CASE AUTH/3199/5/19

PHARMACOSMOS/DIRECTOR v VIFOR

Alleged breach of undertaking

Pharmacosmos alleged that Vifor Pharma, during the course of promoting Ferinject (ferric carboxymaltose for injection or infusion), breached its undertaking given in Cases AUTH/2830/3/16 and AUTH/2828/3/16. Ferinject was indicated for the treatment of iron deficiency when oral iron was ineffective or could not be used. Pharmacosmos marketed Monofer (iron isomaltoside 100 mg/ml solution for injection or infusion) which was similarly indicated but could also be used where there was a clinical need to deliver iron rapidly.

As the complaint was about an alleged breach of undertaking, it was taken up by the Authority in the Director's name as the Authority was responsible for ensuring compliance with undertakings.

Pharmacosmos alleged that Vifor representatives continued to disparage the safety profile of Monofer by misleadingly using selected information from European countries that did not represent the European-level regulatory stance on the safety of Monofer. This directly breached the undertaking given in Case AUTH/2830/3/16. Additionally, Vifor medical information continued to send emails that highlighted the above mentioned information in a misleading and promotional manner, in breach of the undertaking given in Case AUTH/2828/3/16. Pharmacosmos stated that the evidence for these breaches was provided in an email to the company from a nurse who had asked for information about Monofer following a promotional visit from a Vifor representative; the request for information was again not unsolicited as it was made in response to issues of Monofer safety raised by a Vifor representative.

Pharmacosmos submitted that the response sent from medical information could not take benefit of the exemption in Clause 1.2 because apart from not being unsolicited, it again did not put the results of the Lareb report into context; and it now included additional safety reports from other authorities, again failing to place the data into context.

These additional reports, focussed on Monofer, were based on spontaneous reporting of adverse events, which the European Medicines Agency (EMA) had stated could not be used in isolation to support comparative safety claims. Additionally, Vifor had altered the wording taken from the 2013 EMA report on IV iron safety to imply that some differences might be detectable with severe reactions, thus distorting the original meaning of the statement that no differences could be detected because the data were mainly drawn from post-marketing data.

Pharmacosmos submitted that Vifor's response additionally excluded the head-to-head comparisons of Ferinject and Monofer that were now available (Emrich *et al* 2019 and Wolf *et al* 2019) and which showed that, in terms of hypersensitivity reactions ie the safety aspect upon which Vifor's response had focussed, Ferinject and Monofer were

broadly comparable. However, the Vifor response avoided mentioning IV iron induced hypophosphataemia, which was the only aspect where data seemed to indicate a difference in safety profile between the two products, which was, if anything, in favour of Monofer. Therefore, Pharmacosmos alleged that Vifor's response was yet again a promotional email that was solicited and was not fair or balanced but gave a misleading comparison of Ferinject and Monofer, without the necessary context.

Pharmacosmos alleged that the sending of the medical information response at issue was a breach of the undertaking given in Case AUTH/2828/3/16, as essentially the same actions that led to a breach in that case had been repeated.

In this case Pharmacosmos alleged that the email trail and Vifor's medical information response made it abundantly clear that the representative had used a misleading statement in promotional material to discuss and solicit questions about the comparative safety of Ferinject v Monofer. The nurse involved wrote (emphasis added): 'I was also interested in the slide you showed about the reduced ADRs when using ferrinject over Monofer …. Are you able to share the slide or the reference from the European drug referencing and WHO demonstrating that there are less ADRs than monofer'.

Pharmacosmos stated that a breach of Clause 2 was ruled in Case AUTH/2828/3/16 because Vifor's overall pattern of behaviour was unacceptable in that it used representatives and medical information to raise misleading, unsubstantiated concerns about the safety of Monofer by highlighting European safety reports.

Pharmacosmos stated that Vifor continued to scaremonger and use medical information to ensure that copies of the Lareb report (and similar) were received by the nurse in question. Pharmacosmos thus contended that Vifor's behaviour again brought discredit upon, and reduced confidence in, the pharmaceutical industry, in breach of its undertaking as they were the same actions that led to a breach of Clause 2 in Case AUTH/2828/3/16.

Pharmacosmos stated that from the points made above, it was clear that Vifor's representatives and its medical information department had again provided misleading information about the safety of Monofer on essentially the same matters as before – the likelihood of causing hypersensitivity reactions. It seemed clear from the nurse's wording regarding 'the reduced ADRs when using ferinject over Monofer' that the representative had disparaged Monofer.

Pharmacosmos contended that this continuing disparaging and misleading behaviour was a breach of undertaking as it was the same behaviour that led to breaches of the Code in Case AUTH/2830/4/16.

The detailed response from Vifor is given below.

The Panel noted that a form of undertaking and assurance was an important document. Companies had to give an undertaking that the activity or use of the material in question and any similar material (if not already discontinued or no longer in use) would cease forthwith and give an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the nurse had emailed the Vifor representative stating 'I was also interested in the slide you showed about the reduced ADRs when using ferrinject over Monofer, I have been giving iron for 2 years and helping nervous ward staff administer confidently and so I am very keen on the safety aspects of administering parenteral iron' and 'Are you able to share the slide or the reference from the European drug referencing and WHO demonstrating that there are less ADRs than monofer'. The Panel disagreed with Vifor's submission that the nurse's request for information was ambiguous. In the Panel's view, medical information wrongly interpreted the request as a reference to an alternative existing approved claim by stating 'I understand from my colleague [name] that you have requested references for the statement "European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons"'. It thus appeared that medical information had simply ignored the nurse's references to the slides upon which he/she had based his/her request for information.

The references cited in the medical information response included the Ferinject SPC, the minutes of the EMA Pharmacovigilance Risk Assessment Committee (PRAC) meeting on 6-9 March 2017, EMA list of medicinal products under additional monitoring, the Lareb report, the Spanish Health Authority (AEMPS) report, the WHO Pharmaceuticals newsletter, and the Swissmedic Vigilance-News, Edition 11 newsletter.

The medical information response included a summary of some of the references provided and hyperlinks to access the full documents for all of the references apart from the Ferinject SPC. The medical information response letter started by explaining that findings by EMA as part of the referral procedure (EMEA/H/A-31/1322) led to revisions in the labels for the entire class of IV iron products and the outcome of the referral procedure concluded that the reviewed data did not allow clear differentiation between IV iron products and their relation to severe hypersensitivity reactions. In that regard the Panel noted, however, that the EMA Assessment report for iron containing intravenous (IV) medicinal products dated 13 September 2013 stated that as the conclusions of the assessment were mainly drawn from post-marketing data, differentiation between the iron complexes in terms of hypersensitivity reactions could not be identified. The medical information response then went on to state that a lab report published by the Netherlands Pharmacovigilance Centre Lareb reported that they have received concerns regarding the safety of IIM [iron isomaltoside] from multiple Dutch hospitals wherein the doctors and nurses have observed an increase in the severity and incidence of allergic reactions after switching from FCM [ferric carboxymaltose] to IIM.4. It further went on to state that the AEMPS issued a warning recently to not start new patients with Monofer due to the risk of severe hypersensitivity reactions (HSRs). The data available to AEMPS was being reviewed in detail and as a precaution the AEMPS recommended health professionals not to initiate new treatments with Monofer. It then stated that the rate of reporting on severe HSRs with iron isomaltoside was much higher than for other IV iron preparations which was referenced to the AEMPS report and the WHO newsletter.

The letter concluded with please also find attached the Swissmedic Vigilance-News 7 which looks at the risk of intravenous treatment of iron deficiency.

In the Panel's view, the medical information response misrepresented the EMA position and then selectively discussed two reports, one from the Netherlands and one from

Spain, both of which unfavourably compared Monofer with Ferinject and ended with a Swiss reference which reported on ADRs with Ferinject but not with Monofer.

The Panel noted Vifor's initial submission that it did not have a slide 'claiming reduced ADRs when using Ferinject vs Monofer', and that it did not suggest that regulators or the WHO had demonstrated that there were fewer ADRs for Ferinject than for Monofer. Despite Vifor's submission that the only statement approved for use was '… European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons…', that statement did not appear in any of the material supplied by Vifor; it appeared only to have been used in the introductory paragraph of the medical information response. The Panel noted that it was only following a request for further information that Vifor provided a copy of the Ferinject Objection Handler (UK-FCM-1900026) entitled 'Why Ferinject', which was used by representatives, and the relevant briefing document (UK-FCM-1900027). Vifor stated that certain slides of the objection handler were used by the representative at the meeting in question but did not state which slides in particular were used. (The Panel noted that the objection handler had since been withdrawn.)

The executive summary in the briefing document stated, inter alia, 'We want you to actively differentiate between IV irons using information in your sales aid'. The stated proactive growth and active differentiation strategy included getting health professionals to understand how IV irons were different and use Ferinject preferentially.

Representatives were to have reactive differentiation discussions if health professionals stated that they considered all IV irons were the same in terms of, inter alia, tolerability. The briefing document summary stated 'Only use the 'Ferinject objection handler' reactively when a health professional considers that all IV irons are the same; requests a comparison of tolerability of irons or requests a comparison of the efficacy of IV irons'. In the Panel's view, it was clear that Vifor intended to clearly, and favourably, differentiate Ferinject from other IV irons including on grounds of tolerability.

The objection handler included a number of slides comparing the tolerability of Ferinject vs Monofer, the majority of which focussed on hypersensitivity reactions. The first slide within the Tolerability profile section was titled 'IV irons and hypersensitivity reactions: a European assessment' and gave a timeline which according to the briefing document showed why Ehlken et al (2018) was commissioned. The next slide reported on Ehlken *et al*, a retrospective pharmacoepidemiologic study using data from the European Union Drug Regulating Authorities Pharmacovigilance database and data from the WHO VigiBase database both of which showed that hypersensitivity reactions were more common in patients receiving iron isomaltoside 1000 vs Ferinject (10.7 x and 8.4 x respectively). Whilst the relative frequencies appeared quite different, a pop-up graph (which might or might not have been used at the meeting) showed that the absolute numbers of reported severe hypersensitivity reactions, adjusted for exposure, per 100mg dose equivalent, per 100,000 administrations were still very small in both groups and no more than 5 in the iron isomaltoside 1000 group. There was no indication in the objection handler as to whether the apparently meaningful difference between Ferinject and iron isomaltoside 1000 was clinically or statistically significant. Ehlken *et al* was sponsored by Vifor and was described in the briefing notes as presenting 'important information' about Ferinject and iron isomaltoside 1000 (Monofer and Diafer). It was thus likely that representatives would be keen to show this slide. Diafer (iron isomaltoside 50

mg/ml solution for injection) was also marketed by Pharmacosmos and was indicated in adults for the treatment of iron deficiency in patients with chronic kidney disease on dialysis, when oral iron preparations were ineffective or could not be used.

