CASE AUTH/3224/7/19

PHARMACOSMOS v VIFOR

Promotion of Ferinject

Pharmacosmos complained that Vifor Pharma was using misleading and inaccurate safety claims with regard to Ferinject (ferric carboxymaltose) and Monofer (iron isomaltoside 100mg/ml solution for injection or infusion). Ferinject and Monofer were indicated for the treatment of iron deficiency where oral iron preparations were ineffective or could not be used.

Pharmacosmos alleged that the comparative safety claim 'European health authorities have reported differences in the adverse drug reaction profile of the available intravenous irons' used by Vifor in its promotional materials was misleading and inaccurate. Pharmacosmos submitted that alongside the claim, Vifor representatives had made unsubstantiated, incorrect and misleading safety superiority claims that Ferinject had fewer adverse drug reactions (ADRs) than Monofer. This was evidenced by an email from a nurse to Vifor and a follow up email from Vifor medical information which recognised that the above claim was used promotionally by the representatives and the references chosen to support the claim showed that the representatives had specifically discussed hypersensitivity reactions. Pharmacosmos alleged that the contents of, and the supporting information contained in, the unsolicited medical information letter sent to the nurse was similarly misleading and inaccurate on several grounds.

Pharmacosmos submitted that the claims made by Vifor were inconsistent with and disregarded the current official stance taken by the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) ie that no differentiation had been identified between Ferinject and Monofer in terms of hypersensitivity reactions. In that regard, Vifor knew that the claims were incorrect.

Pharmacosmos explained that in 2013 the EMA published a report following a referral requesting that the Committee for Medicinal Products for Human Use (CHMP) gave its opinion on concerns about hypersensitivity and intravenous irons. This procedure included Ferinject and Monofer and was based on all data from marketing authorization holders regarding preclinical and clinical studies, post-marketing reports, and the published literature. The report stated that, inter alia, differentiation between these iron complexes in terms of hypersensitivity reactions could not be identified. Therefore, findings and recommendations were applicable to all the iron complexes. This remained the current position of the EMA and the MHRA.
That the statements made by Vifor's representative to the nurse were present in written promotional materials, which were made for and used by Vifor representatives to make these inaccurate and misleading promotional comparative claims of a superior hypersensitivity profile with Ferinject over Monofer, was evident by Vifor's response which made it clear that nothing unusual was considered about a representative's request for the references to the above claim to be sent to the nurse.

Unfortunately, the inter-company dialogue response from Vifor, received in June 2019, did not address that the use of the claim verbally and in written promotional materials

alongside superiority safety claims of fewer ADRs (hypersensitivity reactions) with Ferinject over Monofer was misleading and inaccurate for several reasons, instead it focussed on the medical information response sent, which Vifor claimed was non-promotional and not in breach of the Code. This clearly disregarded case precedent from the Panel ruling in Case AUTH/2828/3/16, upheld on appeal, which found that requests made in response to Vifor representatives raising issues about the safety of a competitor product were not unsolicited and therefore medical information responses to such requests were subject to Code requirements. It was also stated in Case AUTH/2828/3/16 that it was 'absolutely imperative that communications from medical information were correct', which Pharmacosmos alleged not to be the case in this instance. Therefore, the medical information letter in this case was solicited and promotional in nature.

Pharmacosmos submitted that the continued dissemination by Vifor medical information of blatantly promotional, inaccurate and misleading information was a clear breach of the trust placed in medical information across the industry. Furthermore, for Vifor representatives to use misleading claims to proactively raise concerns about the safety of Monofer could be viewed as a deliberate attempt to solicit requests to allow medical information to supply disparaging, biased, and inaccurate information about a competitor product via a route usually exempt from full Code requirements. Such behaviour by Vifor was previously censured in Case AUTH/2828/3/16, and the continuation of such behaviour further compounded the breach of trust between Vifor and health professionals.

Pharmacosmos stated that to undermine the trusted position of medical information through such biased and promotional behaviour was a blatant and shocking action that clearly brought the industry into disrepute, in breach of Clause 2.

Pharmacosmos submitted that Vifor's conduct as described above should be considered in the context of presenting a clear risk to patient safety.

An article about the management of hypersensitivity reactions recognised that anxiety on behalf of the patient and/or health professional administering the IV iron infusion was a risk factor for a patient having an infusion reaction (Rampton et al 2014). Therefore, Pharmacosmos considered that the anxiety produced through the misleading promotional claims, and the misinformation being provided about Monofer by Vifor, placed patients unacceptably at risk. Not only had the interaction with the Vifor team raised concern about the safety of Monofer with the nurse involved, leading him/her to contact Pharmacosmos medical department for information, but the ruling against Vifor in Case AUTH/2828/3/16 demonstrated that Vifor had a documented history of causing health professionals to doubt the safety of Monofer. In Case AUTH/2828/3/16 Vifor representatives offered misleading comparisons of Monofer with Ferinject, thereby causing the health professionals to feel that scaremongering regarding Monofer safety was occurring.

In summary, Pharmacosmos alleged that the claim 'European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons' should not be used by Vifor in any promotional or non-promotional materials. Nor should any Vifor employees make claims that suggested that Ferinject had a superior safety profile to Monofer. Given the widely recognised limitations of using data based

solely on spontaneous adverse event reporting to compare product safety profiles, Pharmacosmos also considered that Vifor should not use such data without additional necessary data and context, in any of its materials or activities. Pharmacosmos was also extremely concerned about the understanding of Vifor, in particular its medical, marketing and compliance teams, about the scientific validity of data and Code requirements for making comparative claims.

The detailed response from Vifor appears below.

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 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 was ambiguous and referred to alleged claims and materials which simply did not exist. In the Panel's view, the medical information team had wrongly interpreted the request as a reference to an alternative existing approved claim. The response from medical information stated '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 iv 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 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 thus 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 that Pharmacosmos had alleged that the claim '... European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons ...' was misleading and inaccurate. The Panel noted that the only material before it which included the claim at issue was the medical information letter which began 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"'. The Panel noted Vifor's submission that the claim was an approved promotional claim and that the references provided by Vifor medical information in support of the claim all focussed on hypersensitivity reactions. The Panel noted that although individual health authorities in Europe had reported differences between the available IV irons, the current European-wide stance of the EMA was that current data did not allow any differentiation between IV iron preparations in terms of hypersensitivity reactions. In the Panel's view, the claim was therefore misleading and inaccurate and breaches of the Code were ruled.

