CASE AUTH/3159/2/19

PHARMACOSMOS v VIFOR

Promotion of Ferinject

Pharmacosmos UK Ltd complained that medical department personnel from Vifor Pharma UK Limited had proactively contacted health professionals to discuss information about Ferinject (ferric carboxymaltose) which was misleading with regard to the Pharmacosmos product, Monofer (iron isomaltoside 1000). Ferinject and Monofer were both indicated for the treatment of iron deficiency when oral iron preparations were ineffective or could not be used.

Pharmacosmos stated that in December 2018 it was contacted by several UK health professionals who were concerned about the way in which safety data about Monofer, from Ehlken *et al* (2018) had been proactively brought to their attention and discussed by Vifor including members of the Vifor medical team. Ehlken *et al* evaluated the rates of severe hypersensitivity reactions reported with Ferinject and Monofer in Europe based on data from Eudrovigilance and VigiBase between 2014 and 2017. The study was funded by Vifor.

Pharmacosmos was concerned that this might have occurred in relation to promotional activity by Vifor and opened inter-company dialogue in December 2018 to discuss concerns over the validity, accuracy and quality of the publication being used in this way and to ask for further clarification on the use of Ehlken *et al*. In its response, Vifor stated that it had not proactively disseminated Ehlken *et al,* it was not using the paper for promotional activities and its medical teams had not solicited requests for it.

Subsequent to the inter-company exchange, Pharmacosmos received a written statement from a health professional regarding the same article, where he/she had been contacted by Vifor Pharma headquarters, and that the data had been discussed by Vifor Pharma, including by a member of the Vifor medical team. Pharmacosmos submitted that it had received similar verbal reports from other UK health professionals, which also indicated that the article was sent to them by a weblink in an email, without this having been requested by the health professionals.

The health professional in question was a consultant working at an NHS hospital. He/she was emailed by Vifor in the middle of December. The contact was initiated through Vifor Headquarters and was unsolicited. Vifor asked for a telephone meeting to discuss a potential study between Ferinject and Monofer. The health professional understood this was an invitation to participate in a potential future study and accepted the invitation. The Vifor employees that telephoned were not known to the health professional although at least one was believed to be from the medical department. The health professional was surprised to discover that the call was to inform him/her of the results from Ehlken *et al*. The content of the call described data focussing on a difference between Monofer and Ferinject with regards to hypersensitivity risk. No evidence from other studies was

presented. The health professional did not receive an honorarium and no contract was created (so this was not a consultancy arrangement to seek advice on the paper).

Pharmacosmos contended that, based on the evidence provided by the statements, the information provided by Vifor in this case was solicited through proactive contact with health professionals and the topic of discussions was decided upon by Vifor, not in response to any enquiry by the health professionals. The activity was thus promotional.

Pharmacosmos was further concerned about the accuracy of the information provided to health professionals; it did not consider that the information provided was balanced. The article viewed in isolation was fundamentally misleading. Pharmacosmos therefore considered that the matter fell within the scope of the Code.

Given that Vifor had again provided misleading information, unsolicited, to health professionals, that could cast doubt on the safety of Monofer through misleading comparison with Ferinject, it appeared that the same pattern of behaviour had continued despite rulings in two previous cases, Case AUTH/2828/3/16 and Case AUTH/2830/4/16.

Pharmacosmos thus alleged that Vifor had not maintained high standards.

Pharmacosmos alleged that Ehlken *et al* provided and discussed with the health professionals, contained inappropriate and misleading content.

The study design could not be legitimately used to compare the safety of two products.

The article was not based on an up-to-date evaluation of all the evidence and did not reflect that evidence clearly, and the wider context of the data was not provided in the meetings.

Pharmacosmos alleged that as the article and associated activities could not take the benefit of the exemption from the definition of promotion, they could only be regarded as promotional. The data discussion was led by a member of the medical team and in the context of the delivery in this case, the activity's promotional nature was disguised. This was highlighted by the health professional's statement above that the impression given to him/her was that he/she was being asked to discuss potential future studies.

Pharmacosmos stated that Vifor's letter in response to inter-company dialogue made it clear that Ehlken *et al*, and associated activities, had not been certified for promotional use. As the health professional statements made clear that this paper was used in a promotional manner, this indicated that Vifor had failed to adhere to Code requirements for certifying promotional materials.

Given the nature of Vifor's reported activity, the concern that it had raised amongst health professionals, and that Vifor had continued a pattern of behaviour that resulted in multiple clause breaches in two previous cases, Pharmacosmos alleged that the company's conduct had brought the industry into disrepute, in breach of Clause 2.

The detailed response from Vifor is given below.

The Panel noted that there were differences between and within the parties' accounts; it was extremely difficult in such cases to know exactly what had transpired. The

complainant bore the burden of proof on the balance of probabilities. A judgement had to be made based on the evidence provided by both parties.

The Panel noted that Pharmacosmos provided an unsigned statement which appeared to have been written based on information from a health professional it referred to as HCP1 (health professional 1). Pharmacosmos did not disclose health professional 1's identity. Vifor identified health professional 1 as there were only two people with whom the Vifor Chief Medical Officer (CMO) discussed his paper. Vifor provided a signed statement from a named Professor referred to as health professional 2.

The Panel noted that the complaint concerned the use of the article by Ehlken *et al* (2018) which evaluated the rates of severe hypersensitivity reactions reported with Ferinject and Monofer in Europe based on data from EudraVigilance and VigiBase between 2014 and 2017 and was funded by Vifor.

Pharmacosmos alleged that Ehlken *et al*, which in its view contained inappropriate and misleading content, was being proactively provided to or brought to the intention of several health professionals and was being discussed with them by Vifor.

The Panel noted Vifor's submission that it had not used Ehlken *et al* promotionally and had not briefed medical teams either locally or globally to disseminate the publication to any health professionals in the UK. Vifor submitted that its CMO, one of the co-authors of Ehlken *et al,* contacted three but only spoke to two professors to explain the rationale, results and limitations of the study and answer any questions.