Another slide followed claiming, in bold type, a 75% lower risk of severe hypersensitivity reactions with Ferinject vs Monofer (p<0.0001) (Mulder *et al* 2018). In smaller font below it was explained that hypersensitivity reactions occurred in 18/836 (2.1%) of Ferinject and 43/496 (8.7%) of Monofer administrations. Mulder *et al* was a single centre Dutch study and although the briefing notes referred to study limitations and that the study indicated that there might be differences in the clinical profiles of the two IV irons the slide in the objection handler itself was unequivocally headed 'A recent study showed Ferinject is associated with a lower risk of severe hypersensitivity reactions than Monofer'.

A third slide detailed Bager *et al* (2017) which was a single centre Danish study which showed that Monofer was associated with a higher incidence of hypersensitivity reactions (10.7%) compared with Ferinject (2.5%) (p<0.01). A pop-up slide showed the absolute difference of 11 reactions in the Monofer group and 4 in the Ferinject group. Although it was stated in the objection handler that all hypersensitivity reactions were grade 1 or 2, there was no information as to how many of each grade occurred in either group. The Panel further noted that the briefing document stated that 'When using Monofer they observed a relatively high number of [hypersensitivity reactions] and for safety reasons, they switched back to Ferinject …. However, a drawback when using Ferinject was a higher rate of Hypophosphataemia compared with Monofer'.

The Panel considered that Vifor had clearly set out to differentiate Ferinject from Monofer in terms of the incidence of hypersensitivity reactions despite both SPCs listing anaphylactoid/anaphylactic reactions as rare (≥1/10000 to <1/1000)). The Monofer SPC listed hypersensitivity including severe reactions as uncommon (≥1/1,000 to <1/100) and the Ferinject SPC stated that hypersensitivity was uncommon.

The Panel considered, on the balance of probabilities, that the slides described above prompted the nurse to refer to 'the slide you showed about the reduced ADRs when using Ferinject over Monofer' and to ask for 'the slide or reference from European referencing and WHO demonstrating that there are less ADRs than Monofer'. In that regard it was wholly disingenuous for Vifor to have stated that it did not have a slide claiming reduced ADRs when using Ferinject vs Monofer and that it had not suggested that regulators or the WHO had demonstrated that there were fewer ADRs with Ferinject than with Monofer. The matter was not complicated and even a cursory glance at the objection handler would have shown that Vifor's original response was incorrect.

The Panel noted that a reply made in response to an enquiry from a health professional was exempt from the definition of promotion provided that the enquiry was unsolicited and the reply related solely to the subject matter of the enquiry, was accurate, did not mislead and was not promotional. The Panel noted its comments above and considered that the medical information response to the nurse could not take the benefit of the exemption to promotion in the Code. In the Panel's view, the response from medical information was not in reply to an unsolicited enquiry, it did not relate solely to the subject matter of the enquiry and the content was not accurate, balanced or fair. In that regard the nurse had been sent a promotional email without his/her permission which

was in breach of the undertaking given in Case AUTH/2828/3/16 and the Panel ruled accordingly.

The Panel noted its comments above about the content of the objection handler and the accompanying briefing document. There appeared to be no doubt that Vifor had set out to clearly and favourably compare Ferinject with Monofer with regard to tolerability and hypersensitivity reactions. There was, however, little or no difference between the two products with regard to relevant statements in their SPCs and the EMA currently concluded that data did not allow clear differentiation between IV iron products and their safety profile in relation to hypersensitivity reactions.

The Panel noted that in Case AUTH/2828/3/16 Vifor was ruled in breach of the Code for spreading doubt about the safety of Monofer; and in Case AUTH/2830/4/16 the company was ruled in breach for disparaging Monofer. In the Panel's view, the objection handler continued to spread doubt about the safety of Monofer and the briefing document was such that, when using the objection handler, the representative would have, on the balance of probabilities, disparaged Monofer. Both the objection handler and the briefing document were in breach of the previous undertakings and further breaches were ruled as acknowledged by Vifor.

The Panel noted its rulings and that inadequate action leading to a breach of undertaking was one of the reasons likely to lead to a breach of Clause 2, a sign of particular censure. The Panel considered that breaches of undertakings brought discredit upon, and reduced confidence in the industry. The Panel further noted Vifor's submission that whilst the whole organisation was trained following Cases AUTH/2828/3/16 and AUTH/2830/4/16, it was clear that there was not a comprehensive record of the medical information staff being trained on the impact of the rulings, and on future conduct or material produced by Vifor such as medical information or promotional items. A breach of Clause 2 was ruled.

The Panel was very concerned to note that despite being asked by the case preparation manager to provide copies of relevant material including the slides used by the representative in question with the nurse and copies of the current relevant representative's briefing which referred to Monofer and side-effects, Vifor did not provide any of this information The Panel was concerned to note that it was only in response to a request for further information that Vifor provided a copy of the Ferinject Objection Handler (UK-FCM-1900026) certain slides of which it stated were used by the representative at the meeting in question and the briefing document (ref UK-FCM-1900027) which clearly set out differences in the occurrence of hypersensitivity reactions between Ferinject and Monofer in favour of Ferinject and specifically referred to the European Union Drug Regulating Authorities Pharmacovigilance Database and the WHO VigiBase Database which showed that hypersensitivity reactions were reported more frequently in patients receiving iron isomaltoside 1000 vs Ferinject. The Panel queried why this information was not provided initially. The Panel noted that self-regulation and the reputation of the industry in that regard, relied upon full and frank disclosure at the outset.

The Panel was extremely concerned to note that its request for further information appeared to mark a complete turn-around by Vifor. Having previously provided none of the relevant material and vigorously denying all allegations Vifor now acknowledged

potential breaches of the Code and noted a number of inaccuracies in its original response; the company only appeared to take this more open and transparent approach following the engagement of external advisors. Although Vifor's abrupt and complete reversal of its position had clarified the matters in hand, the Panel considered that the company's original response appeared obstructive and uncooperative despite its protestations that it was committed to adhering to the Code and willingly accepted the jurisdiction of the PMCPA. In that regard, the Panel decided to report Vifor to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board noted the Panel's comments and rulings of breaches of the Code including Clause 2 and its decision to report Vifor to the Appeal Board. The Appeal Board noted that Vifor had provided brief details about its plan to address the issues and had apologised.

The Appeal Board was very concerned that the initial response from Vifor (dated 3 June 2019) could be described as obstructive, defensive, aggressive, dissembling and untrue. Vifor's follow up letter (29 November 2019) referred to the case as a 'fishing exercise by Pharmacosmos' to obtain Vifor promotional material. Subsequently, Vifor's response to a request for further information (dated 6 December 2019) which referred to Case AUTH/3199/5/19 and Case AUTH3224/7/19 admitted that the company's initial response was inaccurate and provided the Ferinject Objection Handler (UK-FCM-1900026) and the briefing document (ref UK-FCM-1900027). This version of the Objection Handler had been withdrawn in September 2019. The form of undertaking provided in Case AUTH/3224/7/19 stated that the Objection Handler was last used on 29 September 2019.

The Appeal Board noted that Vifor accepted full responsibility for its initial response to Case AUTH/3199/3/19 dated 3 June 2019. Vifor stated that it became apparent that that letter was not appropriate. Further the request was clearly in relation to statements made within the objection handler. Concerns about the content of the initial response were subsequently investigated by Vifor. The investigation resulted in a change in the senior leadership team and following its advice and that of an external agency resulted in Vifor's reversal of position declared to the PMCPA. The Vifor representatives at the report hearing also referred to very recent changes in leadership at the global level. In response to a question the Vifor representatives confirmed that the letter of 6 December 2019 was written by the external third party contracted to provide compliance advice.

The Appeal Board was concerned about the length of time it had taken for Vifor to change its approach to the complaint. Vifor representatives at the report hearing explained that the delay, in part was caused by the need to follow certain internal processes and that the legal team insisted that Vifor continued to submit that the case be dismissed rather than provide the materials including the objection handler. The Appeal Board also noted Vifor's subsequent response to the PMCPA and Vifor's admission of errors and that it accepted responsibility for the breach of undertakings given in previous cases.

The Appeal Board noted the submission from Vifor's representatives at the report hearing that Vifor was now committed to change how it would promote its medicines. First line managers were briefed in late February. The Appeal Board welcomed the change in approach from Vifor and its plans to ensure that such issues did not recur.

However, the Appeal Board was very concerned about the prevailing company culture within which the initial response was submitted. The Appeal Board noted that company culture took time to change. The Appeal Board noted that self-regulation relied, *inter alia*, upon the provision of complete and accurate information from pharmaceutical companies.

The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Vifor should be publicly reprimanded for its failure to provide accurate and truthful information to the Panel and its disingenuous approach to responding to the complaint. The Appeal Board also decided to require an audit of Vifor's procedures in relation to the Code in the present case. The Appeal Board required Vifor to provide a comprehensive and detailed corrective and preventive action (CAPA) plan with timelines in time for it to be considered at the next Appeal Board meeting on 11 March. On consideration of the CAPA plan the Appeal Board would confirm the date of the audit. In any event this audit would take place at the same time as that required in Case AUTH/3224/7/19. On receipt of the report of the audit the Appeal Board would consider whether further sanctions were necessary.

On receipt of the requested CAPA plan from Vifor, the Appeal Board noted the timelines in the CAPA plan. There were completion dates between February and August 2020. The Appeal Board queried whether the timelines were sufficient and reflected the urgency of the situation given its comments about the seriousness of these cases. In that regard it noted that Vifor was still yet to brief all employees about the current cases. The Appeal Board decided that the audits should take place in September 2020 by which time it expected to see substantial progress. On receipt of the report for the audits it would decide whether further sanctions were necessary.

On receipt of the report of the audit the Appeal Board was very concerned about the apparent lack of progress, and the number and nature of ongoing issues and concerns to be addressed as highlighted in the audit report. The Appeal Board noted changes in senior personnel at Vifor global and that communication between Vifor UK and Vifor global had started to improve.