The Panel further noted Pharmacosmos' allegation that the exclusion of key data, including comparative safety randomised control trial data between Monofer and Ferinject which demonstrated broad comparability in terms of hypersensitivity reactions, with any slight differences in favour of Monofer, in the information sent to the nurse was a deliberate attempt by Vifor to selectively favour Ferinject and disparage Monofer. The Panel noted, however, that the medical information letter set out, albeit apparently wrongly given the nurse's specific questions, to provide references for the statement 'European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons'. The Panel noted its rulings above and comments that the statement was misleading and inaccurate and disparaged Monofer. On that basis, the claim could not be made any more acceptable by the provision of data which was not from European health authorities and so the Panel considered that on this exceptional and very narrow ground there was no breach with regard to the failure to include additional references as cited by Pharmacosmos.
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. 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 the representatives, and the

relevant briefing document. 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 a health professional 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 50mg/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 reaction 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, 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 show that Vifor's original response was incorrect.

The Panel noted its comments above and considered overall that the claims in the objection handler used by the representative at the meeting in question were misleading; some of the data was not sufficiently complete to allow readers to form their own opinion of the therapeutic value of Ferinject vs Monofer. The objection handler did not reflect the fact that, in a review of data, the EMA had been unable to clearly differentiate between IV irons in terms of hypersensitivity reactions. The objection handler also did not reflect the fact that the SPCs for Monofer and Ferinject were almost identical in terms of hypersensitivity reactions; both SPCs listed anaphylactoid/anaphylactic reactions as rare (≥ 1/10 000 to <1/1000). The Monofer SPC listed hypersensitivity including severe reactions as uncommon (≥ 1/1000 to <1/100) and the Ferinject SPC stated that hypersensitivity was uncommon. The Panel therefore ruled breaches of the Code including that the objection handler disparaged Monofer.

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 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 which was subject to the requirements of the Code. The Panel noted its comments above and considered that the medical information letter was misleading and disparaged Monofer. Breaches of the Code were ruled.

The Panel noted its comments and rulings above and considered that Vifor had failed to maintain high standards in breach of the Code.

The Panel noted its comments above and was particularly concerned that the medical information letter was misleading and disparaging. In that regard the Panel noted Pharmacosmos' comment that reducing a health professional's confidence in Monofer might increase a patient's anxiety and lead to an infusion reaction. It was thus

absolutely imperative that communications from medical information were accurate, fair and balanced. In the Panel's view, the medical information letter at issue was poor and, in that regard, it reduced confidence in the pharmaceutical industry. 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 it now acknowledged potential breaches of the Code including Clause 2; 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 submission that it was committed to self-regulation. 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 its decision to report Vifor to the Appeal Board. The material at issue was the same as that in Case AUTH/3199/5/19. The allegations were different in that Case AUTH/3224/7/19 dealt with the claims whereas Case AUTH/3199/5/19 dealt with the breach of undertaking. 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 responses from Vifor (dated 29 July 2019 and 19 September 2019) in addition to the response to Case AUTH/3199/5/19 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 AUTH/3224/7/19 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 responses to Case AUTH/3224/7/19 dated 29 July and 19 September 2019.

Vifor stated that it became apparent that its initial response to Case AUTH/3199/5/19 dated 3 June 2019 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 in Case AUTH/3199/5/19 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 explained that the delay, in part was caused by the need to follow certain internal processes and that the lteam (which included legal and medical representation) 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 breaches of the Code.

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 had been briefed in late February 2020. 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/3199/5/19. 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 complained that Vifor Pharma UK Limited was using misleading and inaccurate safety claims with regards to Ferinject (ferric carboxymaltose) and Monofer (iron isomaltoside 100mg/ml solution for injection or infusion). Vifor's product Ferinject and Pharmacosmos' product Monofer were indicated for the treatment of iron deficiency where oral iron preparations were ineffective or could not be used.

COMPLAINT

Pharmacosmos alleged that the comparative safety claim 'European health authorities have reported differences in the adverse drug reaction profile of the available intravenous irons' used by Vifor in its promotional materials was misleading and inaccurate. Pharmacosmos submitted that alongside the claim, Vifor representatives had made unsubstantiated, incorrect and misleading safety superiority claims that Ferinject had fewer adverse drug reactions (ADRs) than Monofer. This was evidenced by an email from a nurse to Vifor and a follow up email from Vifor medical information which recognised that the above claim was used promotionally by the representatives and the references chosen to support the claim showed that the representatives had specifically discussed hypersensitivity reactions. Pharmacosmos alleged that the contents of, and the supporting information contained in, the unsolicited medical information letter sent to the nurse was similarly misleading and inaccurate on several grounds.

Pharmacosmos submitted that the claims made by Vifor were inconsistent with and disregarded the current official stance taken by the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) ie that no differentiation had been identified between Ferinject and Monofer in terms of hypersensitivity reactions. In that regard, Vifor knew that the claims were incorrect.

Pharmacosmos explained that in 2013 the EMA published a report following a referral requesting that the Committee for Medicinal Products for Human Use (CHMP) gave its opinion on concerns about hypersensitivity and intravenous irons. This procedure included Ferinject and Monofer and was based on all data from marketing authorization holders regarding preclinical and clinical studies, post-marketing reports, and the published literature. The report stated that, *inter alia*, differentiation between these iron complexes in terms of hypersensitivity reactions could not be identified. Therefore, findings and recommendations were applicable to all the iron complexes. This remained the current position of the EMA and the MHRA.
That the statements made by Vifor's representative to the nurse were present in written promotional materials, which were made for and used by Vifor representatives to make these

inaccurate and misleading promotional comparative claims of a superior hypersensitivity profile with Ferinject over Monofer, was evident by Vifor's response which made it clear that nothing unusual was considered about a representative's request for the references to the above claim to be sent to the nurse.

Unfortunately, the inter-company dialogue response from Vifor, received 7 June 2019, did not address that the use of the claim verbally and in written promotional materials alongside superiority safety claims of fewer ADRs (hypersensitivity reactions) with Ferinject over Monofer was misleading and inaccurate for several reasons, instead it focussed on the medical information response sent, which Vifor claimed was non-promotional and not in breach of the Code. This clearly disregarded case precedent from the Panel ruling in Case AUTH/2828/3/16, upheld on appeal, which found that requests made in response to Vifor representatives raising issues about the safety of a competitor product were not unsolicited and therefore medical information responses to such requests were subject to Code requirements. It was also stated in Case AUTH/2828/3/16 that it was 'absolutely imperative that communications from medical information were correct', which Pharmacosmos alleged not to be the case in this instance. Therefore, the medical information letter in this case was solicited and promotional in nature.