The Panel considered that Pharmacosmos had, on the balance of probabilities, established that the paper in question had been discussed with at least one health professional. Vifor accepted that it had discussed the paper with two health professionals. The first matter to be determined by the Panel was whether the interaction was promotional or non-promotional. The second matter to be determined was whether, on the balance of probabilities, Pharmacosmos had established what was said about the paper in question and if so whether what was said was in breach of the Code.

The Panel noted Vifor's submission about the importance of peer-to-peer interactions. In the Panel's view, peer-to-peer interactions between senior company medical employees and senior health professionals were not unacceptable so long as they complied with the Code. Whether such interactions were promotional or non-promotional would depend on a consideration of all the circumstances whilst noting the broad definition of promotion in Clause 1.2. Relevant circumstances would include whether the discussion was an integral and relevant part of an ongoing consultancy. In the Panel's view, Vifor had submitted conflicting accounts about whether there was a current consultancy at the time of the interaction. It appeared that, according to Vifor, both health professionals were currently consultants in the context of NICE HTA procedures; there was no evidence before the Panel that the paper in question was relevant or integral to that consultancy. The Panel noted that the employee's statement referred to seeking the health professionals' scientific advice. The Panel noted Vifor's submission that the advisory nature of the relationship in relation to the discussions as described by Vifor were not formalised in any consultancy agreement. Given these points the Panel did not consider, on the evidence before it, that the arrangements could be described as an advisory board or similar bearing in mind the requirements of Clause 23.

The Panel noted Vifor's submission that neither health professional considered the interaction promotional. The Panel noted the broad definition of the term 'promotion' at Clause 1.2 of the Code which, in the Panel's view, was likely to be different to a lay person's use of that term. A discussion of clinical matters, depending on the circumstances, might fall within the broad definition of promotion in the Code.

Given its comments above, the Panel queried how the proactive discussion of the paper which directly compared two products and appeared to be in favour of Vifor's product could be anything other than promotional.

The Panel further noted Vifor's submission that health professional 1 was confused about the initial purpose of the call. Vifor refused to provide details about what the confusion was despite a number of requests nor did the Panel have before it emails etc about the arrangements for the call. Nonetheless, Vifor's submission about initial confusion was consistent with the evidence from Pharmacosmos that health professional 1 had agreed to be contacted on the assumption that the telephone call was arranged to discuss a potential future study and was surprised that the call was to inform him/her about the results from the recent publication, Ehlken *et al*. In the Panel's view, in relation to health professional 1, the promotional nature of the call was, on balance, disguised. A breach of the Code was ruled.

In relation to health professional 2, according to his/her statement, he/she understood that the reason for the call was to discuss the study and referred to both giving advice and the importance of him/her being aware of such data; that such discussions were an important aspect of clinical work; the importance of listening to multiple opinions and the evidence on which they were based to make the best decisions for patients. In the Panel's view it appeared that health professional 2 was clear that the call in question would involve a discussion of the paper and in that regard the promotional nature of the call was not disguised. No breach of the Code was ruled.

The Panel noted Vifor's submission that the article and activities had not been certified for promotional use. The Panel noted Vifor's submission that it did not provide the two health professionals with a copy of the paper, inform them where they could find it or circulate any emails containing links to the paper. It was unclear to the Panel what exactly was discussed during the conversations between Vifor and the two health professionals. Whilst the Panel had some concerns, it considered that Pharmacosmos had not provided evidence that Ehlken *et al* had been sent unsolicited to any health professional and therefore that it required certification for such use. The Panel, however, further noted Vifor's submission that there was no brief to the employee, since he would be discussing his own research. In the Panel's view, in the absence of briefing material Ehlken *et al* was the basis of the discussion and therefore should have been certified for such use. The Panel therefore ruled a breach of the Code.

The Panel noted that in Ehlken *et al* information on spontaneously reported severe hypersensitivity reactions was obtained from and analysed separately for two established safety surveillance databases between 2014 and 2017. The Panel noted Pharmacosmos' submission that the EMA had previously stated that '… 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'.

According to Ehlken *et al* findings suggest that iron (III) isomaltoside 1000 was associated with higher reporting rates of severe hypersensitivity reactions related to estimated exposure than ferric carboxymaltose in European countries.

The Panel noted that Ehlken *et al* concluded that further research investigating the occurrence of severe hypersensitivity reactions associated with iv ferric carboxymaltose and iron (III) isomaltoside 1000 was needed to broaden the evidence for benefit-risk assessment. The Panel noted that Pharmacosmos' specific concerns included that Ferinject entered most markets 3-5 years earlier than Monofer and it was well-known that spontaneous suspected adverse event reporting rates tended to decrease over time and so it was fundamentally biased and misleading to compare the frequencies during the limited time period from 2014 – 2017. In addition, Pharmacosmos noted that several countries where Monofer was not available had been included in Ehlken *et al* and rather than this leading to over-representation of adverse events for Ferinject, inclusion of selected markets where Ferinject had been long-established and known to have lower than average reporting rates, could lead to artificial lowering of the reported hypersensitivity rates with Ferinject.

The Panel noted that Ehlken *et al* acknowledged both of these points as limitations including that the reporting of adverse events might be higher directly after launch compared to when products were well-established on the market but stated that in order to overcome the limitation, the 4-year period from 2014-2017 was chosen as both products had already been on the European market for several years. Ehlken *et al* noted that for the majority of countries both products were available. Whilst an impact of differential marketing on the level of the reporting rate could not be ruled out, it was considered to be minor. The Panel noted each companies' submission about Ehlken *et al*. Whilst noting the conclusions of Ehlken *et al* and the limitations discussed by the study authors, the Panel had very little detail before it about precisely what was said about the study during the conversations with the two health professionals. The statement from health professional 2 did not detail what exactly was said about Ehlken *et al* during the call. The unsigned statement of health professional 1 provided by Pharmacosmos stated that the content of the call described data focussing on a difference between iron isomaltoside and ferric carboxymaltose with regards to hypersensitivity risk. The Panel did not consider that Pharmacosmos had proved, on the balance of probabilities, what was said about Ehlken *et al* during the conversations with the two health professionals and whether such statements were misleading; no breach was ruled.

The Panel did not consider that Pharmacosmos had established, on the balance of probabilities, that the discussions about Ehlken *et al* were misleading because they were not based on an up to date evaluation of all of the evidence as alleged. The Panel therefore ruled no breach of the Code in this regard.