The Appeal Board considered that the audit report indicated that the understanding of the Code and compliance was limited in the UK, and that there was a need for senior staff to improve their knowledge, visibility and leadership on compliance matters ensuring all understood the importance of compliance and the role of self-regulation. A number of issues were highlighted including that it was important that the company had the appropriate speak-up culture so that employees were confident to raise concerns. The Appeal Board considered that significant commitment was required to address these issues.

The Appeal Board noted that Vifor's comments on the audit report did not address some of the serious criticisms in the report of the audit. The Appeal Board was concerned about the prioritisation of matters and considered that this needed to be reassessed. This was of particular note given the Appeal Board's previous concern about whether Vifor's CAPA timelines reflected the seriousness of the situation.

Given the exceptional circumstances of this matter, including the scale and seriousness of the difficulties at Vifor, the Appeal Board requested that Vifor representatives be

invited to attend the subsequent Appeal Board meeting to discuss the company's response to the Appeal Board's concerns.

At the subsequent Appeal Board meeting representatives from Vifor attended to discuss the Appeal Board's concerns.

The Appeal Board remained concerned that the reassurance given by Vifor when it first attended the Appeal Board for the consideration of the report from the Panel did not align with the concerns subsequently raised in the report of the audits. The Appeal Board was concerned about the overall rate of progress, including since that audit and that Vifor appeared to take a reactive rather than a proactive approach to the required improvements. There was still a significant amount of work to be done and in that regard the current pace of change remained too slow.

The Appeal Board considered that Vifor needed to take a much more proactive approach in addressing the situation, this would include setting milestones to achieve the significant rate of change, including to the company culture, that was required. The Appeal Board noted the company's responses, but it queried whether compliance was sufficiently resourced or supported within the company to address matters.

The Appeal Board noted its comments and decided that Vifor should be re-audited at which point it expected the company to demonstrate significant progress. On receipt of the report for the re-audit it would decide whether further sanctions were necessary.

On receipt of the report of the re-audit the Appeal Board considered that there had been some progress, but it appeared that the pace of improvement was unacceptably slow, especially given the nature of ongoing issues highlighted in the re-audit report. The Appeal Board noted its previous concerns about the pace of change including that Vifor was concerned that it had not managed to show greater improvement between February 2020 and the October 2020 audit.

The Appeal Board noted the company's continued apparent confusion between promotional and non-promotional materials and activities. Senior staff needed to continue to improve their knowledge and leadership on compliance matters. The company had reorganised its structure and downsized its headcount. A brief staff survey had taken place and a further survey was due in November 2021. The company must be confident that all activities were carried out in compliance with the Code particularly given the new structure and the launch of new products.

A number of issues were of concern to the Appeal Board including the need to update standard operating procedures and improve the quality of the job bags. A further job bag review was planned for the end of 2021.

The Appeal Board considered that there was a significant amount of work to do, and it queried whether Vifor had sufficient urgency and compliance resource to make the necessary improvements within the expected timescale. It was disappointing that material which was to be withdrawn following the October 2020 audit was only withdrawn in June 2021 prior to the re-audit and that the current materials list was still incorrect.

Given the exceptional circumstances of this matter, including the scale and seriousness of the difficulties at Vifor, the Appeal Board requested that Vifor representatives be invited to attend the Appeal Board meeting in October to provide an update and to discuss the company's response to the Appeal Board's concerns. The Appeal Board requested Vifor be asked to submit a short overview of its progress since the re-audit in July 2021 and a comprehensive compliance action plan with a timetable of key dates before the meeting.

The Appeal Board noted that it was so concerned about the re-audit and Vifor's comments that it discussed the possibility of reporting Vifor to the ABPI Board but it decided not to do so at the moment. The Appeal Board decided that Vifor should be re-audited. The Appeal Board noted there was still a significant amount of work to do. The Appeal Board decided that the re-audit should take place in January 2022 with the expectation that everything should be completed and in place by the end of 2021. The Appeal Board expected the company to demonstrate significant and embedded progress. On receipt of the report for the January 2022 re-audit the Appeal Board would decide whether further sanctions were necessary including a report to the ABPI Board.

At a subsequent Appeal Board meeting Vifor welcomed the opportunity to provide more detail and to demonstrate its commitment to continually improve and build a robust compliance framework.

Vifor accepted there was still a significant amount of work to do. Vifor submitted that over the longer term its focus would be to ensure that there was a clear change in its culture supported by clear SOPs and robust training around its activities and the Code.

Vifor submitted that it was building on the progress acknowledged by the PMCPA at the July 2021 re-audit, and continued to cultivate a collaborative approach and the necessary transformation to a compliant culture, but it recognised that a higher level of commitment was needed, and the pace of change needed to be expedited.

The Appeal Board noted that it had previously decided that Vifor should be re-audited in early 2022 and its expectation that Vifor should have completed the work needed by the end of 2021.

The Appeal Board made a number of comments and although it remained concerned about the speed of progress and the need to accelerate the work on improving the company compliance culture, the Appeal Board did not consider that, following the presentation from Vifor and discussions with the company, there needed to be changes to the timetable and actions it had previously decided upon (at the 16 September meeting of the Appeal Board). It was now for Vifor to do the work and demonstrate significant progress at the re-audit in 2022.

At its meeting in March 2022 the Appeal Board received the report of the January 2022 re-audit of Vifor. The Appeal Board noted at its meeting on 22 October 2021, which Vifor had attended, it had remained concerned about the speed of progress and the need to accelerate the work on improving the company compliance culture and it had considered that it was now for Vifor to do the work and demonstrate significant progress at the re-audit in January 2022.

The Appeal Board considered from the January 2022 re-audit report that although there had been some changes there had been little significant progress. The Appeal Board considered that the scale of the difficulties at Vifor coupled with the lack of urgency was very concerning. There had now been three audits/re-audits of Vifor and given the Appeal Board's comments in October 2021 the rate of improvement was unacceptable.

The Appeal Board noted that the re-audit report highlighted a number of concerns. The Appeal Board considered that it was essential that Vifor invested in appropriate compliance support and resource for the work that needed to be done. In that regard the Appeal Board was concerned about how the recent sale of Vifor would impact on its progress to improve.

The Appeal Board was very concerned that the PMCPA was unable to access certain materials despite several requests. The Appeal Board considered that it was the responsibility of the company to ensure access to any materials requested as part of an audit/re-audit. Any issue in this regard needed to be resolved with immediacy by the company. Vifor's failing in this regard was unacceptable.

The Appeal Board was concerned that there were a number of instances of inconsistencies between the company's submissions, for example what was said at the January 2022 re-audit and what the company stated in its written response to the re-audit report.

The Appeal Board was deeply concerned with the existing amount of work still required and queried Vifor's commitment to self-regulation. The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Vifor should be publicly reprimanded for its lack of progress.

The Appeal Board also decided that Vifor should be re-audited in six months' time at which point it required the company to demonstrate significant progress. The Appeal Board required Vifor to provide an interim written report detailing progress and an updated 2022 compliance plan in 3 months. The Appeal Board considered whether to report Vifor to the ABPI Board, however it decided to reserve any further sanctions until receipt of the report for the next re-audit.

The Appeal Board considered from the September 2022 re-audit report that Vifor had made good progress since the January 2022 re-audit and that there was now a strong commitment to improve. Compliance was now embedded. Despite these improvements there was still further work needed, particularly within the three areas of documentation governance, governance over hybrid promotional/non promotional roles and consistency in the quality of promotional materials.

The Appeal Board noted from Vifor's response to the September 2022 re-audit that it had already taken steps to begin to address the comments in the re-audit report, including the three areas above. However, the Appeal Board considered that Vifor should be re audited to ensure that this momentum continued, particularly given the recent acquisition, the launch of new medicines and that progress up until the September 2022 re-audit had been relatively slow. The Appeal Board considered that the re-audit should take place in October 2023 to give the company sufficient time to embed new processes and demonstrate improvements, and at which point it expected to see significant

progress. The Appeal Board requested that the re-audit in October 2023 should particularly focus on the three areas identified above. The re-audit should also look at progress in relation to all the September 2022 re-audit recommendations.

The Appeal Board reserved any further sanctions until receipt of the report for the next re-audit in 2023.

The Appeal Board observed that CSL Vifor had made progress in the three main areas targeted at the September 2023 re-audit, namely end-to end governance of activities, governance over hybrid roles and quality of promotional materials. Overall, it appeared that the standard of promotional material had improved, and the governance of hybrid roles enhanced, since the September 2022 re-audit. Given it was the company's fifth audit, the Appeal Board was expecting CSL Vifor to have made more significant improvement in relation to end-to-end governance of activities. However, the Appeal Board acknowledged that the acquisition of Vifor by CSL, and the resulting restructuring which impacted both people and processes, would inevitably cause a delay in implementing some of the recommendations from the September 2022 re-audit, particularly in relation to procedural documents.

The Appeal Board observed that the new compliance model included a comprehensive internal monitoring programme conducted by the regional team at CSL. While it was too early to see the full operational impact of the new model, the Appeal Board had confidence in the significantly improved culture within the organisation.

The Appeal Board observed that there were still some areas for improvement, including governance of Transfers of Value (ToV). However, the Appeal Board was encouraged by the company's comprehensive response to the recommendations in the re-audit report, which demonstrated the company's timely action and commitment to compliance.

The Appeal Board decided on the basis that progress was continued, planned work was completed and the commitment to compliance was maintained, that no further action was required.

Pharmacosmos UK Ltd alleged that Vifor Pharma Limited, during the course of promoting Ferinject (ferric carboxymaltose for injection or infusion), breached its undertaking given in Cases AUTH/2830/3/16 and AUTH/2828/3/16. Ferinject was indicated for the treatment of iron deficiency when oral iron was ineffective or could not be used. Pharmacosmos marketed Monofer (iron isomaltoside 100 mg/ml solution for injection or infusion) which was similarly indicated but could also be used where there was a clinical need to deliver iron rapidly.

As the complaint was about an alleged breach of undertaking, it was taken up by the Authority in the Director's name as the Authority was responsible for ensuring compliance with undertakings.

COMPLAINT

Pharmacosmos alleged that Vifor representatives continued to disparage the safety profile of Monofer by misleadingly using selected information from European countries, information that did not represent the European-level regulatory stance on the safety of Monofer. This directly

breached the undertaking given in Case AUTH/2830/3/16. Additionally, Vifor medical information continued to send emails that highlighted the above mentioned information in a misleading and promotional manner, in breach of the undertaking given in Case AUTH/2828/3/16. Pharmacosmos stated that the evidence for these breaches was provided in an email to the company from a nurse who had asked for information about Monofer following a promotional visit from a Vifor representative.