Facts of the matter

Pharmacosmos stated that the promotional use of the claim 'European health authorities have reported differences in the adverse drug reaction profile of the available intravenous irons,' and the misleading and incorrect claim by a Vifor representative that Ferinject had fewer ADRs than Monofer, was first brought to the company's attention by a nurse. In a promotional meeting, the nurse had been shown a slide by a named Vifor representative, accompanied by claims which implied 'reduced ADRs when using Ferrinject over Monofer' and that this was demonstrated by the World Health Organisation (WHO) and European drug referencing. This was evidenced by the email from the nurse to the representative in which the nurse stated: '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?'. Vifor medical information then sent an email to the nurse (copy provided), which he/she forwarded to the medical team at Pharmacosmos for information on Monofer, as the nurse was concerned about the safety of Monofer as a result of the interaction with Vifor.

The email from Vifor medical information to the nurse stated that according to the representative the nurse required the supporting references for the statement, 'European health authorities have reported differences in the adverse drug reaction profile of the available intravenous irons,' and the following were listed:

1 Ferinject summary of product characteristics (SPC).

2 The EMA assessment report for iron containing intravenous (IV) medicinal products, 13 September 2013: The medical information letter stated that 'EMA concluded that the reviewed data did not allow clear differentiation between IV iron products and their relation to severe hypersensitivity reactions'.

3 EMA list of medicinal products under additional monitoring.

4 Lareb, Intravenous iron preparations and allergic reactions, November 2015. The medical information letter stated 'concerns regarding the safety of IIM.' ie iron isomaltoside.

5 Agencia Espanola de Medicamentos y Productos Sanitaros (AEMPS), Se recomienda no iniciar nuevs tratamientos con Monoferro debido al riesgo de reacciones graves de hipersensibilidad, 19 July 2017. The medical information letter stated '…a warning recently not to start new treatments with Monofer due to the risk of severe HSRs … the rate of reporting on severe HSRs with iron isomaltoside was much higher than for other IV iron preparations'.

6 World Health Organisation (WHO) newsletter No. 5, 2017 referencing the above AEMPS warning.

7 Swissmedic, Vigilance news, 11th Edition, December 2013. The article was attached to the medical information letter which stated that this 'looks at the risks of intravenous treatment of iron deficiency'.

During inter-company dialogue Vifor claimed that an additional publication was cited as a relevant reference in the medical information letter, one which it stated clearly identified that there were differences in the chemical and clinical aspects of intravenous irons. The publication was the EMA publication 'Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product'. Pharmacosmos stated, however, that despite Vifor's assertions, this reference did not seem to have been provided to the nurse. However, the unsent publication did not support Vifor's claim since it made no comment on the safety profiles of Monofer or Ferinject, nor of their comparative safety, but highlighted that properly designed and conducted studies would be required to determine any differences in safety profile that could arise from differences in physiochemical properties of IV irons.

During inter-company dialogue, Vifor claimed that there was no substantiation that the claim at issue had been used by Vifor representatives. However, Pharmacosmos considered that there was clearly evidence that the claim and related claims of comparative safety had been used in promotional materials and verbally by Vifor representatives.

The request to Vifor medical information was for substantiation of statements made during a promotional call, apparently contained within promotional material (a slide) and discussed by the representative. It could be inferred from the email chain that when the nurse asked the representative for supporting information for 'the reduced ADRs when using ferinject 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,' that the representative informed medical information that this request was in relation to the claim 'European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons'. That the medical information department provided what was requested by the representative showed that the company accepted that the claim had been used within a promotional call and suggested that it was a promotional claim which was regularly used company-wide.

In inter-company dialogue, Vifor confirmed that it had had no communication from the nurse to suggest that this was not the claim requiring substantiation, which further demonstrated on the

balance of probabilities that this claim was indeed contained within promotional materials used by the representative in a promotional call.

The claim: 'European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons', the claims made in conjunction by the representative of a superior safety profile of Ferinject compared with Monofer and the medical information follow-up letter raised a number of issues, which Pharmacosmos alleged were in breach of the Code as detailed below.

Alleged misleading comparison

Pharmacosmos submitted that the statement: 'European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons' implied a comparison between Monofer and Ferinject and was misleading.

In the email asking for the references, the nurse stated: '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 email response from Vifor stated: 'I understand from my colleague, [named], 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"'. Therefore, it was clear from the exchanged correspondence that the claim was used to compare the safety profiles of Ferinject and Monofer in respect of hypersensitivity. However, the EMA had concluded that 'the reviewed data did not allow clear differentiation between IV iron products and their relation to severe hypersensitivity reactions', which was also the current position of the, the MHRA and of many other European authorities. Therefore, to infer differences regarding hypersensitivity reactions suggesting that such were supported broadly with the reference to 'European health authorities' was, by definition, misleading in breach of Clause 7.3.

Alleged inaccurate promotional claim

Pharmacosmos alleged that the claim: 'European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons' misleadingly and incorrectly suggested that at the European-wide regulatory level there was a recognised and reported difference in the adverse drug reaction profiles of currently available IV irons. The claim was made in the context of the information provided verbally by the representative, and the choice of references to support the claim showed that the ADRs discussed by Vifor representatives were specifically hypersensitivity reactions. This was not correct as the current stance of the EMA and the MHRA was that current data did not allow any differentiation between IV iron preparations in terms of hypersensitivity reactions to be identified. So, differences between products in relation to hypersensitivity was not recognised at a European level.

Pharmacosmos thus considered that the use of this inaccurate and misleading claim in promotional material and by Vifor representatives was in breach of Clause 7.2.

<u>Supporting information provided to the nurse about the comparative statement was alleged to be misleading and inaccurate</u>

Pharmacosmos stated that as the medical information letter was not an unsolicited email it was subject to the requirements of the Code. Although the supporting information was provided within a medical information response, to take the exemption from the Code under Clause 1.2, such responses must be unsolicited, accurate and not misleading.

The email from the nurse made it clear that his/her request was in response to the Vifor representative raising issues about the safety of Monofer: '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' **(emphasis added)**.