The Panel noted its rulings above and did not consider that, based on the narrow allegation, Pharmacosmos had established that Vifor had failed to maintain high standards in relation to the discussion of misleading information with regard to Ehlken *et al* as alleged and ruled no breach of the Code.

The Panel noted Pharmacosmos' reference to the rulings in Cases AUTH/2828/3/16 and AUTH/2830/4/16 and its allegation that Vifor was failing to maintain high standards by once again providing misleading information to health professionals that could cast doubt on the safety of Monofer. The Panel noted its comments and rulings above and considered that based on the narrow allegation there was no evidence that Vifor had failed to maintain high standards and no breach was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use and ruled accordingly.

Pharmacosmos UK Ltd complained that medical department personnel from Vifor Pharma UK Limited had proactively contacted health professionals to discuss information about Ferinject (ferric carboxymaltose) which was misleading with regard to the Pharmacosmos product, Monofer (iron isomaltoside 1000). Ferinject and Monofer were both indicated for the treatment of iron deficiency when oral iron preparations were ineffective or could not be used.

COMPLAINT

Pharmacosmos stated that in December 2018 it was contacted by several UK health professionals who were concerned about the way in which safety data about Monofer, from Ehlken *et al* (2018) had been proactively brought to their attention and discussed by Vifor including members of the Vifor medical team. Ehlken *et al* evaluated the rates of severe hypersensitivity reactions reported with Ferinject and Monofer in Europe based on data from Eudrovigilance and VigiBase between 2014 and 2017. The study was funded by Vifor.

Pharmacosmos was concerned that this might have occurred in relation to promotional activity by Vifor and opened inter-company dialogue on 27 December 2018 to discuss concerns over the validity, accuracy and quality of the publication being used in this way and to ask for further clarification on the use of Ehlken *et al*. In its response, Vifor stated that it had not proactively disseminated Ehlken *et al,* it was not using the paper for promotional activities and its medical teams had not solicited requests for it. Thus, the article and activities did not appear to have been certified for promotional use.

Subsequent to the inter-company exchange, Pharmacosmos received a written statement from a health professional regarding the same article, where he/she had been contacted by Vifor Pharma headquarters, and that the data had been discussed by Vifor Pharma, including by a member of the Vifor medical team. The health professional did not want to be identified to Vifor and so the statement was initially presented anonymously. However, the health professional was willing to be contacted directly by the PMCPA, so long as his/her identity remained protected. Pharmacosmos submitted that it had received similar verbal reports from other UK health professionals, which also indicated that the article was sent to them by a weblink in an email, without this having been requested by the health professionals. However, they wished to be completely anonymous to Vifor and had not made a written statement.

Health professional statement

The health professional in question was a consultant working at an NHS hospital. He/she was emailed by Vifor in the middle of December. The contact was initiated through Vifor Headquarters and was unsolicited. Vifor asked for a telephone meeting to discuss a potential study between Ferinject and Monofer. The health professional understood this was an invitation

to participate in a potential future study and accepted the invitation. The Vifor employees that telephoned were not known to the health professional although at least one was believed to be from the medical department. The health professional was surprised to discover that the call was to inform him/her of the results from Ehlken *et al*. The content of the call described data focussing on a difference between Monofer and Ferinject with regards to hypersensitivity risk. No evidence from other studies was presented. The health professional did not receive an honorarium and no contract was created (so this was not a consultancy arrangement to seek advice on the paper).

Pharmacosmos submitted that to take benefit of the exemption from the definition of promotion set out in the Code, information supplied by companies to health professionals must be in response to unsolicited enquires, specific to the enquiry, and must be accurate, not promotional in nature and not misleading.

Pharmacosmos contended that, based on the evidence provided by the statements, the information provided by Vifor in this case was solicited through proactive contact with health professionals and the topic of discussions was decided upon by Vifor, not in response to any enquiry by the health professionals. The activity was thus promotional.

Pharmacosmos was concerned that Vifor did not appreciate the difference between promotional and non-promotional activities and materials, despite a previous audit of its compliance procedures following Case AUTH/2411/6/11, in which the Appeal Board stated that Vifor's actions demonstrated a fundamental lack of understanding of the Code and its requirements. Pharmacosmos was further concerned about the accuracy of the information provided to health professionals; it did not consider that the information provided was balanced. The article viewed in isolation was fundamentally misleading. Pharmacosmos therefore considered that the matter fell within the scope of the Code.

Pharmacosmos noted that in Case AUTH/2828/3/16, Vifor's medical department provided inaccurate, misleading, unfair and unbalanced safety information about Monofer that was subsequently deemed to be a promotional communication as there had not been an unsolicited request for the information. The Panel also found that, on the balance of probabilities, Vifor employees specifically targeted Monofer sales and spread doubt about the safety of Monofer. The Appeal Board considered that the briefing material and the company's use of particular data (the document sent by Vifor's medical information department), were consistent with the allegation of scaremongering. Given the content and tone of briefing material, the Appeal Board considered that, on the balance of probabilities, Vifor employees had caused health professionals to doubt the safety of Monofer and had thereby offered misleading comparisons with Ferinject. Vifor was in breach of a number of clauses of the Code and the Appeal Board, noting the whole of its rulings, upheld a breach of Clause 9.1.

Similarly, in related Case AUTH/2830/4/16, the proactive provision of misleading and disparaging safety information about Monofer to health professionals, including by the Vifor medical team, led the Panel to consider there was no doubt that Vifor had specifically targeted Monofer sales and that, on the balance of probabilities, Vifor employees had provided misleading information about the safety of Monofer and had disparaged Monofer. This was supported by the Appeal Board which also considered that, on the balance of probabilities, it was likely that Vifor representatives had disparaged Monofer and provided misleading information about the safety of Monofer, and the Appeal Board upheld the Code breaches.

Given that Vifor had again provided misleading information, unsolicited, to health professionals, that could cast doubt on the safety of Monofer through misleading comparison with Ferinject, it appeared that the same pattern of behaviour had continued despite the rulings from the two cases above.

Pharmacosmos thus alleged that Vifor had not maintained high standards in breach of Clause 9.1.