Pharmacosmos stated that the essence of the ruling in Case AUTH/2828/3/16 was that Vifor medical information wrote to a health professional following a visit by a representative. The letter provided the substantiating evidence originally raised and presented by the Vifor representative (thus was not unsolicited) and misleadingly represented the safety profile of Monofer as presented in the Lareb report (from the Netherlands Pharmacovigilance Centre). The ruling in Case AUTH/2828/3/16 stated:

> 'The complainant replied stating "No problem. Can you just highlight to me the issues **you mentioned** re: safety of Monofer etc? That **you raised** yesterday" [emphasis added in ruling]. In that regard, the Panel considered that it seemed clear that issues about the safety of Monofer had been raised by the representative, not by the complainant. The Panel noted Vifor's submission that the complainant questioned the safety data and asked for comparative safety data. In that regard the complainant's request for more information was not unsolicited.'
>
> 'The Panel noted that Clause 1.2 of the Code stated that replies made in response to individual enquiries from, *inter alia,* a health professional were not included in the definition of promotion but only if such replies related solely to the subject matter of the enquiry, were accurate and did not mislead and were not promotional in nature. Supplementary information to Clause 1.2 made it clear that the exemption was only in respect of unsolicited enquiries. In that regard the Panel noted that the query was not unsolicited….'

Pharmacosmos stated that in this case, Case AUTH/3199/5/19, the request for more information was again not unsolicited, as it was made in response to issues of Monofer safety raised by a Vifor representative. A relevant email trail showed that the nurse involved wrote (emphasis added):

> 'I was also interested in the **slide you showed** about the **reduced ADRs when using ferrinject over Monofer**…. Are you able to share the slide or the reference from the European drug referencing and WHO [World Health Organisation] demonstrating that there are less ADRs than monofer.'

It was thus clear that Vifor medical information still used the European safety reports to raise concerns about Monofer. Pharmacosmos further noted that the ruling in Case AUTH/2828/3/16 stated:

> 'Further the email from the medical information department did not put the results of the Lareb report into context and did not note that there were no direct head-to-head comparisons of Ferinject and Monofer.'
>
> 'The Panel thus considered that the email from medical information could not take the benefit of the exemption in Clause 1.2 to the definition of promotion, it was neither

> unsolicited nor fair and balanced. The complainant had thus been sent a promotional email without her prior permission. A breach of Clause 9.9 was ruled.'

Pharmacosmos submitted that in the case now at issue (Case AUTH/3199/5/19), the response sent from medical information could also not take benefit of the exemption in Clause 1.2 because apart from not being unsolicited, it again did not put the results of the Lareb report into context; and it now included additional safety reports from other authorities, again failing to place the data into context.

These additional reports, focussed on Monofer, were based on spontaneous reporting of adverse events, which the European Medicines Agency (EMA) had stated could not be used in isolation to support comparative safety claims. Additionally, Vifor had altered the wording taken from the 2013 EMA report on IV iron safety to imply that some differences might be detectable with severe reactions, thus distorting the original meaning of the statement that no differences could be detected because the data were mainly drawn from post-marketing data.

Pharmacosmos submitted that Vifor's response additionally excluded the head-to-head comparisons of Ferinject and Monofer that were now available (Emrich *et al* 2019 and Wolf *et al* 2019) and which showed that, in terms of hypersensitivity reactions ie the safety aspect upon which Vifor's response had focussed, Ferinject and Monofer were broadly comparable. However, the Vifor response avoided mentioning IV iron induced hypophosphataemia, which was the only aspect where data seemed to indicate a difference in safety profile between the two products, which was, if anything, in favour of Monofer. Therefore, Pharmacosmos alleged that Vifor's response was yet again a promotional email that was solicited and was not fair or balanced but gave a misleading comparison of Ferinject and Monofer, without the necessary context.

Pharmacosmos alleged that the sending of the medical information response at issue was a breach of Clause 29, as essentially the same actions that led to breach of Clause 9.9 in Case AUTH/2828/3/16 had been repeated.

Pharmacosmos stated that the essence of the rulings in Case AUTH/2828/3/16 was that Vifor representatives had visited health professionals and raised misleading, unsubstantiated concerns about the safety of Monofer by highlighting European safety reports. The ruling in Case AUTH/2828/3/16 stated:

> 'In the Panel's view, there was no doubt that Vifor was specifically targeting Monofer sales and that the representatives had been briefed to discuss, or solicit ('be proactively reactive') questions about, the comparative safety of Ferinject vs Monofer ….'
>
> 'The Panel considered that on the balance of probabilities, given the strident tone and content of the sales materials and briefings, the representatives had started to spread doubt amongst infusion nurses about the safety of Monofer as alleged and in that regard had offered misleading comparisons with Ferinject. Breaches of Clauses 7.2, 7.4 and 7.9 were ruled.'

In Case AUTH/3199/5/19, Pharmacosmos alleged that the email trail and Vifor's medical information response made it abundantly clear that the representative had used a misleading statement in promotional material to discuss and solicit questions about the comparative safety of Ferinject v Monofer. The nurse involved wrote (emphasis added): 'I was also interested in

the **slide you showed** about the **reduced ADRs when using ferrinject over Monofer** …. Are you able to share the slide or the reference from the European drug referencing and WHO demonstrating that there are less ADRs than monofer'.

The substantiating evidence provided by Vifor medical information again included the Lareb report (provided in Case AUTH/2828/3/16) and now additionally, a report from another European country.

Pharmacosmos stated that comparison of Monofer with Ferinject regarding safety profile was misleading as no such European-wide data currently existed that definitively demonstrated any difference in ADR numbers between IV iron products, as discussed above in relation to the medical information email, and certainly not in terms of hypersensitivity reactions which were clearly the focus of Vifor's messaging.

On the basis of the above, Pharmacosmos thus alleged that the behaviour of the Vifor representatives in proactively offering misleading safety comparisons of Monofer with Ferinject, spreading doubt amongst infusion nurses about the safety of Monofer was in breach of Clause 29, as the same actions that led to breaches of Clauses 7.2, 7.4 and 7.9 being ruled in Case AUTH/2828/3/16 had been repeated.

Pharmacosmos stated that a breach of Clause 2 was ruled in Case AUTH/2828/3/16 because Vifor's overall pattern of behaviour was unacceptable in that it used representatives and medical information to raise misleading, unsubstantiated concerns about the safety of Monofer by highlighting European safety reports. This ruling stated:

> 'The Panel noted the complainant's and her colleagues' views that the two had been scaremongering and that their approach was challenging and aggressive. The representatives had ensured that the complainant had received a copy of the Lareb report and in the Panel's view the covering medical information email had been promotional. The Panel noted its rulings and comments above and considered that, on the balance of probabilities, Vifor's activities and materials associated with the promotion of Ferinject had been such that they brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.'

Pharmacosmos stated that from the points above, it was clear that Vifor continued to scaremonger and use medical information to ensure that copies of the Lareb report (and similar) were received by the nurse in question. Pharmacosmos thus contended that Vifor's behaviour again brought discredit upon, and reduced confidence in, the pharmaceutical industry, in breach of Clause 29 as they were the same actions that led to a breach of Clause 2 in Case AUTH/2828/3/16.

Pharmacosmos further noted that in Case AUTH/2830/3/16:

> 'The Appeal Board considered that, on the balance of probabilities, it was likely that Vifor representatives had disparaged Monofer as alleged. The Panel's ruling of a breach of Clause 8.1 was upheld. The Appeal Board further considered that on the balance of probabilities, it was likely that Vifor representatives had provided misleading information with regard to the safety of Monofer as alleged. The Panel's ruling of a breach of Clause 7.2 was upheld. The appeal was thus unsuccessful.'

Pharmacosmos stated that from the points made above, it was clear that Vifor's representatives and its medical information department had again provided misleading information about the safety of Monofer on essentially the same matters as before – the likelihood of causing hypersensitivity reactions. It seemed clear from the nurse's wording regarding 'the reduced ADRs when using ferinject over Monofer' that the representative had disparaged Monofer.

Pharmacosmos contended that this continuing disparaging and misleading behaviour was a breach of Clause 29 as it was the same behaviour that led to a breach of Clauses 8.1 and 7.2 in Case AUTH/2830/4/16.

When writing to Vifor, the Authority asked it to consider the requirements of Clauses 2 and 29 of the Code.

RESPONSE

Vifor noted that it was obliged to respond to individual enquiries or specific communications from health professionals, provided that the responses related solely to the subject matter of the letter or inquiry, were accurate, did not mislead and were not promotional in nature. This obligation was founded in EU and UK law. Vifor considered that it was under a clear legal and regulatory obligation to send the response in this case and that the manner in which it responded was entirely appropriate and compliant with the Code. It could not be the case that undertakings to the PMCPA could be interpreted or applied in a manner that would require Vifor to breach its legal and regulatory obligations.

Vifor considered the complaint was another example of Pharmacosmos gaming the PMCPA's self-regulatory scheme, while refusing to subject itself to the Code and the jurisdiction of the PMCPA. Vifor considered that the current complaint was yet another example of the type of speculative complaint, often lacking any evidence of a breach, that Pharmacosmos had become accustomed to making. [post meeting note: Following the completion of this case Pharmacosmos denied that it had ever approached the self-regulatory scheme in anything other than a respectful and meaningful manner].

Conversely, Vifor was committed to adhering to the Code and willingly accepted the jurisdiction of the PMCPA. In that regard Vifor noted that Pharmacosmos had also commenced inter-company dialogue clearly with a view to bringing precisely the same issue before the PMCPA separate from these complaints to the Panel about potential breaches of undertakings. Vifor therefore found itself responding to these two complaints while also engaging in inter-company dialogue on exactly the same allegations. This caused significant disruption to Vifor. It was thus ironic to note that Pharmacosmos refused to accept the jurisdiction of the PMCPA because of the burden that managing multiple speculative complaints imposed. Furthermore, Vifor alleged that Pharmacosmos employees were offered a cash bonus (details were provided) if they could create a complainant against Vifor. This was clearly the situation with this case. [post meeting note: Following the completion of this case Pharmacosmos stated that it did not offer any such cash bonus].

With this in mind, Vifor requested that the PMCPA followed subsection c, Section 4. Annex A of the EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals, final consolidated version 2013 which stated*:*

> 'Where a complaint fails to establish a *prima facie* case for a violation of an Applicable Code, such complaint shall be dismissed with respect to the national code. Member associations may also provide that any complaint which pursues an entirely or predominantly commercial interest shall be dismissed.'

and dismiss this complaint as such.