Therefore, as in Case AUTH/2828/3/16, which found that requests made in response to Vifor representatives raising issues about the safety of a competitor product were not unsolicited, this was not an unsolicited email and was thus subject to Code. It was also stated in Case AUTH/2828/3/16 that it was 'absolutely imperative that communications from medical information were correct'. However, the medical information letter and supporting information supplied to the nurse was misleading and inaccurate on several grounds.

<u>The supporting information supplied was alleged to be disparaging, misleading, inaccurate and unbalanced</u>

Of the references discussed (rather than just listed) by Vifor medical information, the first (the EMA report) actually supported the position that no differences in terms of hypersensitivity reactions could be identified between available IV irons, which was contrary to the claim made by the representative.

Of the remaining four references discussed by Vifor Medical Information, three (Lareb, AEMPS and the WHO Newsletter) were used to place particular emphasis on an alleged negative safety profile for Monofer:

Lareb: '*… doctors and nurses have observed an increase in the severity and incidence of allergic reactions after switching from FCM to IIM.'*

AEMPS: *'The rate of reporting severe HSRs with iron isomaltoside was much higher than for other i.v. iron preparations.'*

The WHO newsletter referenced the AEMPS report. A ruling from the Swedish Association of the Pharmaceutical Industry's Information Practices Committee on 19 February 2019 about Vifor Sweden's use of reference to the same WHO newsletter, determined that because neither the Swedish Medical Products Agency nor the EMA had chosen to implement the same measure, the WHO newsletter could not be considered to support an established or clinically significant safety-related uncertainty with regard to Monofer. Therefore, the claim implied was misleading and Vifor was found in breach of article 4 of the Code of the Swedish Association of the Pharmaceutical Information Practices by communicating this claim and was fined.

A letter of response from Vifor to Pharmacosmos, in relation to the above ruling and dated 14 March 2019 clearly stated 'As to WHO Pharmaceuticals Newsletter No 5, 2017, p. 11 mentioning the Spanish AEMPS informative notice Vifor Pharma can confirm that the WHO Pharmaceuticals Newsletter is not part of its promotional material. This has been verified by all our country organizations'.

The nurse's email to Vifor's representative, which stated, '***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***' **(emphasis added)**, showed that Vifor was knowingly and willingly still using the reference to AEMPS and the WHO newsletter during promotional activities and in promotional materials. This was despite the undertaking given by Vifor several weeks before the promotional call in which Vifor's representative showed Vifor promotional slides and/or made promotional claims, referenced to the prohibited WHO newsletter.

The final reference listed in the medical information letter, the Swissmedic report, did not contain information on Monofer, but detailed 340 ADRs with Ferinject, 239 of which were serious, including three fatal cases. However, although the article was attached to the medical information response, the actual medical information letter ignored these specific facts and failed to discuss the report in the same level of detail as the other reports, instead simply stating that the report 'looks at the risks of intravenous treatment of iron deficiency'. Thus, the letter itself showed inherent bias and so was promotional and drew attention specifically to adverse events with Monofer.

The medical information letter was therefore disparaging, misleading and, as a comparison, it was inaccurate, unbalanced and did not reflect the evidence. Pharmacosmos alleged breaches of Clauses 8.1 and 7.2.

Alleged distorted and scientifically invalid information used to make misleading and inaccurate claims and comparison

Pharmacosmos stated that the letter also distorted the meaning of the original EMA report. The insertion (by Vifor medical information) of the words in bold in the statement 'EMA concluded that the reviewed data did not allow **clear** differentiation between IV iron products and their relation to **severe** hypersensitivity reactions' (**emphasis added**), suggested the possibility of some difference, in relation to severe hypersensitivity reactions.

This was contrary to the original meaning of the EMA, which stated that 'As the conclusions of this assessment were mainly drawn from the post-marketing data, differentiation between these iron complexes in terms of hypersensitivity reactions could not be identified. So the CHMP conclusions are applicable to all the iron complexes assessed in this referral'.

Therefore, data based on spontaneous reporting of ADRs could not be used to compare safety profiles. That comparative safety claims could not be made on the basis of such data has also been confirmed by the Head of Pharmacovigilance and Epidemiology at EMA who stated:

'… to conclude that one product is safer than the other, based on numbers of spontaneous suspected adverse reaction reports alone, without consideration of all other relevant data, including clinical trials and epidemiological studies, is in our view ostensibly simplistic, invalid and misleading.'

The invalidity of making such comparisons was previously communicated to Vifor by Pharmacosmos in an inter-company letter dated 27 December 2018 (copy provided), yet it appeared that Vifor continued to make such unscientifically unsound comparisons, despite knowing it was invalid, inaccurate and misleading.

In addition to the distorted EMA statement, the nurse was also provided with statements about the Lareb and AEMPS reports.

The Lareb report contained information on numbers of adverse events with both Monofer and Ferinject (including several anaphylactic reactions reported for Ferinject). However, the information provided to the nurse only drew attention to reactions with Monofer, and did not provide the necessary context required to allow health professionals to form their own opinion, that is, the context given in the report that 'it can be expected that reporting rates are higher for new products compared to products that have been marketed for a longer time'.

Further, the reports had been provided with the implication that they supported the comparison of Monofer safety with Ferinject safety. However, neither of these reports were comparative in design or nature, and so it was inaccurate and misleading to imply that they were.

Pharmacosmos noted that whilst local health authorities were of course obliged to investigate any pharmacovigilance concerns, any ongoing investigations were not the equivalent to a clear conclusion that any product was definitively associated with any particular safety concern. The experiences contained within these reports were based on a relatively low number of reports and were not in keeping with the overall stance of the EMA regarding the risk of hypersensitivity with IV iron preparations, or other data.

Pharmacosmos stated that it was therefore inaccurate and misleading to link the claim that 'European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons' to these reports.

Additionally, both these reports were based only upon spontaneous adverse reaction reports and so, as noted above, that comparative safety claims could not be made on the basis of such data had been confirmed by the Head of Pharmacovigilance and Epidemiology at EMA. Pharmacosmos submitted that the information provided in the medical information letter was thus not accurate or objective, it was misleading and did not allow recipients to form their own opinion.

The company alleged a breach of Clause 7.2. The considerable inaccuracies in the response and information provided were also a failure to maintain high standards and in breach of Clause 9.1.