Pharmacosmos stated that articles, materials and information used or provided by pharmaceutical companies must be accurate, balanced, fair, objective and unambiguous and based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis.

Pharmacosmos alleged that Ehlken *et al* provided and discussed with the health professionals, contained inappropriate and misleading content as detailed below.

a) The study design could not be legitimately used to compare the safety of two products:

i) Invalidity of using data from spontaneous suspected adverse reaction reports alone:

The article provided an analysis of spontaneously reported pharmacovigilance data and compared reported rates of severe hypersensitivity reactions for Ferinject and Monofer. However, according to the European Medicines Agency (EMA), studies like this were invalid and misleading. The EMA recently 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'.

ii) Incorrect and biased selection of data for inclusion:

Pharmacosmos noted that Ferinject was launched in 2007 whereas the earliest launch of Monofer was in 2010. Ferinject therefore entered most markets 3-5 years earlier than Monofer. It was well-known that spontaneous suspected adverse event reporting rates tended to decrease over time and so it was fundamentally biased and misleading to compare the frequencies during the limited time period from 2014-2017. In that regard, Pharmacosmos noted a published Swissmedic pharmacovigilance report on Ferinject that covered the period from January 1, 2010 to October 1, 2013, a period of the product's life cycle similar to the current life cycle stage of Monofer. This report revealed a rate of 3.7 anaphylactic reactions per 100,000 defined daily doses of ferric carboxymaltose, compared to the 3.1 and 3.4 reported by Ehlken *et al* for Monofer. Therefore, analysis of data from similar periods of product lifecycles reveals broadly comparable rates which were, if anything, in favour of Monofer.

Furthermore, several countries where Monofer was not available had been included in Ehlken *et al*. As this study purported to compare both products, it defied logic to include countries where one product was not available. Far from this leading to over-representation of adverse events for Ferinject, inclusion of selected markets where Ferinject had been long-established and known to have lower than average reporting rates, could lead to artificial lowering of the reported hypersensitivity rates with Ferinject.

b) The article was not based on an up-to-date evaluation of all the evidence and did not reflect that evidence clearly, and the wider context of the data was not provided in the meetings.

The publication by the EMA in the 2013, 'Assessment report for: Iron containing intravenous (IV) medicinal products', and the associated guidance from the Medicines and Healthcare products Regulatory Agency (MHRA), currently provided the highest level of accurate and balanced information about intravenous irons and hypersensitivity reactions. One of the outcomes of the reports was that the data could not detect differences between IV iron preparations and recommended that further safety data were collected. Pharmacosmos had continually gathered safety data on its products and had received confirmation from the Pharmacovigilance Risk Assessment Committee that, based on most recent data, the safety profile of Monofer remained unchanged and comparable to the 2013 assessment. This position was also supported by the wider body of data including, for example, a systematic comparative analysis which found a similar incidence of hypersensitivity reactions between modern IV irons, and any differences detected were in favour of Monofer, as there were statistically significantly fewer serious or severe hypersensitivity events with Monofer compared with other commonly used IV irons in Europe (Kalra and Bhandari 2016).

Thus, in relation to both section (a) and (b) Pharmacosmos alleged a breach of Clause 7.2. The overall extent of misleading content was such that it further alleged a breach of Clause 9.1.

Pharmacosmos stated that as the article and associated activities could not take the benefit of the exemption from the definition of promotion, they could only be regarded as promotional. The data discussion was led by a member of the medical team and in the context of the delivery in this case, the activity's promotional nature was disguised. This was highlighted by the health professional's statement above that the impression given to him/her was that he/she was being asked to discuss potential future studies.

Pharmacosmos alleged a breach of Clause 12.1.

Furthermore, the information provided indicated that the Vifor-organised meetings to discuss Ehlken *et al* were on or around 20 December, just 10 days after publication. This rapid turn-around indicated that Vifor had prepared for this activity before the actual publication of the article. (Typical lead times to plan and execute such meetings would be more than 10 days in all but the most urgent medical activities). This was of concern because such pre-planning implied intent regarding use of Ehlken *et al*. If this was so, such commercial interaction could undermine the integrity of true scientific research.

Pharmacosmos stated that Vifor's letter in response to inter-company dialogue made it clear that Ehlken *et al*, and associated activities, had not been certified for promotional use. As the

health professional statements made clear that this paper was used in a promotional manner, this indicated that Vifor had failed to adhere to Code requirements for certifying promotional materials.

Pharmacosmos alleged a breach of Clause 14.1.

Given the nature of Vifor's reported activity, the concern that it had raised amongst health professionals, and that Vifor had continued a pattern of behaviour that resulted in multiple clause breaches in two previous cases, Pharmacosmos alleged that the company's conduct had brought the industry into disrepute, in breach of Clause 2.

RESPONSE

Vifor stated that Pharmacosmos had been engaged in inter-company dialogue in relation to the above. As Vifor was not aware of any promotional use of Ehlken *et al*, it asked Pharmacosmos to provide evidence so that the matter could be investigated. Pharmacosmos had not responded or provided any evidence and therefore Vifor rejected that inter-company dialogue had been unsuccessful because it had not been completed.

The only difference between the uncompleted inter-company dialogue and the complaint was the addition of a reference to health professional 1. It was only now that Vifor had seen and been asked to respond to the alleged statement of the health professional; this was an example of clear abuse of the accepted inter-company guidance process published by PMCPA.

No distribution of Ehlken *et al* and Vifor activity

Vifor noted that the alleged health professional's statement did not refer to the manner of Vifor's contact with him/her. Vifor queried the statement's admissibility as evidence and whether it was genuinely made by a health professional or a liberal interpretation by Pharmacosmos. Vifor suggested that PMCPA spoke to the health professional to confirm the fully appropriate manner of the contact as outlined below and requested that the PMCPA ask explicitly if the health professional considered the interaction to be promotional.

Vifor categorically refuted that the published paper had been proactively distributed by any Vifor medical department, either global or UK based. Senior medical employees at Vifor strove to foster a respectful and open relationship with clinicians with whom the company worked and Vifor's Chief Medical Officer (CMO), one of the co-authors of Ehlken *et al*, wished to have a peer-to-peer discussion of his publication with selected international professors and senior consultants who were investigators and consultants to Vifor in order to inform them of the purpose and of the publication of the paper.