The undertakings alleged by Pharmacosmos to have been breached were in relation to Cases AUTH/2828/3/16 and AUTH/2830/4/16, the former in relation to the sending of promotional material by Vifor's medical information department without prior consent of a health professional and the latter in relation to Vifor representatives disparaging a competitor product.

Pharmacosmos had alleged four separate breaches of undertakings by Vifor and Vifor responded to each.

1 Ruling of a breach of Clause 9.9 in relation to Vifor Pharma Medical Information sending unsolicited promotional emails; Undertaking for Case AUTH/2828/3/16

Vifor stated that the undertaking it had given in Case AUTH/2828/3/16 was not to send promotional material from medical information, specifically the Lareb report, to health professionals without their prior consent. Vifor had admitted a breach and put in place measures to prevent a similar occurrence happening.

Vifor stated that the matter now at hand was clearly outside the scope of this undertaking, since Vifor had responded to two specific requests for medical information. The original email request from the nurse asked the Vifor representative to provide 'any information on giving iron to cyanotic heart disease namely pulmonary hypertension Anyone else doing it' (sic). The only prior communication from the Vifor representative in question was to ask if the health professional would email his/her request so that it could be forwarded onto medical information. This was a wholly appropriate response.

A subsequent email sent by the nurse to the Vifor representative stated 'I was also interested in the slide you showed about the reduced ADRs when using ferrinject over Monofer, I have been giving iron for 2 years and helping nervous ward staff administer confidently and so I am very keen on the safety aspects of administering parenteral iron. Are you able to share the slide or the reference from the European drug referencing and WHO demonstrating that there are less ADRs than monofer'.

The email exchange made clear that Vifor had not sent any information, promotional or otherwise, to the nurse without his/her prior consent. The medical information response was sent at the express written request of the health professional and therefore there could be no breach of the previous undertaking in this respect.

The request from the health professional was somewhat ambiguous. Vifor did not have a slide 'claiming reduced ADRs when using Ferinject vs Monofer', nor did Vifor suggest that regulators or the World Health Organisation (WHO) had demonstrated that there were fewer ADRs for Ferinject than for Monofer. The only statement approved for use was '… European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons …' Vifor made the nature and scope of the response very clear in the first four

lines of the medical information response. Vifor had not received communication from the nurse that this was not the nature of his/her request.

Thus, and in compliance with Clause 1.2 of the Code, the medical information response related solely to the subject matter of the request, but in a strictly accurate, neutral, non-selective, non-misleading and non-promotional manner. Pharmacosmos complained in Case AUTH/2828/3/16 that Vifor was selective in the reports it provided and that it should have included the Swiss Medic communication of December 2013 which included a report on ADRs with Ferinject. In this regard, Vifor noted that the Swiss Medic Communication compared ADRs with Ferinject with other IV irons but did not refer to Monofer as it was not available in Switzerland. If anything, however, it discredited Vifor's own product. Nonetheless, as a commitment to the undertaking given in Case AUTH/2828/3/16, medical information responses had been adapted to ensure a full, balanced review of all of the available European regulatory authority reports on the matter including the Swiss Medic report on Ferinject.

Pharmacosmos claimed in the alleged breach of undertaking that Vifor should have provided additional data from other sources and cited two abstracts of as yet unpublished, non-peer reviewed abstracts as examples (Emrich *et al* and Wolf *et al*). Clearly, that would have gone beyond the scope of the request. Moreover, given the very limited scientific value of the sources cited by Pharmacosmos and their lack of any relevance to the request, they would not have been an appropriate addition to the data provided.

Vifor submitted that it had not breached its undertaking.

2 Ruling of a breach of Clauses 7.2, 7.4 and 7.9 in relation to Vifor representatives making misleading claims about the safety profile of Monofer; undertaking for Case AUTH/2828/3/16

Vifor stated that it was difficult to see how this could have occurred with respect to its response to the nurse; Vifor did not have a slide, or indeed any information in any format, showing reduced ADRs when using Ferinject over Monofer. Information published by European health authorities did however exist in relation to differences between intravenous irons, specifically including observed differences between Ferinject and Monofer. As the medical information response was only to address specific questions asked by the health professional '… are you able to share the reference from the European drug referencing and WHO …' and as the information provided related solely to the subject matter of the enquiry, then Vifor deemed it appropriate to send the response as written '… I understand from my colleague, (name omitted), that you have requested for the following; References for the statement; European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons …'. Vifor medical information responses were based on a standard set of responses which were approved globally and locally.

This was therefore not a breach of Vifor's undertaking to not make misleading statements about the safety of Monofer; the Vifor representative in question referred a genuine, legitimate and unsolicited request for information from the nurse to the Vifor medical information department in a fully appropriate, compliant manner; this was not a Vifor representative making misleading statements about the safety profile of Monofer as alleged. The subsequent medical information response addressed directly the question raised, providing the information requested on European health authority reports on ADRs with iv irons and did so in a balanced, appropriate manner. Vifor therefore submitted that there had been no breach of undertaking.

3 Ruling of a breach of Clause 2 in relation to overall behaviour of Vifor regarding scaremongering and using medical information; Undertaking for Case AUTH/2828/3/16

Vifor submitted that as clearly indicated above, it had neither inappropriately solicited a medical information request, nor provided unbalanced information in response to a legitimate medical information request, nor had Vifor representatives made misleading statements about the safety profile of Monofer. There could therefore be no breach of undertaking or of Clause 2.

4 Ruling of breaches of Clauses 8.1 and 7.2 in relation to Vifor representatives making disparaging and misleading claims about the safety profile of Monofer; undertaking for Case AUTH/2830/4/16

The undertaking by Vifor in Case AUTH/2830/4/16 was that Vifor representatives, and hence any Vifor promotional material, would not disparage Monofer. This also applied to any material produced by Vifor. Vifor amended its material as required following the undertaking.

In the current case, Case AUTH/3199/5/19, Pharmacosmos alleged a breach of undertaking not to make disparaging and misleading statements about the safety profile of Monofer based on an ambiguous email from a health professional. The statement contained the words 'reduced ADRs when using ferrinject over Monofer'. There was no evidence to support the allegation that the Vifor representative had used these exact words during the meeting with the nurse and hence disparaged Monofer. Vifor vigorously contested Pharmacosmos' assumption in this regard. Surely the burden of proof of such a strong, unsubstantiated allegation must be higher than this?

Vifor thus submitted that there was no evidence to support Pharmacosmos' allegation that a Vifor representative had disparaged Monofer and so there had been no breach of the undertaking from Case AUTH/2830/4/16 and no breach of Clause 29 or Clause 2.

In conclusion, sending a response to an individual enquiry by the medical information department was appropriate and in accordance with the requirements of Clause 1.2 and that representatives had not made misleading statements or disparaged a competitor product and indeed there was no evidence of this. Vifor therefore submitted there had been no breach of the undertakings given in Cases AUTH/2828/3/16 or Case AUTH/2830/4/16 and hence no breaches of Clause 29 or Clause 2.

In response to a request for further information, Vifor stated that given the seriousness of the situation and its commitment to self-regulation it had engaged with external expert advisors and consultants and as a result of its fresh approach noted that the Authority would see a greater level of detail and some corrections to previous information.

Vifor provided copies of the Ferinject Objection Handler (UK-FCM-1900026), certain slides of which were used by the representative at the meeting in question. The briefing document was also provided (ref UK-FCM-1900027). Vifor noted that this version of the objection handler was withdrawn in September.

Vifor acknowledged that the medical information email and certain statements in the objection handler could amount to a breach of undertaking given in Cases AUTH/2828/3/16 and AUTH/2830/4/16 for the following reasons:

- The request for information from the nurse could have been prompted by the statements in the objection handler, and this could have solicited the medical information request, however this was not clear.

- The medical information email might be considered promotional, not balanced and not providing appropriate context, given that it was not clear that the Summary of Product Characteristics (SPCs) for both medicines had the same warning in relation to hypersensitivity.

- The objection handler contained statements in relation to hypersensitivity reactions for Ferinject compared with Monofer that could be misleading in that there was no clarification that the SPCs for both medicines had the same warning in relation to hypersensitivity.

- Given the points above, the objection handler and medical information email could therefore be disparaging in relation to Monofer.

Vifor thus acknowledged a potential breach of Clauses 29 and 2.

Vifor submitted that when it received the current complaints Cases AUTH/3199/5/19 and AUTH/3224/7/19, it discussed them in detail with certain staff who were in post when the rulings in Cases AUTH/2828/3/16 and AUTH/2830/4/16 were received. Whilst training took place across the whole organisation, it was clear that there was not a comprehensive record that the medical information staff were trained on the impact of the rulings, and on future conduct or material produced by Vifor such as medical information responses or promotional items.

As a result of ongoing investigations into all matters relating to these complaints which started in June, certain staff ceased working for Vifor.

Vifor acknowledged and submitted that it was a serious matter and noted that it had engaged experienced staff and a third party to review all undertakings given by Vifor to the PMCPA, and input into all processes and procedures in order to guide future activities.

Vifor apologised for the number of inaccuracies in its letter of response to Case AUTH/3199/5/19 dated 3 June 2019, for example in relation to steps that were taken following Cases AUTH/2828/3/16 and AUTH/2830/4/16.

Overall, Vifor recognised the gravity of the situation that Vifor was in, in relation to the materials at issue, the previous responses that it provided to Cases AUTH/3199/5/19 and AUTH/3224/7/19 and the lack of action in relation to previous undertakings. Vifor submitted that it had engaged a third party to conduct an audit of its processes in relation to the Code in order to address these matters.

This notwithstanding, Vifor remained concerned that Pharmacosmos might use the self-regulatory process to obtain commercially sensitive competitor material. Vifor reiterated that the objection handler must not be shared with Pharmacosmos.

PANEL RULING

The Panel noted Vifor's reference to the EFPIA Code on the Promotion of Prescription-Only Medicines To, And Interactions With, Healthcare Professionals (approved in 2014, the EFPIA HCP Code). This included in its introduction that the EFPIA HCP Code was not intended to restrain the promotion of medicinal products to, or limit interactions with, healthcare professionals in a manner that was detrimental to fair competition.

Since then, the EFPIA Board agreed that member national associations could dismiss any complaint which pursued an entirely or predominantly commercial interest. That decision was reflected in Section 28.04d of the agreed, but not yet operational EFPIA Code of Practice (due to be implemented by member associations by 31 December 2020). The ABPI Code 2019 did not include similar wording, nor did the PMCPA Constitution and Procedure so no complaints could be dismissed on these grounds.