The medical information letter was alleged to be disparaging and not based upon an up-to-date evaluation of all the evidence, as key data was excluded

Pharmacosmos alleged that key information had been excluded from the medical information letter; information sent to the nurse appeared to have been deliberately cherry-picked to present Monofer less favourably than Ferinject.

Of the four reports detailed, only one, the Swissmedic report, specifically focussed on Vifor's products, including Ferinject. However, although the article was attached to the medical information response, the letter itself simply stated that it 'looks at the risks of intravenous treatment of iron deficiency,' without making further comment on the safety of the specific Vifor products mentioned. Thus, the letter showed inherent bias; it drew attention specifically to adverse events with Monofer to leave an overall impression of negative safety reports with Monofer, rather than provide unbiased objective, balanced information.

That a comparison of drug safety profiles could not be made solely upon spontaneous adverse event reports, had been discussed above. It was a scientific principle that head-to-head randomised clinical trials (RCTs) were the gold standard for comparing the safety profiles of medicines. However, whilst such data existed to provide comparative safety data between Monofer and Ferinject, the data had been excluded from the information provided to the nurse. The RCTs demonstrated broad comparability between Monofer and Ferinject in terms of hypersensitivity reactions, with any slight differences in favour of Monofer. This had also been the finding of a meta-analysis of RCTs which found that any slight differences in severe hypersensitivity reaction rates favoured Monofer.

Publication of an article by MedWatch on 1 April 2019 (copy provided), contained a statement from Vifor, regarding a pooled analysis of the two head-to-head RCTs discussed above. Therefore, the existence of this data was clearly known to Vifor before the medical information response was sent on 2 April 2019.

Consequently, the exclusion of key data and resulting unbalanced information not based on an up to date evaluation of the data which was sent to the nurse could only be seen as a deliberate attempt by Vifor to selectively favour Ferinject and disparage Monofer. On that basis, Pharmacosmos alleged a breach of Clauses 7.2 and 8.1.

Undermining trust in the industry

Pharmacosmos alleged that the continued dissemination by Vifor medical information of blatantly promotional, inaccurate and misleading information was a clear breach of the trust placed in medical information across the industry. Furthermore, for Vifor representatives to use misleading claims to proactively raise concerns about the safety of Monofer could be viewed as a deliberate attempt to solicit requests to allow medical information to supply disparaging, biased, and inaccurate information about a competitor product via a route usually exempt from full Code requirements. Such behaviour by Vifor was previously censured in Case AUTH/2828/3/16, and the continuation of such behaviour further compounded the breach of trust between Vifor and health professionals.

Pharmacosmos stated that to undermine the trusted position of medical information through such biased and promotional behaviour was a blatant and shocking action that clearly brought the industry into disrepute, in breach of Clause 2.

Risk to patient safety

Pharmacosmos submitted that Vifor's conduct as described above should be considered in the context of presenting a clear risk to patient safety.

An article about the management of hypersensitivity reactions recognised that anxiety on behalf of the patient and/or health professional administering the IV iron infusion was a risk factor for a patient having an infusion reaction (Rampton *et al* 2014). Therefore, Pharmacosmos alleged that the anxiety produced through the misleading promotional claims, and the misinformation being provided about Monofer by Vifor, placed patients unacceptably at risk. Not only had the interaction with the Vifor team raised concern about the safety of Monofer for the nurse involved, leading him/her to contact Pharmacosmos medical department for information, but the ruling against Vifor in Case AUTH/2828/3/16 demonstrated that Vifor had a documented history of causing health professionals to doubt the safety of Monofer. In Case AUTH/2828/3/16 Vifor

representatives offered misleading comparisons of Monofer with Ferinject, thereby causing the health professionals to feel that scaremongering regarding Monofer safety was occurring.

Concluding remarks

In summary, Pharmacosmos alleged that the claim 'European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons' should not be used by Vifor in any promotional or non-promotional materials. Nor should any Vifor employees make claims that suggested that Ferinject had a superior safety profile to Monofer. Given the widely recognised limitations of using data based solely on spontaneous adverse event reporting to compare product safety profiles, Pharmacosmos also considered that Vifor should not use such data without additional necessary data and context, in any of its materials or activities. Pharmacosmos was also extremely concerned about the understanding of Vifor, in particular its medical, marketing and compliance teams, about the scientific validity of data and Code requirements for making comparative claims.

RESPONSE

Vifor submitted that it remained committed to the UK self-regulatory scheme for the appropriate promotion of medicines but was disappointed to again note that the PMCPA and its processes had been manipulated by Pharmacosmos. Vifor submitted that it saw a clear pattern of repeated complaints regarding the same alleged facts designed to cause maximum commercial disruption to Vifor's legitimate business activities. Vifor stated that there were four main issues where it and the Authority seemed to have differing interpretations in this case as follows:

1 <u>The relevance of Section 28.04(d) of the new EFPIA Code to this case</u>

Vifor noted that the PMCPA correctly stated that the above Section of the EFPIA Code was not yet in operation. However, the EFPIA Code also provided that: '… Member Associations must, at a minimum, adopt in their National Codes provisions no less rigorous than the provisions contained in the EFPIA Code ...'. Unfortunately, Section 28.04d did not oblige member associations, such as the ABPI, to adopt a right to dismiss complaints that were commercially motivated, but simply provided the option to do so. However, equally, member associations must comply with 'the spirit, as well as the provisions of the EFPIA Code'. The PMCPA seemed to have taken an approach that was far removed from the spirit of the EFPIA Code.

Vifor stated that it was difficult to understand why the PMCPA considered itself unable to apply the same approach as EFPIA. Indeed, the PMCPA statement that 'the Code is an important means of building and maintaining confidence in the pharmaceutical industry' appeared disingenuous. Allowing a pharmaceutical company to pursue vexatious claims did not maintain confidence in the industry. Indeed, if anything, it furthered distrust by the industry itself in the viability of the self-regulatory regime and encouraged companies to withdraw from it.

It was a well-established judicial principle that the courts had the power to strike out a case that they considered constituted abuse of process, including where a claimant pursued litigation with the intention to cause the defendant distress. Therefore, Vifor queried why the PMCPA, as a quasi-judicial body, found itself unable to apply the same standard.

In Vifor's view, the PMCPA should abide by the spirit of the EFPIA Code and dismiss this case out of hand as a clear example of a purely commercially motivated case.