Vifor contacted three such UK health professionals and telephone conversations were held with two professors; the third clinician was unable to speak because of other commitments. The CMO explained the rationale, results and limitations of the study in separate non-promotional conversations with the two professors and answered any questions arising. Both professors were grateful to have been informed of the study publication and implied no negativity in the way they had been approached. The discussions were of a scientific nature and the paper was not provided to any of the senior clinicians who were contacted.

Vifor submitted that the activity was not promotional and was not within the scope of the Code and therefore no breach could have occurred.

Methodological criticism of the paper

Vifor submitted that Pharmacosmos' complaint about the methodology of the peer reviewed, published clinical paper should be addressed directly to the publisher, as publishing protocols and ethics were not within the scope of the Code.

Conclusion

Vifor noted that it knew who the health professional was. Vifor only spoke to 2 professors, one of whom was not associated with a hospital trust. This fact provided clear evidence that Ehlken *et al* was not being disseminated widely in an inappropriate manner as alleged. As the complaint contained no substantiable evidence and its sole motivation could be that of competition, there was no *prima facie* case to answer and the complaint should be dismissed.

Vifor would not respond to the unsubstantiated allegations of potential Code breaches. If Pharmacosmos could provide substantial evidence that Vifor had acted as alleged, Vifor would respond. Until such evidence was provided, Vifor would not enter into further dialogue on this matter.

In response to a further request to respond to the complaint, Vifor noted that the PMCPA considered that inter-company dialogue had been exhausted and commented that during the inter-company dialogue Vifor should have referred to the contact made between the Vifor CMO and health professional 1. Vifor contested that assessment and noted that Pharmacosmos had consistently referred to being '… contacted by several UK based health professionals who had concerns …', yet to date Vifor had not seen any evidence to support Pharmacosmos' allegation and to Vifor's knowledge, neither had the PMCPA. Clarification of the alleged 'several UK based healthcare professionals' should be sought and the statement substantiated.

Pharmacosmos' allegation was in reference to promotional activity but the contact between the Vifor CMO and the health professional was clearly a peer-to-peer interaction between two academics. It would therefore have been inappropriate to associate this with Pharmacosmos' inquiry. As stated, Vifor had not used Ehlken *et al* promotionally and had not briefed medical teams either locally or globally to disseminate the publication to any health professionals in the UK.

Vifor asserted that there was no evidence to support any breach of the Code. The Constitution and Procedure stated that 'a complainant has the burden of proving their complaint on the balance of probabilities …' and that '… all complaints are judged on the evidence provided …' and yet the statement made by Pharmacosmos could not under any circumstances be considered evidence and appeared to be its interpretation of a legitimate discussion between Vifor's CMO and a professor who worked with Vifor in both clinical research and as a consultant advising on health technology assessment (HTA) submissions. As expected for genuine peer-to-peer interactions, the discussions were unstructured and no minutes were produced.

The original Pharmacosmos complaint contained no evidence of a Code breach and in the absence of such there was no *prima facie* case to answer. Vifor requested that the case was handled according to Paragraph 5.5 of the Constitution and Procedure.

Vifor stated that it would not respond to unfounded allegations of potential Code breaches and reiterated that it would not enter into further dialogue about the matter until and if relevant and

substantiated evidence was provided by Pharmacosmos and/or the health professional and a case was established.

In response to a second request from the PMCPA for a response to the complaint, Vifor stated that it considered that it had been, and continued to be, the subject of repeated complaints by Pharmacosmos that were often without any foundation. This was magnified by Pharmacosmos' disregard for the self-regulatory scheme, as evidenced by its refusal to accept adverse findings by the Panel and its decision to turn its back on the PMCPA and its processes – at least to the extent the PMCPA had the potential to impact Pharmacosmos' own activities.

Vifor noted that Pharmacosmos' complaints typically contained vague and unsubstantiated allegations and that it expected the PMCPA to investigate and substantiate, with the onus being on Vifor to 'prove its innocence', rather than for Pharmacosmos to substantiate its complaint. This was one such complaint. Ehlken *et al* was a legitimate, peer-reviewed scientific publication and Vifor had not used the publication promotionally. Contrary to Pharmacosmos' unsubstantiated allegation of widespread dissemination and promotion of the publication by Vifor, the interactions with the two clinicians in question were entirely legitimate, peer-to-peer, non-promotional, scientific exchanges which involved the Vifor CMO who was a co-author of the paper. The clinicians were both well known to the CMO and to Vifor. Pharmacosmos had not provided any evidence of the promotional use of the paper, other than an alleged 'statement' by a health professional (which was clearly not prepared by the health professional).

Vifor noted that although Pharmacosmos had never identified health professional 1, Vifor identified him/her by name. It also named the only other person the health professional could be as these were the only two people with whom the CMO discussed his paper. Both of these health professionals had links with Vifor and details were provided. Both had been regular members of Vifor advisory boards in the past and were currently both consultants to Vifor in the context of the National Institute for health and Care Excellence (NICE) HTA procedures. Given the ongoing relationship between Vifor and these academics, Vifor considered that it was appropriate for senior company medics to engage in ongoing communication regarding Vifor and new scientific developments, studies and the like that were material and relevant to their clinical practice and their work with Vifor. That was exactly what happened in this situation.

Vifor stated that, as a courtesy, its CMO wished to discuss his paper and other recently published studies with the two health professionals wishing to engage in a peer-to-peer discussion relevant to their activities as consultants and investigators. The CMO was joined by another Vifor global medical employee. There was no brief to the CMO, since he would discuss his own research. As expected for genuine peer-to-peer interactions, the discussions were unstructured and not minuted.

Vifor stated that it did not provide the two health professionals with a copy of the paper, inform them where they could find it or circulate any emails containing links to the paper to these or any other health professionals. As indicated previously, Vifor urged the PMCPA to contact health professional 1 directly for an unmodified, non-misleading version of events. Vifor was confident that health professional 1 would report that while the initial purpose of the call from Vifor's CMO did cause some confusion, the call was not promotional. The health professional had indicated that he/she would be willing to confirm this to the PMCPA should he be asked.