The general, and long held principle in the UK, was that the arrangements for self-regulation must, as a minimum, cover any complaint that could be made under UK advertising law about ABPI members or non-member companies which had agreed to comply with the Code and accept the jurisdiction of the PMCPA and so the EFPIA Board position referred to above was not proposed as part of the consultation concluding with the 2019 ABPI Code. There was no exception to UK law in relation to complaints which pursued an entirely or predominantly commercial interest and thus this could not be a reason for not dealing with a complaint under the ABPI Code. The pharmaceutical industry's strong commitment to self-regulation in the UK would be undermined if it was to put the PMCPA in a position where the Authority would have to refer complaints about pharmaceutical companies which were either ABPI members or had agreed to comply with the Code and accept the jurisdiction of the PMCPA, to the MHRA for consideration under UK law. The Code was an important means of building and maintaining confidence in the pharmaceutical industry.

The Panel noted that a form of undertaking and assurance was an important document. Companies had to give an undertaking that the activity or use of the material in question and any similar material (if not already discontinued or no longer in use) would cease forthwith and give an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future (Paragraph 7.1 of the Constitution and Procedure). It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the nurse had emailed the Vifor representative stating 'I was also interested in the slide you showed about the reduced ADRs when using ferinject over Monofer, I have been giving iron for 2 years and helping nervous ward staff administer confidently and so I am very keen on the safety aspects of administering parenteral iron' and ' Are you able to share the slide or the reference from the European drug referencing and WHO demonstrating that there are less ADRs than monofer'. The Panel disagreed with Vifor's submission that the nurse's request for information was ambiguous. In the Panel's view, medical information wrongly interpreted the request as a reference to an alternative existing approved claim by stating 'I understand from my colleague [name] that you have requested references for the statement "European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons"'. It thus appeared that medical information had simply ignored the nurse's references to the slides upon which he/she had based his/her request for information.

The references cited in the medical information response included the Ferinject SPC, the minutes of the EMA Pharmacovigilance Risk Assessment Committee (PRAC) meeting on 6-9

March 2017, EMA list of medicinal products under additional monitoring, the Lareb report, the AEMPS report, the WHO Pharmaceuticals newsletter, and the Swissmedic Vigilance-News, Edition 11 newsletter. The Panel noted that Pharmacosmos provided the Swissmedic Vigilance-News, Edition 11 with the email trail between the nurse and Vifor including the medical information response which included hyperlinks to the references referred to above. Vifor provided the Ferinject SPC.

The medical information response included a summary of some of the references provided and hyperlinks to access the full documents for all of the references apart from the Ferinject SPC. The medical information response letter started by explaining that findings by EMA as part of the referral procedure (EMEA/H/A-31/1322) led to revisions in the labels for the entire class of IV iron products and the outcome of the referral procedure concluded that the reviewed data did not allow clear differentiation between IV iron products and their relation to severe hypersensitivity reactions. In that regard the Panel noted, however, that the EMA Assessment report for iron containing intravenous (IV) medicinal products dated 13 September 2013 stated that as the conclusions of the assessment were mainly drawn from post-marketing data, differentiation between the iron complexes in terms of hypersensitivity reactions could not be identified. The medical information response then went on to state that a lab report published by the Netherlands Pharmacovigilance Centre Lareb reported that they have received concerns regarding the safety of IIM from multiple Dutch hospitals wherein the doctors and nurses have observed an increase in the severity and incidence of allergic reactions after switching from FCM to IIM.4. It further went on to state that the AEMPS issued a warning recently to not start new patients with Monofer due to the risk of severe HSRs. The data available to AEMPS was being reviewed in detail and as a precaution the AEMPS recommended health professionals not to initiate new treatments with Monofer. It then stated that the rate of reporting on severe HSRs with iron isomaltoside was much higher than for other IV iron preparations which was referenced to the AEMPS report and the WHO newsletter.

The letter concluded with please also find attached the Swissmedic Vigilance-News 7 which looks at the risk of intravenous treatment of iron deficiency.

In the Panel's view, the medical information response misrepresented the EMA position and then selectively discussed two reports, one from the Netherlands and one from Spain, both of which unfavourably compared Monofer with Ferinject and ended with a Swiss reference which reported on ADRs with Ferinject but not with Monofer.

The Panel noted Vifor's initial submission that it did not have a slide 'claiming reduced ADRs when using Ferinject vs Monofer', and that it did not suggest that regulators or the WHO had demonstrated that there were fewer ADRs for Ferinject than for Monofer. Despite Vifor's submission that the only statement approved for use was '… European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons…', that statement did not appear in any of the material supplied by Vifor; it appeared only to have been used in the introductory paragraph of the medical information response. The Panel noted that it was only following a request for further information that Vifor provided a copy of the Ferinject Objection Handler (UK-FCM-1900026) entitled 'Why Ferinject', which was used by representatives, and the relevant briefing document (UK-FCM-1900027). Vifor stated that certain slides of the objection handler were used by the representative at the meeting in question but did not state which slides in particular were used. (The Panel noted that the objection handler had since been withdrawn.)

The executive summary in the briefing document stated, *inter alia*, 'We want you to ***actively*** differentiate between IV irons using information in your sales aid'. The stated proactive growth and active differentiation strategy included getting health professionals to understand how IV irons were different and use Ferinject preferentially. Representatives were to have reactive differentiation discussions if health professionals stated that they considered all IV irons were the same in terms of, *inter alia*, tolerability. The briefing document summary stated 'Only use the 'Ferinject objection handler' **reactively** when a health professional considers that all IV irons are the same; requests a comparison of tolerability of irons or requests a comparison of the efficacy of IV irons. In the Panel's view, it was clear that Vifor intended to clearly, and favourably, differentiate Ferinject from other IV irons including on grounds of tolerability.

The objection handler included a number of slides comparing the tolerability of Ferinject vs Monofer, the majority of which focussed on hypersensitivity reactions The first slide within the Tolerability profile section was titled 'IV irons and hypersensitivity reactions: a European assessment and gave a timeline which according to the briefing document showed why Ehlken *et al* (2018) was commissioned. The next slide reported on Ehlken *et al*, a retrospective pharmacoepidemiologic study using data from the European Union Drug Regulating Authorities Pharmacovigilance database and data from the WHO VigiBase database both of which showed that hypersensitivity reactions were more common in patients receiving iron isomaltoside 1000 vs Ferinject (10.7 x and 8.4 x respectively). Whilst the relative frequencies appeared quite different, a pop-up graph (which might or might not have been used at the meeting) showed that the absolute numbers of reported severe hypersensitivity reactions, adjusted for exposure, per 100mg dose equivalent, per 100,000 administrations were still very small in both groups and no more than 5 in the iron isomaltoside 1000 group. There was no indication in the objection handler as to whether the apparently meaningful difference between Ferinject and iron isomaltoside 1000 was clinically or statistically significant. Ehlken *et al* was sponsored by Vifor and was described in the briefing notes as presenting 'important information' about Ferinject and iron isomaltoside 1000 (Monofer and Diafer). It was thus likely that representatives would be keen to show this slide. Diafer (iron isomaltoside 50 mg/ml solution for injection) was also marketed by Pharmacosmos and was indicated in adults for the treatment of iron deficiency in patients with chronic kidney disease on dialysis, when oral iron preparations were ineffective or could not be used.

Another slide followed claiming, in bold type, a 75% lower risk of severe hypersensitivity reactions with Ferinject vs Monofer ($p<0.0001$) (Mulder *et al* 2018). In smaller font below it was explained that hypersensitivity reactions occurred in 18/836 (2.1%) of Ferinject and 43/496 (8.7%) of Monofer administrations. Mulder *et al* was a single centre Dutch study and although the briefing notes referred to study limitations and that the study indicated that there **might** be differences in the clinical profiles of the two iv irons the slide in the objection handler itself was unequivocally headed 'A recent study showed Ferinject **is** associated with a lower risk of severe hypersensitivity reactions than Monofer' (**emphasis added**).

A third slide detailed Bager *et al* (2017) which was a single centre Danish study which showed that Monofer was associated with a higher incidence of hypersensitivity reactions (10.7%) compared with Ferinject (2.5%) ($p<0.01$). A pop-up slide showed the absolute difference of 11 reactions in the Monofer group and 4 in the Ferinject group. Although it was stated in the objection handler that all hypersensitivity reactions were grade 1 or 2, there was no information as to how many of each grade occurred in either group. The Panel further noted that the briefing document stated that 'When using Monofer they observed a relatively high number of [hypersensitivity reactions] and for safety reasons, they switched back to Ferinject …. However,

a drawback when using Ferinject was a higher rate of Hypophosphataemia compared with Monofer'.

The Panel considered that Vifor had clearly set out to differentiate Ferinject from Monofer in terms of the incidence of hypersensitivity reactions despite both SPCs listing anaphylactoid/anaphylactic reactions as rare (≥1/10000 to <1/1000)). The Monofer SPC listed hypersensitivity including severe reactions as uncommon (≥1/1,000 to <1/100) and the Ferinject SPC stated that hypersensitivity was uncommon.

The Panel considered, on the balance of probabilities, that the slides described above prompted the nurse to refer to 'the slide you showed about the reduced ADRs when using Ferinject over Monofer' and to ask for 'the slide or reference from European referencing and WHO demonstrating that there are less ADRs than Monofer'. In that regard it was wholly disingenuous for Vifor to have stated that it did not have a slide claiming reduced ADRs when using Ferinject vs Monofer and that it had not suggested that regulators or the WHO had demonstrated that there were fewer ADRs with Ferinject than with Monofer. The matter was not complicated and even a cursory glance at the objection handler would have shown that Vifor's original response was incorrect.

The Panel noted that a reply made in response to an enquiry from a health professional was exempt from the definition of promotion provided that the enquiry was unsolicited and the reply related solely to the subject matter of the enquiry, was accurate, did not mislead and was not promotional. The Panel noted its comments above and considered that the medical information response to the nurse could not take the benefit of the exemption to promotion as set out in Clause 1.2. In the Panel's view, the response from medical information was not in reply to an unsolicited enquiry, it did not relate solely to the subject matter of the enquiry and the content was not accurate, balanced or fair. In that regard the nurse had been sent a promotional email without his/her permission which was in breach of the undertaking given in Case AUTH/2828/3/16; the Panel ruled a breach of Clause 29.

