inconsistency between the EMA approved European Tolvaptan RMP version 14.1 and the conditions to the marketing authorisation (Annex IID) with respect to the requirements pertaining to aRMMs and the inclusion of references to pregnancy and dehydration (which existed since the grant of the Jinarc marketing authorisation). The reference to pregnancy and dehydration was removed from central aRMM material for Jinarc before it was sent to affiliates for internal review as required by the company process. The omission was picked up by affiliates as part of the formal internal review process. EU affiliates had been instructed to pause the review of local aRMM materials vs the revised centralised material and roll out was stopped. This problem was then raised with the regulator by Otsuka Europe to resolve and understand its root cause.

The Appeal Board noted the unusual circumstances of the inconsistency between the regulatory documents which had not been picked up by Otsuka Europe or the regulator. It also noted Otsuka's submission that at no point were any aRMM materials issued by Otsuka to health professionals or patients that did not include reference to pregnancy and dehydration. The Appeal Board noted from Otsuka Europe that this issue was under investigation independent of the complaint in this case. The Appeal Board was concerned about the length of time it was taking to resolve this issue, but it noted that it required an iterative process with the regulator that was bound by pre-set timescales. The Appeal Board noted from Otsuka Europe that its processes had been further improved to ensure that the annexes to the marketing authorisation were reviewed when a RMP was developed. In addition, the company had applied for a variation to the marketing authorisation and this was ongoing.

The Appeal Board noted Otsuka's submission that the current aRMM materials available to health professionals and patients contained the required references to pregnancy and dehydration. The Appeal Board therefore considered, based on the very narrow allegation, that the aRMMs provided to health professionals and patients were not misleading as alleged and it upheld the Panel's ruling of no breach of Clause 7.2. The Appeal Board similarly and for the same reasons upheld the Panel's ruling of no breach of Clause 7.9. The appeal on both points was unsuccessful.

Although concerned that Otsuka Europe had not originally identified the inconsistency, the Appeal Board noted that feedback from the Otsuka affiliates to Otsuka Europe was part of the

internal review of the Jinarc aRMM materials and this process had been effective at ensuring that neither health professionals nor patients had received materials which did not include reference to pregnancy and dehydration. Thus, the Appeal Board did not consider that Otsuka had failed to maintain high standards in this regard, and it upheld the Panel's ruling of no breach of Clauses 9.1. The Appeal Board consequently upheld the Panel's ruling of no breach of Clause 2. The appeal on both points was unsuccessful.

The Appeal Board noted the complainant's other concerns but it noted that the complainant bore the burden of proof and did not consider that he/she had provided evidence to show that on the balance of probabilities Otsuka had demonstrated a lack of urgency in addressing the issues highlighted during the recent PMCPA audit, or that senior leaders in OPEL 'have yet to understand the seriousness' of OPEL's current compliance situation, or that Otsuka Europe had no processes in place, or that Otsuka was not putting patient safety first but was focussing on frivolous activities. The Appeal Board noted Otsuka's detailed submission on all these points. The Appeal Board upheld the Panel's ruling of no breach of Clauses 9.1 and 2 in relation to each matter alleged and described above. The appeal on these points was unsuccessful.

Complaint received **10 October 2019**

Case completed **22 October 2020**