2 The similarities between this case and Case AUTH/3199/5/19

Concerning the similar nature of the two complaints, Vifor noted that the case preparation manager had stated that '… The material in question is the same, but the allegations are different …' which seemed counter-intuitive to Paragraph 5.1 of the Constitution and Procedure, which gave the case preparation manager the authority to 'amalgamate a complaint with an ongoing complaint or complaints where two or more complaints are based on essentially the same evidence'. This was clearly the case here. Joining the complaints would streamline the workload for all involved. Additionally, allowing two similar complaints to run in parallel was likely to undermine procedural fairness because Vifor would have to bear the burden of defending both complaints in parallel, which required a significant investment of time and resources, which was not conducive to the self-regulatory process. Moreover, there was a high risk that the Panel would adjudicate one complaint before the other. In doing so, the first ruling would inevitability taint the outcome of the second and raise questions about *res judicata* and double-jeopardy.

Again, the Constitution and Procedure reflected established principles which were also found in civil litigation. The White Book, a commentary on the Civil Procedure Rules, noted that abuse of the court's process also applied to vexatious proceedings: 'It is an abuse to bring vexatious proceedings, i.e. two or more sets of proceedings in respect of the same subject matter which amount to harassment of the defendant in order to make them fight the same battle more than once with the attendant multiplication of costs, time and stress. In this context it is immaterial whether the proceedings are brought concurrently or serially'.

Vifor considered that both cases should be dismissed as *prima facie* unfounded, but if the PMCPA, nevertheless, decided to proceed then the two should be amalgamated.

3 Background to the generation of the medical information request

Vifor stated it was extremely concerned about the manner in which the medical information request was generated and considered the PMCPA should also be concerned.

It was clear by even a cursory examination of the correspondence between the Vifor representative, the nurse in question and Pharmacosmos that Pharmacosmos had tried to entrap Vifor. The nurse's original request for medical information at the meeting with the Vifor representative related to cyanotonic heart disease. The Vifor representative simply responded by asking the nurse to email the request so that he/she could forward it to medical information. This was a wholly appropriate response from the Vifor representative. Yet, for reasons unknown, the nurse then submitted a different, unrelated and somewhat vague request for medical information which suggested that Vifor's representative had made a number of statements on slides. Vifor was confident that its representatives could not possibly have made such claims based on the slides used by its representatives.

It seemed reasonably clear to Vifor that the nurse had passed his/her correspondence with Vifor on to Pharmacosmos which suggested that Pharmacosmos was involved or had instigated the nurse's second request. Pharmacosmos then used that information to submit multiple identical complaints in order to disrupt Vifor's business. [post meeting note: Following the completion of this case Pharmacosmos stated that the nurse informed it of his/her interaction with Vifor autonomously].

Vifor noted that health professionals had a right to submit requests for medical information and the company valued the contribution the medical information system made to the practice of medicine. Vifor was fully committed to its legal obligations to provide medical information in response to genuine requests, however it was concerned about a competitor's apparent attempt to manipulate a health professional and the medical information regime in order to generate a complaint, claiming the activity was promotional in nature.

Vifor submitted that the statement by Pharmacosmos that the medical information department was happy to provide what was requested by the representative showed that the company accepted that this claim had been used within a promotional call and suggested that this was a promotional claim which was regularly used company-wide' was not only false, but also constituted a massive leap in assumption:

- The medical information request was not made by the representative, it was made by the nurse. The nurse's request referred to an alleged statement by the representative and material he/she allegedly relied on. As explained above, Vifor was confident that its representative could not have made the alleged statement and the alleged materials simply did not exist.

- The medical information team did its best to provide an answer that discharged its obligation to respond and it provided the information that it understood the nurse had requested. This position was clearly stated at the beginning of the response.

- The assertion that this meant that '… this claim had been used within a promotional call, suggesting that this was a promotional claim used company-wide on a regular basis' was not only entirely incorrect and unsubstantiated, it was absurd to imply that one isolated, manufactured situation could possibly indicate a regular company-wide practice.

Vifor urged the PMCPA not to allow such complaints to succeed. If such practices were permitted, there was a risk that health professionals would struggle to obtain the information they needed in their practice, as pharmaceutical companies would feel unable to respond to requests meaningfully.

Vifor alleged that Pharmacosmos employees were offered a cash bonus (details were provided) bonus if they could create a complaint against Vifor This was clearly the situation with this case and as such it should be dismissed out of hand as a clear message that such behaviour would not be tolerated. [post meeting note: Following the completion of this case Pharmacosmos stated that it did not offer any such cash bonus]. As set out above, there were established principles in civil litigation, which allowed courts to dismiss claims, which were vexatious or brought for an improper purpose. This

was also clearly reflected in the EFPIA Code. Consequently, Vifor considered that the PMCPA, as a *quasi*-judicial body, could justifiably reject the claims as *prima facie* unfounded on such grounds.

4 The actual content of the Vifor response to the medical information request

With respect to the specific allegations of breaches of the Code, Vifor noted that Clause 1.2 of the Code made it clear that 'promotion' did not include: 'replies made in response to individual enquiries from members of the health professions or other relevant decision makers or in response to specific communications from them whether or enquiry or comment, including letters published in professional journals, but only if they solely relate to the subject matter of the letter or enquiry, are accurate and do not mislead and are not promotional in nature'.

Vifor maintained that it had responded to a genuine request from the nurse for information about reports from regulatory authorities. The information provided was limited to reports of regulatory authorities, it was thus directly responsive to the request and it was given in a non-promotional manner. Against this, Vifor queried how any of the alleged violations could possibly succeed, given that the information provided was obviously non-promotional.

Alleged misleading comparison

The original request by the nurse read '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'.

As explained above, Vifor noted that it was obliged to respond to individual enquiries or specific communications from health professionals, provided that the response related solely to the subject matter of the letter or inquiry, was accurate, did not mislead and was 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 medical information response in this case and that the manner in which it responded was entirely appropriate and complied with the Code. Indeed, Clause 1.2 made clear that any such responses to requests for information did not fall within the scope of 'promotion'.

The request from the nurse was ambiguous. Vifor did not have a slide claiming 'reduced ADRs when using ferrinject vs. Monofer', nor did Vifor suggest that regulators or WHO had demonstrated that there were less 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 ...'. This rather ambiguous request was therefore interpreted by medical information as a request for references for that approved statement. This interpretation was clearly stated in the first four lines of the response and there had been no communication from the nurse that this interpretation was incorrect.