The Panel noted its comments above about the content of the objection handler and the accompanying briefing document. There appeared to be no doubt that Vifor had set out to clearly and favourably compare Ferinject with Monofer with regard to tolerability and hypersensitivity reactions. There was, however, little or no difference between the two products with regard to relevant statements in their SPCs and the EMA currently concluded that data did not allow clear differentiation between IV iron products and their safety profile in relation to hypersensitivity reactions.

The Panel noted that in Case AUTH/2828/3/16 Vifor was ruled in breach of the Code for spreading doubt about the safety of Monofer; and in Case AUTH/2830/4/16 the company was ruled in breach for disparaging Monofer. In the Panel's view, the objection handler continued to spread doubt about the safety of Monofer and the briefing document was such that, when using the objection handler, the representative would have, on the balance of probabilities, disparaged Monofer. Both the objection handler and the briefing document were in breach of the previous undertakings and further breaches of Clause 29 were ruled as acknowledged by Vifor.

The Panel noted its rulings of breaches of Clause 29 above and that inadequate action leading to a breach of undertaking was one of the reasons likely to lead to a breach of Clause 2, a sign of particular censure. Given that Clause 29 underpinned self-regulation, the Panel considered that breaches of undertakings brought discredit upon, and reduced confidence in the industry.

The Panel further noted Vifor's submission that whilst the whole organisation was trained following Cases AUTH/2828/3/16 and AUTH/2830/4/16, it was clear that there was not a comprehensive record of the medical information staff being trained on the impact of the rulings, and on future conduct or material produced by Vifor such as medical information or promotional items. A breach of Clause 2 was ruled.

The Panel was very concerned to note that despite being asked by the case preparation manager to provide copies of relevant material including the slides used by the representative in question with the nurse and copies of the current relevant representative's briefing which referred to Monofer and side-effects, Vifor did not provide any of this information. In response Vifor stated that it did not have a slide 'claiming reduced ADRs when using Ferinject vs Monofer', nor did it suggest that regulators or the WHO had demonstrated that there were fewer ADRs for Ferinject than for Monofer. A cursory glance at the objection handler would have shown that that statement was incorrect. The Panel was concerned to note that it was only in response to a request for further information that Vifor provided a copy of the Ferinject Objection Handler (UK-FCM-1900026) certain slides of which it stated were used by the representative at the meeting in question and the briefing document (ref UK-FCM-1900027) which clearly set out differences in the occurrence of hypersensitivity reactions between Ferinject and Monofer in favour of Ferinject and specifically referred to the European Union Drug Regulating Authorities Pharmacovigilance Database and the WHO VigiBase Database which showed that hypersensitivity reactions were reported more frequently in patients receiving iron isomaltoside 1000 vs Ferinject. The Panel queried why this information was not provided initially. The Panel noted that self-regulation and the reputation of the industry in that regard, relied upon full and frank disclosure at the outset.

The Panel was extremely concerned to note that its request for further information appeared to mark a complete turn-around by Vifor. Having previously provided none of the relevant material and vigorously denying all allegations Vifor now acknowledged potential breaches of Clauses 29 and 2 and noted a number of inaccuracies in its original response; the company only appeared to take this more open and transparent approach following the engagement of external advisors. Although Vifor's abrupt and complete reversal of its position had clarified the matters in hand, the Panel considered that the company's original response appeared obstructive and uncooperative despite its protestations that it was committed to adhering to the Code and willingly accepted the jurisdiction of the PMCPA. In that regard, the Panel decided to report Vifor to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

COMMENTS FROM VIFOR ON THE REPORT

The following comments from Vifor were made in relation to both Case AUTH/3199/5/19 and Case AUTH/3224/7/19.

Vifor accepted and acknowledged the Panel's rulings in these matters and sincerely apologised for its failings.

Vifor also acknowledged that in both cases the Panel had reported Vifor to the Appeal Board. Vifor fully accepted this decision and understood that self-regulation relied on companies providing a full and frank disclosure to the PMCPA in response to any complaint.

As an organisation, Vifor was aware that it faced a number of compliance challenges and submitted it was already working diligently to address these. Vifor very much appreciated the opportunity to attend the report hearing for both cases in order to provide the Appeal Board with further information on the improvement activities that it was undertaking.

The company provided a summary of its ongoing actions and plans which had been initiated with the help of external Code experts. These included a review of policies and procedures, a review of materials and plans for training staff.

The following comments were made by Vifor at the consideration of the two reports, Case AUTH/3199/5/19 and Case AUTH/3224/7/19.

The representatives from Vifor stated that the company understood that it had serious compliance failings for which it apologised. Vifor submitted that it had started and would continue to address these matters as a matter of urgency and it had started reviewing its policies and practices. Vifor expected a PMCPA audit and submitted that this would help it expedite the self-improvement process.

Vifor submitted that it currently had experienced interim staff and an external agency to support its work.

Vifor submitted that it reviewed all medical compliance procedural documents for validity and correctness and details were provided. A job bag audit was ongoing for all active materials (200 plus items). Some issues with material and housekeeping were identified as well as system issues which it was addressing as a matter of urgency.

Training was planned for all updated policies and procedures (online and face to face). Formal training on medical information was to take place. In addition, initial stages of 'culture of Compliance' training would be accelerated with outputs of these cases.

Vifor submitted that it had recruited a new staff to start by early July. Vifor fully appreciated the seriousness of the situation and apologised for its failings. Vifor submitted that it was working to ensure that it had a robust and sustainable compliance framework.

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board noted the Panel's comments and rulings of breaches of Clauses 2 and 29 of the Code in Case AUTH/3199/5/19, including its decision to report Vifor to the Appeal Board. The Appeal Board noted that Vifor had provided brief details about its plan to address the issues and had apologised.

The Appeal Board was very concerned that the initial response from Vifor (dated 3 June 2019) could be described as obstructive, defensive, aggressive, dissembling and untrue. Vifor's follow up letter (29 November 2019) referred to the cases as a 'fishing exercise by Pharmacosmos' to obtain Vifor promotional material. Subsequently, Vifor's response to a request for further information (dated 6 December 2019) which referred to Case AUTH/3199/5/19 and Case AUTH3224/7/19 admitted that the company's initial response was inaccurate and provided the Ferinject Objection Handler (UK-FCM-1900026) and the briefing document (ref UK-FCM-1900027). This version of the Objection Handler had been withdrawn in September 2019. The

form of undertaking provided in Case AUTH/3224/7/19 stated that the objection handler was last used on 29 September 2019

The Appeal Board noted that Vifor accepted full responsibility for its initial response of 3 June 2019. Vifor stated that it became apparent that the letter was not appropriate. Further the request was clearly in relation to statements made within the objection handler. Concerns about the content of the initial response were subsequently investigated by Vifor. The investigation resulted in a change in the senior leadership team and following its advice and that of an external agency resulted in Vifor's reversal of position declared to the PMCPA. The Vifor representatives at the report hearing also referred to very recent changes in leadership at the global level. In response to a question the Vifor representatives confirmed that the letter of 6 December 2019 was written by the external third party contracted to provide compliance advice.

The Appeal Board was concerned about the length of time it had taken for Vifor to change its approach to the complaint. Vifor representatives at the report hearing explained that the delay, in part was caused by the need to follow certain internal processes and that the legal team insisted that Vifor continued to submit that the case be dismissed rather than provide the materials including the objection handler. The Appeal Board also noted Vifor's subsequent response to the PMCPA and Vifor's admission of errors and that it accepted responsibility for the breach of undertakings given in previous cases.

The Appeal Board noted the submission from Vifor's representatives at the report hearing that Vifor was now committed to change how it would promote its medicines. First line managers were briefed in late February. The Appeal Board welcomed the change in approach from Vifor and its plans to ensure that such issues did not recur. However, the Appeal Board was very concerned about the prevailing company culture within which the initial response was submitted. The Appeal Board noted that company culture took time to change. The Appeal Board noted that self-regulation relied, *inter alia*, upon the provision of complete and accurate information from pharmaceutical companies.

The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Vifor should be publicly reprimanded for its failure to provide accurate and truthful information to the Panel and its disingenuous approach to responding to the complaint. The Appeal Board also decided to require an audit of Vifor's procedures in relation to the Code in the present case. The Appeal Board required Vifor to provide a comprehensive and detailed corrective and preventive action (CAPA) plan with timelines in time for it to be considered at the next Appeal Board meeting on 11 March. On consideration of the CAPA plan the Appeal Board would confirm the date of the audit. In any event this audit would take place at the same time as that required in Case AUTH/3224/7/19. On receipt of the report of the audit the Appeal Board would consider whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

On receipt of the requested CAPA plan from Vifor, the Appeal Board noted the timelines in the CAPA plan. There were completion dates between February and August 2020. The Appeal Board queried whether the timelines were sufficient and reflected the urgency of the situation given its comments about the seriousness of these cases. In that regard it noted that Vifor was still yet to brief all employees about the current cases. The Appeal Board decided that the audits should take place in September 2020 by which time it expected to see substantial

progress. On receipt of the report for the audits it would decide whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

At its meeting in January 2021, the Appeal Board considered the report for the October 2020 audit. The Appeal Board noted its comments at its meetings in February 2020 and March 2020 set out above particularly in relation to the prevailing company culture within which the initial response was submitted and Vifor's corrective and preventative action (CAPA) plan. The Appeal Board had queried whether the timelines in the CAPA were sufficient and reflected the urgency of the situation given its comments about the seriousness of these cases.

In considering the materials now before it, these being the audit report and Vifor's response to it, the Appeal Board was very concerned about the apparent lack of progress, and the number and nature of ongoing issues and concerns to be addressed as highlighted in the audit report. The Appeal Board noted changes in senior personnel at Vifor global and that communication between Vifor UK and Vifor global had started to improve.

The Appeal Board considered that the audit report indicated that the understanding of the Code and compliance was limited in the UK, and that there was a need for senior staff to improve their knowledge, visibility and leadership on compliance matters ensuring all understood the importance of compliance and the role of self-regulation. In the Appeal Board's view these concerns also applied to global staff in relation to their relevant interactions with the UK. Vifor UK needed to focus on ensuring that its activities and materials complied with the Code. A number of issues were highlighted including that it was important that the company had the appropriate speak-up culture so that employees were confident to raise concerns. The Appeal Board considered that significant commitment was required to address these issues.

The Appeal Board noted that Vifor's comments on the audit report did not address some of the serious criticisms in the report of the audit The Appeal Board was concerned about the prioritisation of matters on the compliance improvement plan and considered that this needed to be reassessed. This was of particular note given the Appeal Board's previous concern in March 2020 about whether Vifor's CAPA timelines reflected the seriousness of the situation.

