CASE AUTH/2830/4/16

PHARMACOSMOS v VIFOR PHARMA

Promotion of Ferinject

Pharmacosmos alleged that Vifor's promotion of Ferinject (ferric carboxymaltose for injection/ infusion) represented a clear and national pattern of misleading and disparaging claims about the safety profile of its product, Monofer (iron isomaltoside). Both medicines were for the treatment of iron deficiency when oral iron was ineffective or could not be used.

Pharmacosmos noted that there were no comparative efficacy or safety studies for Monofer and Ferinject. Further, a review of all medicines in the same class by the European Medicines Agency (EMA) concluded that there were no meaningful differences in the safety profiles of the available products.

Pharmacosmos stated that many of the issues that it had raised with Vifor in inter-company dialogue stemmed from comments made to it by health professionals. The health professionals were reluctant to be named and so it was difficult to substantiate their allegations. Pharmacosmos had recently raised six new examples with Vifor which it stated supported its position. Pharmacosmos recognised that the examples were anecdotal but that for clarity it had not made specific allegations for each one but wished to portray them as part of the overall picture to give credence to its concerns of a pattern of disparaging comments.

Pharmacosmos stated that although Vifor consistently denied inappropriate activity, it had made several commitments during inter-company dialogue including an agreement to brief all employees about the use of certain documents and the nature of discussions regarding the adverse events profile of Ferinject and Monofer. Unfortunately, however, a report from one health professional led Pharmacosmos to question the integrity of Vifor's commitments.

Pharmacosmos drew particular attention to an additional report it had received about a medical information email sent by Vifor to a named hospital specialist nurse who stated that she did not request the letter. The letter referred to a report from a pharmacovigilance body in the Netherlands; Pharmacosmos queried whether the UK nurse would know about or request such a report. Pharmacosmos noted that the medical information letter stated that a representative had asked for the report to be sent. Pharmacosmos alleged that Vifor had provided the information proactively and that as this was one example of a representative disparaging Monofer, it was likely that the other cited examples of disparagement were also true. Pharmacosmos stated that an appraisal of Vifor's representatives' training material would corroborate its concerns because it was likely to link the dextran-derived nature of the Monofer molecular structure to a higher (alleged) propensity for adverse events. Further, the nurse's experience referred to above raised doubts about the quality of investigations undertaken by Vifor and the effectiveness of the direction given to representatives with regard to comparing product safety profiles in response to concerns raised in inter-company dialogue.

Pharmacosmos alleged that Vifor had misled health professionals by implying there was a difference in the safety profiles of Monofer and Ferinject when no formal comparison between the two existed. The consistent and widespread pattern of comments from health professionals indicated that, on the balance of probability, Vifor representatives had proactively raised the safety profile of Monofer in order to imply differences between the products. Pharmacosmos referred to the six recent examples.

Pharmacosmos concluded that whilst it had hoped that Vifor had adequately and appropriately addressed the six alleged cases of disparaging and misleading claims highlighted during inter-company dialogue, it was shocked and concerned to learn that this activity had continued, as outlined in the nurse's first-hand account. Anxiety of clinical staff could increase the incidence of adverse events and given the nature of Vifor's alleged activities this was likely to have a direct impact on staff's confidence with Monofer and therefore put patients' lives at risk.

Pharmacosmos stated that the referenced incidents of alleged disparaging and misleading claims by Vifor representatives had all been raised verbally to Pharmacosmos by health professionals in the UK and Ireland. To provide further context to what and how the information was shared with Pharmacosmos the relevant members of the Pharmacosmos team were asked to provide written statements, copies of which were provided. For completeness, Pharmacosmos provided statements to each case referenced in its complaint and noted that it had anonymised the names of the health professionals as it did not have their permission to identify them. Pharmacosmos further stated that it was its interpretation that 'information from [named] Hospital' related to Grant *et al* (2013) that described a local hospital audit of Monofer.

The detailed response from Vifor is given below.