Vifor stated that its medical information team never stated or inferred, as alleged by Pharmacosmos, differences regarding hypersensitivity reactions. As stated above, the information provided consisted of all of the information currently available from the only four

country regulatory authorities which had reported upon 'the adverse drug reaction profiles of the available intravenous irons'. The nurse requested regulatory authority stances on the safety of intravenous irons. The information sent provided only this and did so in a non-selective, factual, balanced, non-promotional way, including all the available regulatory authority reports.

Vifor noted that Clause 7.3 only applied to 'promotional material'. However, Clause 1.2 made clear that responses to requests for information did not fall within the scope of 'promotion'. Indeed, Vifor's medical information team provided reports from regulatory authorities. Such reports could simply not, by their very nature, be promotional. Therefore, Clause 7.3 did not apply.

Moreover, Vifor noted that Pharmacosmos maintained that Vifor inaccurately provided only information on hypersensitivity reactions, which was not the point. The point was that these were the only country regulatory authority reports on intravenous irons, that they reported in part on hypersensitivity reactions was secondary; in responding to the nurse's request it would have been impossible for Vifor to have provided any other reports.

Vifor submitted that it had not breached Clause 7.3.

Alleged inaccurate promotional claim

Vifor noted that Pharmacosmos objected to the statement 'European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons' in promotional materials.

It was important to distinguish this alleged breach from the allegations relating to the response to the nurse's medical information request. As explained above, the nurse's request was ambiguous and referred to an alleged claim that was not included in any of Vifor's materials and that the company was confident that none of its representatives would have made. Vifor's medical information team clearly set out its understanding of the request in the response to the nurse who had not replied to indicate that Vifor's interpretation was incorrect.

In any event, the claim was clearly substantiated by the available reports from the only four country regulatory authorities which had reported upon 'the adverse drug reaction profiles of the available intravenous irons', all of which found differences in intravenous iron profiles. The statement was accurate, balanced, fair, objective and unambiguous, since it simply summarized the conclusions of those four regulatory authorities, ie, that they had identified 'differences in the adverse drug reaction profiles'. Vifor had not altered or otherwise exaggerated the findings.

Vifor noted that Pharmacosmos again maintained that Vifor inaccurately provided only information on hypersensitivity reactions, which was not the point. The point was that these were the only country regulatory authority reports on intravenous irons, that they reported in part on hypersensitivity reactions was secondary; in responding to the nurse's request it would have been impossible for Vifor to have provided any other reports other than those provided.

Vifor denied a breach of Clause 7.2.

Supporting information provided to the nurse's request regarding the comparative statement alleged to be misleading and inaccurate

Pharmacosmos alleged that the 'the medical information letter was not an unsolicited email and so was subject to Code requirements'. This was simply not true. The nurse (clearly at Pharmacosmos' instigation) made a direct request to Vifor for information, Vifor did not initiate any contact with the nurse or solicit any request; the response was therefore unsolicited, accurate and not misleading and also non-promotional, ie, fully in accordance with Clause 1.2. The supporting information provided exactly answered the nurse's specific question. Vifor's medical information team provided all of the available information in the form of all of the four available individual European regulatory authority reports relevant to the request, covering all products. Vifor disagreed with Pharmacosmos' view that Vifor should have included additional sources in response to the request. If Vifor had done so, the medical information response would have gone beyond the scope of the request and would not 'solely relate to the subject matter of the letter or enquiry' in accordance with Clause 1.2 of the Code. Moreover, the sources Pharmacosmos referred to were unpublished, non-peer reviewed abstracts. Vifor did not consider such sources adequate scientific publications. Consequently, Vifor maintained that its response did not breach Clause 7.2.

Given that the four regulatory authority reports were the only available information which addressed the nurse's concern, it was unclear how they could have disparaged Pharmacosmos' products. The findings of regulatory authorities spoke for themselves and could not be attributed to Vifor. Consequently, Vifor denied a breach of Clause 8.1.

Vifor submitted that it had always maintained high standards, including when providing the response to the nurse's request for information, in accordance with Clause 9.1 by fully complying with the Code.

Finally, Vifor noted that Pharmacosmos had alleged that Vifor failed to maintain high standards but at the same time it refused to accept the jurisdiction of the PMCPA. Moreover, Pharmacosmos relied on a Swedish NBL ruling, which, in itself, was misleading for a number of reasons; the facts in the Swedish case were very different. This case would be heard by the PMCPA, thus the Swedish case had no relevance. This appeared to be a clear attempt by Pharmacosmos to disparage Vifor by portraying it as a company, which did not abide by the self-regulatory regime, even in other markets. Vifor firmly denied any such suggestions.

The medical information letter was alleged to be disparaging and not based upon an up-to-date evaluation of all the evidence as key data was excluded

Vifor stated that the medical information response contained solely the information requested by the nurse on all of the available individual European regulatory authority reports. As required by the Code, the response could only contain the requested information. Pharmacosmos' alleged breach of Clauses 7.2 could not be justified. As explained above, it would have been totally inappropriate for Vifor to have provided additional data from other sources such as the as yet unpublished, non-peer reviewed abstracts referred to by Pharmacosmos; such additional information would have gone beyond the scope of the request. Moreover, given the very limited scientific value of the sources cited and their lack of any relevance to the specific request, they would have been an inappropriate addition to the data provided.

Vifor stated that Pharmacosmos' position that Vifor inaccurately provided only selected information on hypersensitivity reactions was not the point. The point was that these were the only country regulatory authority reports on intravenous irons, that they reported in part on hypersensitivity reactions was secondary; in responding to the nurse's request it would have

been impossible for Vifor to have provided any other reports. Vifor denied a breach of Clause 7.2.

Vifor stated that it did not disparage Monofer. As explained above, the nurse's request for information was ambiguous. Vifor's medical information team interpreted the request by reference to an approved promotional claim. The nurse had not informed Vifor that such an interpretation was incorrect, or that the information provided was not responsive to the request. In order to substantiate its promotional claim, Vifor relied on the four regulatory authority reports which it had provided to the nurse. The findings in those reports were the findings of the relevant authorities. Vifor not made any statements in respect of how these findings had to be interpreted. Consequently, Vifor denied a breach of Clause 8.1.