Given the exceptional circumstances of this matter, including the scale and seriousness of the difficulties at Vifor, the Appeal Board requested that Vifor representatives be invited to attend the Appeal Board meeting on 10 February 2021 to discuss the company's response to the Appeal Board's concerns. As well as senior UK staff, in addition, it was considered that it would be helpful if appropriate senior staff from Vifor global could also attend. The Appeal Board encouraged Vifor to submit any further written comments with regard to the company's plans and actions to improve in response to the Appeal Board's concerns about the report of the audit.

The Appeal Board was minded to require further sanctions including but not limited to a re-audit, however it reserved use of all of its available sanctions until after its further consideration of Vifor's position at the next Appeal Board meeting on 10 February 2021.

APPEAL BOARD FURTHER CONSIDERATION

At its meeting in February 2021 representatives from Vifor attended to discuss the Appeal Board's concerns.

Vifor appreciated the opportunity to attend, and the company recognised that the Appeal Board's concerns and perception of Vifor were valid and it was committed to address this at any subsequent re-audit.

The Appeal Board remained concerned that the reassurance given by Vifor when it attended the Appeal Board for the consideration of the report from the Panel in February 2020 did not align with the concerns subsequently raised in the report of the audits held on 16 October 2020. The Appeal Board was concerned about the overall rate of progress, including since the audit in October 2020, and that Vifor appeared to take a reactive rather than a proactive approach to the required improvements. The Appeal Board was particularly concerned that senior management had a different view of Vifor's progress to that indicated in the audit report. Vifor needed to address these disconnects and be able to demonstrate improvements.

The Appeal Board noted that the updated improvement plan provided by Vifor for the meeting on 10 February 2021 set out further details but that there was still a significant amount of work to be done and in that regard the current pace of change remained too slow.

The Appeal Board considered that Vifor needed to take a much more proactive approach in addressing the situation, this would include setting milestones to achieve the significant rate of change, including to the company culture, that was required. The Appeal Board noted the company's responses, but it queried whether compliance was sufficiently resourced or supported within the company to address matters.

The Appeal Board welcomed Vifor global's attendance at the meeting and commitment to support and work with Vifor UK.

The Appeal Board noted its comments above and decided that Vifor should be re-audited in June 2021 at which point it expected the company to demonstrate significant progress. On receipt of the report for the re-audit it would decide whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

At its meeting in September 2021, the Appeal Board considered that from the report of the July 2021 re-audit there had been some progress, but it appeared that the pace of improvement was unacceptably slow, especially given the nature of ongoing issues highlighted in the re-audit report. The Appeal Board noted its previous concerns about the pace of change including that Vifor was concerned that it had not managed to show greater improvement between February 2020 and the October 2020 audit.

The Appeal Board noted the company's continued apparent confusion between promotional and non-promotional materials and activities. Senior staff needed to continue to improve their knowledge and leadership on compliance matters. The company had reorganised its structure and downsized its headcount. A brief staff survey had taken place and a further survey was due in November 2021. The company must be confident that all activities were carried out in compliance with the Code particularly given the new structure and the launch of new products.

A number of issues were of concern to the Appeal Board including the need to update standard operating procedures and improve the quality of the job bags. A further job bag review was planned for the end of 2021.

The Appeal Board considered that there was a significant amount of work to do, and it queried whether Vifor had sufficient urgency and compliance resource to make the necessary improvements within the expected timescale. It was disappointing that material which was to be withdrawn following the October 2020 audit was only withdrawn in June 2021 prior to the re-audit and that the current materials list was still incorrect.

Given the exceptional circumstances of this matter, including the scale and seriousness of the difficulties at Vifor, the Appeal Board requested that Vifor representatives be invited to attend the Appeal Board meeting in October to provide an update and to discuss the company's response to the Appeal Board's concerns. The Appeal Board requested Vifor be asked to submit a short overview of its progress since the re-audit in July 2021 and a comprehensive compliance action plan with a timetable of key dates before the meeting.

The Appeal Board noted that it was so concerned about the re-audit and Vifor's comments that it discussed the possibility of reporting Vifor to the ABPI Board but it decided not to do so at the moment. The Appeal Board decided that Vifor should be re-audited. The Appeal Board noted there was still a significant amount of work to do. The Appeal Board decided that the re-audit should take place in January 2022 with the expectation that everything should be completed and in place by the end of 2021. The Appeal Board expected the company to demonstrate significant and embedded progress. On receipt of the report for the January 2022 re-audit the Appeal Board would decide whether further sanctions were necessary including a report to the ABPI Board.

APPEAL BOARD FURTHER CONSIDERATION

At the Appeal Board meeting in October Vifor welcomed the opportunity to provide more detail and to demonstrate its commitment to continually improve and build a robust compliance framework.

Vifor accepted there was still a significant amount of work to do. Vifor submitted that over the longer term its focus would be to ensure that there was a clear change in its culture supported by clear SOPs and robust training around its activities and the Code.

Vifor submitted that it was building on the progress acknowledged by the PMCPA at the July 2021 re-audit, and continued to cultivate a collaborative approach and the necessary transformation to a compliant culture, but it recognised that a higher level of commitment was needed, and the pace of change needed to be expedited.

The Appeal Board noted that it had previously decided that Vifor should be re-audited in early 2022 and its expectation that Vifor should have completed the work needed by the end of 2021.

The Appeal Board made a number of comments and although it remained concerned about the speed of progress and the need to accelerate the work on improving the company compliance culture, the Appeal Board did not consider that, following the presentation from Vifor and discussions with the company, there needed to be changes to the timetable and actions it had

previously decided upon (at the 16 September meeting of the Appeal Board). It was now for Vifor to do the work and demonstrate significant progress at the re-audit in 2022.

APPEAL BOARD FURTHER CONSIDERATION

At its meeting in March 2022 the Appeal Board received the report of the January 2022 re-audit of Vifor. The Appeal Board noted at its meeting on 22 October 2021, which Vifor had attended, it had remained concerned about the speed of progress and the need to accelerate the work on improving the company compliance culture and it had considered that it was now for Vifor to do the work and demonstrate significant progress at the re-audit in January 2022.

The Appeal Board considered from the January 2022 re-audit report that although there had been some changes there had been little significant progress. The Appeal Board considered that the scale of the difficulties at Vifor coupled with the lack of urgency was very concerning. There had now been three audits/re-audits of Vifor and given the Appeal Board's comments in October 2021 the rate of improvement was unacceptable.

The Appeal Board noted that the re-audit report highlighted a number of concerns. The Appeal Board considered that it was essential that Vifor invested in appropriate compliance support and resource for the work that needed to be done. In that regard the Appeal Board was concerned about how the recent sale of Vifor would impact on its progress to improve.

The Appeal Board was very concerned that the PMCPA was unable to access certain materials despite several requests. The Appeal Board considered that it was the responsibility of the company to ensure access to any materials requested as part of an audit/re-audit. Any issue in this regard needed to be resolved with immediacy by the company. Vifor's failing in this regard was unacceptable.

The Appeal Board was concerned that there were a number of instances of inconsistencies between the company's submissions, for example what was said at the January 2022 re-audit and what the company stated in its written response to the re-audit report.

The Appeal Board was deeply concerned with the existing amount of work still required and queried Vifor's commitment to self-regulation. The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Vifor should be publicly reprimanded for its lack of progress.

The Appeal Board also decided that Vifor should be re-audited in six months' time at which point it required the company to demonstrate significant progress. The Appeal Board required Vifor to provide an interim written report detailing progress and an updated 2022 compliance plan in 3 months. The Appeal Board considered whether to report Vifor to the ABPI Board, however it decided to reserve any further sanctions until receipt of the report for the next re-audit.

APPEAL BOARD FURTHER CONSIDERATION

The Appeal Board considered from the September 2022 re-audit report that Vifor had made good progress since the January 2022 re-audit and that there was now a strong commitment to improve. Compliance was now embedded. Despite these improvements there was still further work needed, particularly within the three areas of documentation governance, governance over

hybrid promotional/non promotional roles and consistency in the quality of promotional materials.

The Appeal Board noted from Vifor's response to the September 2022 re-audit that it had already taken steps to begin to address the comments in the re-audit report, including the three areas above. However, the Appeal Board considered that Vifor should be re audited to ensure that this momentum continued, particularly given the recent acquisition, the launch of new medicines and that progress up until the September 2022 re-audit had been relatively slow. The Appeal Board considered that the re-audit should take place in October 2023 to give the company sufficient time to embed new processes and demonstrate improvements, and at which point it expected to see significant progress. The Appeal Board requested that the re-audit in October 2023 should particularly focus on the three areas identified above. The re-audit should also look at progress in relation to all the September 2022 re-audit recommendations.

The Appeal Board reserved any further sanctions until receipt of the report for the next re-audit in 2023.

APPEAL BOARD FURTHER CONSIDERATION

The Appeal Board observed that CSL Vifor had made progress in the three main areas targeted at the September 2023 re-audit, namely end-to end governance of activities, governance over hybrid roles and quality of promotional materials. Overall, it appeared that the standard of promotional material had improved, and the governance of hybrid roles enhanced, since the September 2022 re-audit. Given it was the company's fifth audit, the Appeal Board was expecting CSL Vifor to have made more significant improvement in relation to end-to-end governance of activities. However, the Appeal Board acknowledged that the acquisition of Vifor by CSL, and the resulting restructuring which impacted both people and processes, would inevitably cause a delay in implementing some of the recommendations from the September 2022 re-audit, particularly in relation to procedural documents.

The Appeal Board observed that the new compliance model included a comprehensive internal monitoring programme conducted by the regional team at CSL. While it was too early to see the full operational impact of the new model, the Appeal Board had confidence in the significantly improved culture within the organisation.

The Appeal Board observed that there were still some areas for improvement, including governance of Transfers of Value (ToV). However, the Appeal Board was encouraged by the company's comprehensive response to the recommendations in the re-audit report, which demonstrated the company's timely action and commitment to compliance.

The Appeal Board decided on the basis that progress was continued, planned work was completed and the commitment to compliance was maintained, that no further action was required.

Complaint received **15 May 2019**

Undertaking received **10 February 2020**

Appeal Board consideration	**26 February 2020, 11 March 2020, 21 January, 10 February 2021, 16 September, 22 October, 10 March 2022, 15 December, 25 January 2024.**
Interim case report first published	**13 October 2020**
Case completed	**25 January 2024**