The Panel noted Pharmacosmos' allegation that Vifor representatives had disparaged Monofer and provided misleading information about Monofer safety by implying there was a difference in the safety profiles of Monofer and Ferinject when no formal comparison between the two products existed. Pharmacosmos provided six anecdotal examples and Vifor responded to each with specific details. The Panel did not consider these examples

per se when making its ruling as Pharmacosmos had not made specific allegations for each example but had cited them to substantiate its concerns of a pattern of disparaging comments.

The Panel noted that in addition Pharmacosmos provided a medical information email it alleged was sent proactively (not in response to a request) by Vifor to a specialist nurse at a named hospital as evidence that Monofer had been disparaged. The medical information email was the subject of Case AUTH/2828/3/16. The medical information email stated:

> 'Thank you for your enquiry on Ferinject (ferric carboxymaltose: FCM). I understand from my colleague, [named], that you have requested a copy of the Lareb report.
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> The Netherlands Pharmocovigilance Centre, Lareb, has received concerns from multiple Dutch hospitals in relation to iron isomaltoside after the switch from iron carboxymaltose (FCM). Doctors and nurses reported an increase in the severity and incidence of allergic reaction. The report has not mentioned any specific safety concerns with FCM.'

The Panel noted that the latter statement was untrue as the report detailed 7 reports of hypersensitivity/anaphylactic reactions associated with the use of Ferinject.

The Panel noted Pharmacosmos' disbelief that a typical UK health professional would know about the Lareb report, which was a specific pharmacovigilance assessment of Monofer made by the Dutch pharmacovigilance authority. Pharmacosmos had also submitted that it was difficult to understand why a health professional would proactively request a copy of that report Pharmacosmos considered the provision of the Lareb report most likely occurred following a representative visit which included comments about the safety profile of Monofer.

The Panel noted Pharmacosmos' statement that an appraisal of material used to train Vifor representatives would corroborate its concerns because it was likely to draw attention to Monofer's adverse event profile.

The Panel noted Vifor's submission that during initial training, representatives were briefed not to discuss competitor products in detail beyond the SPC. This briefing included the instruction that for non-Vifor products, representatives had to refer a customer to the product's SPC. The Panel noted Vifor's submission that the Intravenous Iron Differentiator tool and the SPC Comparator were the only materials available to the representatives that mentioned Monofer. Otherwise the customer was advised to contact the medical information department of the product market authorization holder.

The Intravenous Iron Differentiator tool was a slide set which specifically differentiated Ferinject from Monofer and which was according to its briefing material designed to be used proactively in threatened accounts that were considering switching to Monofer and in accounts that had switched to Monofer. Two slides specifically compared the side-effects and contraindications of Ferinject and Monofer. The briefing regarding these two slides referred to confidence with Ferinject and in that regard implied a lack of confidence with Monofer. The briefing material stated, in summary, that 'The Ferinject proposition is strong, be confident, we have the best treatment'. In the Panel's view the briefing material was at odds with Vifor's submission that it did not permit representatives to discuss comparative safety in a promotional environment. The Panel noted Vifor's submission that the slide on the comparison of dosing was based on the relevant products' SPCs. The Panel noted that the slide also stated that the way in which the Monofer dose was calculated (the Ganzoni formula) was 'inconvenient, prone to error, inconsistently used in clinical practice, and it underestimates iron requirements'. The briefing on this slide referred to Ganzoni-based dosing as being problematic.

A briefing document approved in January 2016 (Questions and Answers. Reactive responses to competitor messages, listed the comments and messages from customers regarding Monofer and stated 'What we need to do is reactively discuss the FACTS in an accurate and balanced way, to allow the customer to make an informed decision'. It was stated on one slide that one of the benefits of Ferinject, in an implied comparison with Monofer, was confidence because it was the market leader. The document included an explanation that the misconception of the competitor claim 'Reformulation, old Monofer had [adverse events], new formulation is better' suggested that Pharmacosmos acknowledged Monofer had a problem with adverse events as the only reformulation Vifor was aware of was Diafer which was simply half strength Monofer. The final message of the briefing document was again 'The Ferinject proposition is strong, be confident, we have the best treatment'.