Finally, Vifor considered it inappropriate to comment on the methodology of Ehlken *et al*. It was not a 'paid for' publication, but a peer-reviewed scientific paper published in Drug Safety, the official journal of the International Society of Pharmacovigilance. Drug Safety was globally

respected as 'the premier international journal covering the disciplines of pharmacovigilance, pharmacoepidemiology, benefit-risk assessment, risk management and medication error prevention.' The authors included highly experienced epidemiologist and the study design followed input by eminent academics in the relevant area. The paper was subject to rigorous peer review by the journal's independent expert panel, which considered that it met the journal's high standards for publication. Control of the article and the decision to publish were solely responsibilities of the editors of Drug Safety, not Vifor. The ABPI Code was not an appropriate vehicle to use to engage in a debate upon the scientific merit of published, peer-reviewed clinical research studies.

In response to a request for further information Vifor submitted that having looked at the situation and the respective amount of information provided to date by both parties, it considered that the Authority had more than enough information to be able to find that there was no *prima facie* case to answer.

Vifor accepted and respected the fact that the PMCPA was not an investigatory body; the Constitution and Procedure made it clear. Vifor submitted that Pharmacosmos, however consistently transformed the Panel's role into doing this by making unsubstantiated allegations in the expectation that the Panel would gather the evidence necessary to discharge Pharmacosmos' burden of proof. Vifor noted that Pharmacosmos made numerous allegations of widespread use of a clinical paper by Vifor but its only supporting documentation was an ambiguous interpretation of an alleged conversation with one health professional. Vifor submitted that Pharmacosmos must have misrepresented the discussion because the health professional had since confirmed to Vifor that he/she did not view the interaction as promotional and did not want to be involved in a complaint relating to the contact. Vifor stated that it had already provided a response that made its position clear and it did not have anything to add.

Vifor stated that the PMCPA's Constitution and Procedure made it clear that 'A complainant had the burden of proving their complaint on the balance of probabilities'. Vifor submitted that the Panel could not reverse the burden of proof by asking Vifor to provide evidence or other incidental information proving that it did not violate the Code. The onus must be on the complainant to provide evidence that the Code was violated and Pharmacosmos had failed to do that. Vifor stated that the premise of 'innocent until proven guilty' was the foundation of all British law and must prevail here. The 'balance of probabilities' standard should be applied equally rigorously based on the evidence provided by all parties; if Pharmacosmos had not supplied sufficient evidence, the PMCPA should either request further evidence from Pharmacosmos or reject the complaint as unsubstantiated. Vifor stated that it was happy to supply answers to questions if further meaningful evidence was provided.

In response to a further request from the PMCPA for information Vifor stated that there was no evidence to support a breach of the Code with regard to the matter at issue. Vifor stated that it had already provided a comprehensive response to the allegation and made its position clear on numerous occasions. In the absence of any new evidence, Vifor could not add any information that would further help the analysis.

Vifor submitted that its CMO engaged in peer-to-peer scientific discussions regarding a paper that he co-authored. Vifor did not know what Pharmacosmos had in mind when it wrote the 'HCP statement' it used as the basis for the complaint, but health professional 1 had also made it very clear that he/she did not consider the contact with Vifor to be promotional. Furthermore, he/she also made it clear that he/she did not want to be involved in any way concerning a

complaint to the PMCPA. Vifor reiterated that there was no evidence to support a breach and therefore no case for it to answer.

In response to a request from the PMCPA for further information, Vifor submitted that it considered that inter-company dialogue, as required by Paragraph 5.3 of the PMCPA Constitution and Procedure, had not been unsuccessful at the time that Pharmacosmos escalated the complaint to the PMCPA. According to Vifor the last correspondence from Vifor to Pharmacosmos before this escalation (dated 10 January 2019) stated:

> 'We would be happy to continue to address any concerns that you may have through inter-company dialogue on this matter ….'

Thus Vifor considered that the case preparation manager should not have accepted the complaint.

However, notwithstanding the above, and in the spirit of self-regulation, Vifor provided further clarity on the conversations that its CMO had with two health professionals.

Vifor submitted that, as previously stated, both health professionals had recently been, or were about to be, undertaking some work supported by Vifor. Vifor had a long-standing and ongoing relationship with both health professionals. As such there was an advisory nature to the relationship on both sides that lended itself to mature discussions which, although not formalised in any consultancy agreement, were still important to ensure the appropriate management of any condition. Vifor considered that it was entirely appropriate for it to contact certain experts in the field of iron deficiency to understand the relevance of the publication in question (Ehlken *et al*) in the context of intravenous (iv) iron treatment.

Vifor had written confirmation from the Vifor CMO at the time on the intent and context of the telephone conversations that were held (copy provided). Vifor also provided a written, signed statement from a named health professional (health professional 2) that engaged in the conversations.

Vifor noted that it could be seen from the CMO's written confirmation that the intent of the calls was to seek the health professionals' scientific advice and from health professional 2's signed statement that the intent of the telephone call was clear to him/her; he/she considered it an entirely appropriate activity. Health professional 2 considered that it was a discussion that he/she considered valuable to his/her clinical practice. He/she also did not consider that the conversation was promotional but rather part of an ongoing and essential dialogue.

Vifor stated that should this type of interaction be considered promotional it would have a huge impact on the wider healthcare industry and the conversations that senior medical staff in pharmaceutical companies could have with key health professionals.

Vifor stated that it was aware of the identity of health professional 1 as referred to by Pharmacosmos. Vifor stated that it had discussed the matter with the health professional and considered that the 'statement' provided by Pharmacosmos was its interpretation of a discussion with the health professional rather than reflecting his/her opinions. The health professional informed Vifor that he/she did not consider that there was any promotional intent regarding this contact. In addition, he/she did not wish to be involved in any way with the complaint.

Vifor trusted that this additional information clarified for the Panel that there was no promotional intent by Vifor in arranging and conducting the telephone calls in question, nor was there any such impression given to the health professionals involved. With this in mind, there was no requirement to certify any of the information exchanged during the calls and there had been no breach of Clause 14.1.

Given that there was no promotional content, there could be no disguised promotion and thus there had been no breach of Clause 12.1.

In addition, there was no misleading information provided during these calls; health professional 2's signed statement clarified that the purpose of the call was clear and therefore there had been no breach of Clause 7.2.