Undermining trust in the industry

Vifor stated that its medical information team acted according to the requirements of the Code and under the guidance of the Pharmaceutical Information and Pharmacovigilance Association (PIPA), which made absolutely clear that in the case of a medical information request, the information provided must solely relate to the specific question asked by the health professional. The nurse's request was ambiguous and referred to alleged claims and materials which simply did not exist. Consequently, the medical information team interpreted the request as a reference to an existing approved claim and provided the relevant source material, which Vifor relied on to substantiate that claim. The nurse never indicated to Vifor that this interpretation was inaccurate, or that the medical information provided was not responsive to the request. The response was non-promotional and complied with the Code. Consequently, Vifor denied a breach of Clause 2.

Vifor stated that the spurious mention by Pharmacosmos of previous cases was not relevant to this case and constituted merely a perfidious attempt to disparage Vifor in any way possible. Vifor was confident that the PMCPA would see through such attempts and would judge this case on its individual merits.

Risk to patient safety

As no specific breaches were alleged under this point, Vifor could only note that it considered its response to the nurse's medical information request was appropriate to the specific question asked and, as such, could not constitute a risk to patient safety.

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 advisor 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.

With regard to Case AUTH/3199/2/19, 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 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.

Turning to Case AUTH/3224/7/19 and for the reasons noted above Vifor acknowledged a potential breach of:

- Clauses 7.2 and 7.3 in relation to the objection handler
- Clauses 7.2 and 8.1 in relation to the medical information email and
- Clauses 9.1 and 2 overall.

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 submitted that it was a serious matter and noted that it had engaged experienced interim 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.

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 and in that regard Vifor reiterated that the objection handler was commercially sensitive and 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, health 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 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 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 was ambiguous and referred to alleged claims and materials which simply did not exist. In the Panel's view, the medical information team had wrongly interpreted the request as a reference to an alternative existing approved claim. The response from medical information stated '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 iv 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 AEMPSissued a warning recently to not start new patients with Monofer (iron isomaltoside) 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 thus 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 that Pharmacosmos had alleged that the claim '... European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons ...' was misleading and inaccurate in breach of Clauses 7.2 and 7.3. The Panel noted that the only material before it which included the claim at issue was the medical information letter which began 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"'. The Panel noted Vifor's submission that the claim was an approved promotional claim and that the references provided by Vifor medical information in support of the claim all focussed on hypersensitivity reactions. The Panel noted that although individual health authorities in Europe had reported differences between the available IV irons, the current European-wide stance of the EMA was that current data did not allow any differentiation between IV iron preparations in terms of hypersensitivity reactions. In the Panel's view, the claim was therefore misleading and inaccurate and a breach of Clauses 7.2 and 7.3 were ruled.

The Panel further noted Pharmacosmos' allegation that the exclusion of key data, including comparative safety randomised control trial data between Monofer and Ferinject which demonstrated broad comparability in terms of hypersensitivity reactions, with any slight differences in favour of Monofer, in the information sent to the nurse was a deliberate attempt by Vifor to selectively favour Ferinject and disparage Monofer. The Panel noted, however, that the medical information letter set out, albeit apparently wrongly given the nurse's specific questions,

to provide references for the statement 'European health authorities have reported differences in the adverse drug reaction profiles of the available intravenous irons'. The Panel noted its rulings above and comments that the statement was misleading and inaccurate and disparaged Monofer. On that basis, the claim could not be made any more acceptable by the provision of data which was not from European health authorities and so the Panel considered that on this exceptional and very narrow ground there was no breach of Clauses 7.2 and 8.1 with regard to the failure to include additional references as cited by Pharmacosmos.

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. 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 the representatives, and the relevant briefing document. 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 a health professional 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 50mg/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 reaction 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, 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 show that Vifor's original response was incorrect.

The Panel noted its comments above and considered overall that the claims in the objection handler used by the representative at the meeting in question were misleading; some of the data was not sufficiently complete to allow readers to form their own opinion of the therapeutic value of Ferinject vs Monofer. The objection handler did not reflect the fact that, in a review of data, the EMA had been unable to clearly differentiate between IV irons in terms of hypersensitivity reactions. The objection handler also did not reflect the fact that the SPCs for Monofer and Ferinject were almost identical in terms of hypersensitivity reactions; both SPCs listed anaphylactoid/anaphylactic reactions as rare (≥ 1/10 000 to <1/1000). The Monofer SPC listed hypersensitivity including severe reactions as uncommon (≥ 1/1000 to <1/100) and the Ferinject SPC stated that hypersensitivity was uncommon. The Panel therefore ruled a breach of Clauses 7.2 and 7.3. Overall, the Panel considered that the objection handler disparaged Monofer. A breach of Clause 8.1 was ruled.

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 which was subject to the requirements of the Code. The Panel noted its comments above and considered that the medical information letter was misleading and disparaged Monofer. Breaches of Clauses 7.2 and 8.1 were ruled.

The Panel noted its comments and ruling above and considered that Vifor had failed to maintain high standards. A breach of Clause 9.1 was ruled.

The Panel noted its comments above and was particularly concerned that the medical information letter was misleading and disparaging. In that regard the Panel noted Pharmacosmos' comment that reducing a health professional's confidence in Monofer might increase a patient's anxiety and lead to an infusion reaction. It was thus absolutely imperative that communications from medical information were accurate, fair and balanced. In the Panel's view, the medical information letter at issue was poor and, in that regard, it reduced confidence in the pharmaceutical industry. 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 it now acknowledged potential breaches of the Code including Clause 2; 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 submission that it was committed to self-regulation. 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 at the report hearing 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 staff to start by early July. [Post meeting note following completion of this case Vifor stated that the recruitment of one member of staff had not been completed.] 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 7.2, 7.3, 8.1, 9.1 and 2 of the Code in Case AUTH/3224/7/19, including its decision to report Vifor to the Appeal Board. The material at issue was the same as that in Case AUTH/3199/5/19. The allegations were different in that Case AUTH/3224/7/19 dealt with the claims whereas Case AUTH/3199/5/19 dealt with the breach of undertaking. 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 responses from Vifor (dated 29 July 2019 and 19 September 2019) in addition to the response to Case AUTH/3199/5/19 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 AUTH/3224/7/19 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 responses to Case AUTH/3224/7/19 dated 29 July and 19 September. Vifor stated that it became apparent that its response to Case AUTH/3199/5/19 dated 3 June 2019 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 in Case AUTH/3199/5/19 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 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 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 breaches of the Code.

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/3199/5/19. 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	**14 July 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**