In the Panel's view, there was no doubt that Vifor was specifically targeting Monofer sales and that the representatives had been briefed to discuss the comparative safety of Ferinject vs Monofer.

The Panel noted Vifor's submission that Grant *et al* was included with an overview of all relevant papers in the 'Clinical papers' session of the initial training course. Vifor noted that the aim of including that information was to educate Vifor employees on the place Ferinject's data held within the broader context of other products. The emphasis was on Ferinject and representatives were instructed not to use the competitor data with customers unless the data contained information on a Vifor product.

The Panel noted Vifor's explanation that Grant *et al* was published as an abstract in Gut in September 2013. Grant *et al* was an audit of case notes of 40 patients who had received Monofer. The authors concluded 'Utilisation of Monofer in our clinical practice has shown a sub-optimal attainment of Hb target. Furthermore, the frequency of adverse

reactions was much higher than expected from those reported in the product SPC or previous studies in renal patients. In light of these observations we no longer use Monofer'.

A medical update was provided at the December 2013 sales conference which included information on recent publications for Ferinject and Monofer and included, *inter alia*, Grant *et al* and the authors' conclusion as stated above. The slide set for the session stated on the first slide that it was for internal use for training purposes. The cover slide did not state, as submitted by Vifor that the training session was for information only. The Panel considered that the slides contained material which Vifor would expect its representatives to use. No context had been given to the results from Grant *et al*.

The Panel disagreed with Vifor's submission that it only included safety information relating to Ferinject and Monofer in the Q&A document given that such comparisons appeared in the Intravenous Iron Differentiator tool and in the SPC Comparator tool. With regard to the latter, the Panel noted that the Ferinject and Monofer SPCs were being used by Vifor for a promotional purpose. The Panel noted that the briefing material stated that the tool had been designed to help representatives to directly compare different sections of the SPCs for the most prescribed IV irons including Ferinject and Monofer, it was to be used when asked specific questions about Vifor intravenous (IV) irons and those of its competitors. The briefing also stated that 'You can also project this from your iPad for use with multiple [healthcare professionals] at meetings'. There was no information on how to use the information provided in the tool and how to present the comparisons to a customer. The Panel noted Vifor's submission that representatives were briefed not to discuss competitor products in detail beyond the SPC. In the Panel's view, providing a tool which directly compared SPCs, implying that such direct comparisons of data were valid, went beyond that. The Panel also considered that the SPC Comparator tool went beyond the reminder given in December 2015 that representatives were not to discuss the safety of competitor products and that if a customer requested comparative safety data the request should be forwarded to medical information.

The Panel considered that on the balance of probabilities, given the strident tone and content of the sales materials and briefings, Vifor representatives had disparaged Monofer in promotional calls as alleged. The Panel further considered that on the balance of probabilities, Vifor representatives had provided misleading information with regard to the safety of Monofer as alleged. Breaches of the Code were ruled which were upheld on appeal from Vifor.

Pharmacosmos complained that the promotion of Ferinject (ferric carboxymaltose for injection/ infusion) by Vifor was misleading and disparaging in relation to the safety profile of its product, Monofer (iron isomaltoside). Both medicines were for the treatment of iron deficiency when oral iron was ineffective or could not be used.

COMPLAINT

Pharmacosmos noted that there were no comparative efficacy or safety studies for Monofer and Ferinject. In addition, the European Medicines Agency (EMA) formally reviewed all products in the class, including Monofer and Ferinject, and concluded that there were no meaningful differences in the safety profiles. Pharmacosmos stated that it had had a series of inter-company exchanges with Vifor over the last few years prompted by reports from health professionals which showed that Vifor representatives had disparaged the safety profile of Monofer by:

a) Proactively highlighting Monofer's dextran-derived molecule and implying it was likely to cause particular adverse events (Ferinject did not have a dextran-derived molecule)
b) Implying that comparative data existed between the products and that Ferinject had a relatively cleaner side-effect profile
c) Using an article published in Gut that included misleading comments about the respective safety profiles of Monofer and Ferinject.