Given the above, Vifor did not consider that the actions of Vifor had in any way failed to maintain high standards; there had been no breach of Clause 9.1 and consequently, no breach of Clause 2.

PANEL RULING

The Panel noted that there were differences between and within the parties' accounts; it was extremely difficult in such cases to know exactly what had transpired. The complainant bore the burden of proof on the balance of probabilities. A judgement had to be made based on the evidence provided by both parties.

The Panel noted that Pharmacosmos provided an unsigned statement which appeared to have been written based on information from a health professional it referred to as HCP1 (health professional 1). Pharmacosmos did not disclose health professional 1's identity. Vifor named health professional 1. According to Vifor, the only other person the health professional could be was another named health professional as these were the only two people with whom the Vifor Chief Medical Officer (CMO) discussed his paper. Vifor provided a signed statement from the person referred to as health professional 2.

The Panel noted that the complaint concerned the use of the article by Ehlken *et al* (2018) which evaluated the rates of severe hypersensitivity reactions reported with Ferinject and Monofer in Europe based on data from EudraVigilance and VigiBase between 2014 and 2017 and was funded by Vifor.

Pharmacosmos alleged that Ehlken *et al*, which in its view contained inappropriate and misleading content, was being proactively provided to or brought to the intention of several health professionals and was being discussed with them by Vifor.

The Panel noted Vifor's submission that it had not used Ehlken *et al* promotionally and had not briefed medical teams either locally or globally to disseminate the publication to any health professionals in the UK. Vifor submitted that its CMO, one of the co-authors of Ehlken *et al*, contacted three but only spoke to two to explain the rationale, results and limitations of the study and answer any questions. The interaction would be a peer-to-peer discussion of his publication to inform them of its purpose and publication. The Panel further noted Vifor's submission that given the ongoing relationship between Vifor and these two health professionals, it was appropriate for senior company medical staff to engage in ongoing communication regarding Vifor and new scientific developments, studies and the like and that the interaction in question was material and relevant to their clinical practice and work with Vifor.

The Panel noted Vifor's initial submission that both were involved in work supported by Vifor. Both had been regular members of Vifor advisory boards in the past and were currently both consultants to Vifor in the context of the National Institute for health and Care Excellence (NICE) HTA procedures. In a subsequent response Vifor submitted that both had recently been, or were about to be, involved in work supported by Vifor conducting investigator-initiated studies. This differed from Vifor's initial submission that the investigator led studies were current. Vifor's response dated 26 March 2019 stated that health professional 2 was conducting a particular study. However, health professional 2's signed statement dated 1 November 2019 stated that he/she hoped a contract with Vifor for the support of that study would soon be signed.

Following a number of requests, Vifor submitted that with regard to the relevance of Ehlken *et al* to the health professionals' work for Vifor, Vifor had a long-standing and ongoing relationship with both health professionals and as such there was an advisory nature to the relationship on both sides that lended itself to mature discussions which, although not formalised in any consultancy agreement, were still important to ensure the appropriate management of any condition. The Panel noted Vifor's submission that both health professionals were grateful to have been informed of the study publication.

The Panel noted that according to his/her statement, health professional 2 did not consider that the conversation was promotional but rather peer-to-peer engagement.

The Panel noted that it was only in a subsequent response that Vifor submitted that it could be seen from the CMO's written statement that the intent of the discussions was to seek the health professionals' scientific advice and according to health professional 2's signed statement the intent of the telephone call was clear to him/her. Vifor provided no details of specific questions asked by the CMO. In his/her statement health professional 2 stated that it was a discussion that he/she considered valuable to his/her clinical practice.

The Panel noted that Vifor did not provide any details about how the calls with the two health professionals were arranged including any relevant emails. All parties agreed that Vifor had initiated the contact. The Panel noted Vifor's submission that the advisory nature of the relationship in relation to the discussions as described by Vifor were not formalised in any consultancy agreement. Vifor provided no details of specific questions asked by the CMO. The Panel noted Vifor's submission that there was no brief to the CMO, since he would discuss his own research and the discussions were unstructured and not minuted.

The Panel noted Vifor's comments about the burden of proof. The Panel considered that Pharmacosmos had, on the balance of probabilities, established that the paper in question had been discussed with at least one health professional. Vifor accepted that it had discussed the paper with two health professionals. The first matter to be determined by the Panel was whether the interaction was promotional or non-promotional. The second matter to be determined was whether, on the balance of probabilities, Pharmacosmos had established what was said about the paper in question and if so whether what was said was in breach of the Code.

The Panel noted Vifor's submission about the importance of peer-to-peer interactions. In the Panel's view, peer-to-peer interactions between senior company medical employees and senior health professionals were not unacceptable so long as they complied with the Code. Whether such interactions were promotional or non-promotional would depend on a consideration of all the circumstances whilst noting the broad definition of promotion in Clause 1.2. Relevant circumstances would include whether the discussion was an integral and relevant part of an

ongoing consultancy. In the Panel's view, Vifor had submitted conflicting accounts about whether there was a current consultancy at the time of the interaction in relation to investigator initiated trials. It appeared that, according to Vifor, both health professionals were currently consultants in the context of NICE HTA procedures; there was no evidence before the Panel that the paper in question was relevant or integral to that consultancy. The Panel noted that the CMO's statement referred to seeking the health professionals' scientific advice. The Panel noted Vifor's submission that the advisory nature of the relationship in relation to the discussions as described by Vifor were not formalised in any consultancy agreement. Given these points the Panel did not consider, on the evidence before it, that the arrangements could be described as an advisory board or similar bearing in mind the requirements of Clause 23.

The Panel noted Vifor's submission that neither health professional considered the interaction promotional. The Panel noted the broad definition of the term 'promotion' at Clause 1.2 of the Code which, in the Panel's view, was likely to be different to a lay person's use of that term. A discussion of clinical matters, depending on the circumstances, might fall within the broad definition of promotion in the Code.

Given its comments above, the Panel queried how the proactive discussion of the paper which directly compared two products and appeared to be in favour of Vifor's product could be anything other than promotional.