Pharmacosmos highlighted the history of complaints it had made against Vifor in that regard. In particular Cases:

AUTH/2422/7/11 – Vifor was ruled in breach for claims that dextran-induced hypersensitivity reactions were common with Monofer

AUTH/2442/10/11 – Vifor breached its undertaking given in Case AUTH/2422/7/11

AUTH/2589/3/13 – Pharmacosmos alleged a further breach of the undertaking given in Case AUTH/2422/7/11 (this allegation was not upheld).

Pharmacosmos stated that it had had further inter-company dialogue with Vifor in relation to subsequent allegations which had been made about the safety profile of Monofer, copies were provided.

Pharmacosmos stated that many of the issues it raised in inter-company dialogue resulted from verbal comments it received from health professionals who were reluctant to be named, making the allegations difficult to substantiate. In the most recent exchange with Vifor, initiated in February 2016, Pharmacosmos highlighted five further such allegations that represented a clear and persistent national pattern of disparaging and misleading claims and gave credence to Pharmacosmos' long running concerns about the activities of Vifor's representatives. Pharmacosmos stated that Vifor consistently denied inappropriate activity, but had made several specific commitments in response to inter-company dialogue. Most recently, Vifor agreed to issue a communication to all of its employees about the use of certain documents and the nature of discussions in relation to adverse events with the two products. Regrettably, Pharmacosmos stated that it had since been told about an exchange between Vifor and a named health professional which implied that the

behaviour was continuing. The relevant details of the interaction were outlined below, and Pharmacosmos considered that the existence and nature of that exchange called into question the integrity of the commitments it had previously received from Vifor.

Pharmacosmos alleged that Vifor representatives had disparaged Monofer in promotional calls in breach of Clause 8.1 and had provided misleading information in respect of Monofer safety in breach of Clause 7.2.

Pharmacosmos noted the commitments made by Vifor in its most recent inter-company letter. Vifor specifically stated that it had:

- issued a reminder letter to all representatives (dated shortly before 3 March 2016)
- investigated all of Pharmacosmos' allegations with regard to specific hospitals and specific representatives but found no conclusive evidence
- not trained its representatives to imply that the dextran-derived structure of the Monofer molecule caused a particularly bad adverse event profile, or to compare adverse events between Monofer and Ferinject
- told its representatives not to use Grant *et al* (2013) (published in Gut) in their promotional calls (Vifor confirmed during inter-company dialogue in February/March 2014 that the article would not be discussed/provided either proactively or reactively by Vifor representatives).

Pharmacosmos stated that the very existence of an unsolicited medical information letter provided to a named health professional proved the likelihood that, on the balance of probabilities, conversations in relation to the respective safety of Monofer had occurred; and that the existence of specific adverse event reports had been proactively raised by Vifor representatives. Pharmacosmos found it difficult to believe that a typical UK health professional would be aware of the Lareb report, which was a specific pharmacovigilance assessment of Monofer made by the Dutch pharmacovigilance authority; it was also difficult to understand why a health professional would proactively raise a request to receive a copy of that specific pharmacovigilance assessment. Pharmacosmos considered the provision of the Lareb report most likely occurred following a representative visit which most likely included comments about the safety profile of Monofer; it was difficult to see any other circumstances in which Vifor would provide the report to a health professional.

Pharmacosmos highlighted that the exchange between the Vifor representative and the named health professional occurred after several assurances from Vifor that representatives were not trained to compare the safety profiles of the two products or to cast aspersions about the safety profile of Monofer and that all enquiries relating to Monofer were automatically referred to Pharmacosmos. Pharmacosmos stated that the existence of the letter sent to the named health professional called into question the effectiveness of (or existence of) the communications recently issued by Vifor head office to the sales teams. It also undermined Vifor's assurances that it had not trained/briefed representatives to discuss the safety profile of Monofer. Pharmacosmos advised Vifor that inter-company dialogue had been unsuccessful in this matter and that it would write to the PMCPA directly.

Pharmacosmos provided evidence in respect of each allegation as listed below.