The Panel further noted Vifor's submission that health professional 1 was confused about the initial purpose of the call. Vifor refused to provide details about what the confusion was despite a number of requests nor did the Panel have before it emails etc about the arrangements for the call. Nonetheless, Vifor's submission about initial confusion was consistent with the evidence from Pharmacosmos that health professional 1 had agreed to be contacted on the assumption that the telephone call was arranged to discuss a potential future study and was surprised that the call was to inform him/her about the results from the recent publication, Ehlken *et al*. In the Panel's view, in relation to health professional 1, the promotional nature of the call was, on balance, disguised. A breach of Clause 12.1 was ruled.

The Panel noted its comments on the broad definition of promotion above. In relation to health professional 2, according to his/her statement, he/she understood that the reason for the call was to discuss the study and referred to both giving advice and the importance of him/her being aware of such data; that such discussions were an important aspect of clinical work; the importance of listening to multiple opinions and the evidence on which they are based to make the best decisions for patients. In the Panel's view it appeared that health professional 2 was clear that the call in question would involve a discussion of the paper and in that regard the promotional nature of the call was not disguised. No breach of Clause 12.1 was ruled.

The Panel noted Vifor's submission that the article and activities had not been certified for promotional use. The Panel noted Vifor's submission that it did not provide the two health professionals with a copy of the paper, inform them where they could find it or circulate any emails containing links to the paper. It was unclear to the Panel what exactly was discussed during the conversations between Vifor and the two health professionals. Whilst the Panel had some concerns, it considered that Pharmacosmos had not provided evidence that Ehlken *et al* had been sent unsolicited to any health professional and therefore that it required certification for such use. The Panel, however, further noted Vifor's submission that there was no brief to the employee, since he would be discussing his own research. In the Panel's view, in the absence of briefing material Ehlken *et al* was the basis of the discussion and therefore should have been certified for such use. The Panel therefore ruled a breach of Clause 14.1.

The Panel noted that Vifor considered it inappropriate to respond in relation to the article itself including the methodology as it was not a 'paid for' publication, but a peer-reviewed scientific paper published in Drug Safety, the official journal of the International Society of Pharmacovigilance. The Panel noted that, regardless of where an article was published, the proactive use of the article by a pharmaceutical company meant that its provision to health professionals or discussion about it would have to comply with the Code.

The Panel noted that in Ehlken *et al* information on spontaneously reported severe hypersensitivity reactions was obtained from and analysed separately for two established safety surveillance databases between 2014 and 2017. The Panel noted Pharmacosmos' submission that the EMA had previously stated that '… 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'.

According to Ehlken *et al* findings suggest that iron (III) isomaltoside 1000 is associated with higher reporting rates of severe hypersensitivity reactions related to estimated exposure than ferric carboxymaltose in European countries.

The Panel noted that Ehlken *et al* concluded that further research investigating the occurrence of severe hypersensitivity reactions associated with iv ferric carboxymaltose and iron (III) isomaltoside 1000 was needed to broaden the evidence for benefit-risk assessment. The Panel noted that Pharmacosmos' specific concerns included that Ferinject entered most markets 3-5 years earlier than Monofer and it was well-known that spontaneous suspected adverse event reporting rates tended to decrease over time and so it was fundamentally biased and misleading to compare the frequencies during the limited time period from 2014-2017. In addition, Pharmacosmos noted that several countries where Monofer was not available had been included in Ehlken *et al* and rather than this leading to over-representation of adverse events for Ferinject, inclusion of selected markets where Ferinject had been long-established and known to have lower than average reporting rates, could lead to artificial lowering of the reported hypersensitivity rates with Ferinject.

The Panel noted that Ehlken *et al* acknowledged both of these points as limitations including that the reporting of adverse events might be higher directly after launch compared to when products were well-established on the market but stated that in order to overcome the limitation, the 4-year period from 2014-2017 was chosen as both products had already been on the European market for several years. Ehlken *et al* noted that for the majority of countries both products were available. Whilst an impact of differential marketing on the level of the reporting rate could not be ruled out, it was considered to be minor. The Panel noted each companies' submission about Ehlken *et al*. Whilst noting the conclusions of Ehlken *et al* and the limitations discussed by the study authors, the Panel had very little detail before it about precisely what was said about the study during the conversations with the two health professionals. The statement from health professional 2 did not detail what exactly was said about Ehlken *et al* during the call. The unsigned statement of health professional 1 provided by Pharmacosmos stated that the content of the call described data focussing on a difference between iron isomaltoside and ferric carboxymaltose with regard to hypersensitivity risk. The Panel did not consider that Pharmacosmos had proved, on the balance of probabilities, what was said about Ehlken *et al* during the conversations with the two health professionals and whether such statements were misleading; no breach of Clause 7.2 was ruled.

The Panel further noted Pharmacosmos' submission that the article was not based on an up-to-date evaluation of all the evidence and did not reflect that evidence clearly, and the wider context of the data was not provided in the meetings. The Panel noted Pharmacosmos' detailed submission about the evidence base on intravenous irons and hypersensitivity reactions. The Panel did not know how the paper was discussed with the two health professionals or if any other data was discussed. The unsigned statement of health professional 1 provided by Pharmacosmos stated that no evidence from other studies on the topic was presented. There was very little detail before the Panel about precisely what was said. The Panel did not consider that Pharmacosmos had established, on the balance of probabilities, that the discussions about Ehlken *et al* were misleading because they were not based on an up to date evaluation of all of the evidence as alleged. The Panel therefore ruled no breach of Clause 7.2 in this regard.

The Panel noted its rulings above and did not consider that, based on the narrow allegation, Pharmacosmos had established that Vifor had failed to maintain high standards in relation to the discussion of misleading information with regard to Ehlken *et al* as alleged and the Panel ruled no breach of Clause 9.1.

The Panel noted Pharmacosmos' reference to the rulings in Cases AUTH/2828/3/16 and AUTH/2830/4/16 and its allegation that Vifor was failing to maintain high standards by once again providing misleading information to health professionals that could cast doubt on the safety of Monofer. The Panel noted its comments and rulings above and considered that based on the narrow allegation there was no evidence that Vifor had failed to maintain high standards and no breach of Clause 9.1 was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use and ruled accordingly.

Complaint received **12 February 2019**

Case completed **13 December 2019**