Disparagement of Monofer (Clause 8.1)

Pharmacosmos alleged that the consistent and widespread pattern of comments from health professionals indicated that, on the balance of probability, Vifor representatives had proactively disparaged the safety profile of Monofer. Six new examples were cited in its recent exchange with Vifor including:

- At a named university NHS foundation trust (hospital 1), two health professionals expressed concern and frustration with the disparaging and misleading claims allegedly made by a named Vifor representative (representative 1) who allegedly stated that 'Monofer has a higher rate of adverse drug reactions than Ferinject' and that 'Monofer is a dextran-based iron compound'. This was reported to Pharmacosmos on 4 January 2016.
- At a second named university hospitals NHS trust (hospital 2), a health professional expressed concern and frustration with the disparaging and misleading claims made by a Vifor representative who had allegedly stated that 'Monofer has a higher rate of adverse drug reactions than Ferinject' and 'Monofer is a dextran-based iron compound'. This was reported to Pharmacosmos in November 2015.
- At a third NHS trust (hospital 3), a health professional explained how a Vifor representative allegedly spoke in great detail about Grant *et al* relating to Monofer. This was reported to Pharmacosmos in January 2015.
- At a fourth named NHS foundation trust (hospital 4), a health professional expressed concern that a colleague flagged to them a recent conversation with a Vifor representative who claimed that Monofer had more side-effects than Ferinject. This was reported to Pharmacosmos in February 2016.
- At a fifth named hospital in Ireland (hospital 5), a health professional expressed concern and frustration with the disparaging and misleading claims allegedly made by a Vifor representative who stated that 'Monofer has a higher rate of adverse drug reactions than Ferinject'. This was reported to Pharmacosmos in February 2016.
- At a sixth named hospital in Ireland (hospital 6), a health professional expressed concern and frustration with the disparaging and misleading claims allegedly made by a Vifor representative who stated that 'Monofer has a higher rate of adverse drug reactions than Ferinject'. This was reported to Pharmacosmos in December 2015.

Pharmacosmos recognised that the above examples were anecdotal and the final two related to Eire (hospital 5 and 6), however the promotional material used in Ireland was issued by and approved in the UK. For clarity, Pharmacosmos stated that it had

not made specific allegations for each example cited above but wished to portray them as part of the overall picture to give credence to its concerns of a pattern of disparaging comments.

In addition to the six examples cited, on 11 March 2016 Pharmacosmos was told about a medical information email sent by Vifor to, a named specialist nurse at a hospital. The nurse stated that she did not request the letter. Pharmacosmos wanted to use the letter as evidence that Monofer had been disparaged.

Pharmacosmos contended that it was unlikely that the nurse knew about, or requested a report conducted by a pharmacovigilance body in the Netherlands. Pharmacosmos alleged that Vifor provided the letter proactively (not in response to a request). The medical information letter stated that a named Vifor regional business manager asked for the letter to be sent. Since the nurse clearly stated that she did not request the letter, this was at least one example of a representative proactively disparaging the safety profile of Monofer. Pharmacosmos stated that on the balance of probability, the six other examples cited above were also therefore likely to be true. Pharmacosmos stated that an appraisal of material used to train Vifor representatives would corroborate its concerns because it was likely to draw attention to Monofer's adverse event profile.

Pharmacosmos stated that training material would link the dextran-derived nature of the Monofer molecular structure to a higher (alleged) propensity for adverse events. Further, the nurse's experience raised doubts about the quality of investigations undertaken by Vifor and the effectiveness of the direction given to representatives with regard to comparing product safety profiles in response to concerns raised in inter-company dialogue.

Pharmacosmos provided a copy of the email exchange, including the unsolicited email received and the attached Lareb report. Pharmacosmos alleged that it was clear that Vifor representatives had proactively raised concerns with regard to the safety profile of Monofer and had disparaged the product in breach of Clause 8.1.

Misleading statements (Clause 7.2)

Pharmacosmos alleged a breach of Clause 7.2 on the grounds that Vifor had misled health professionals by implying there was a difference in the safety profiles of Monofer and Ferinject when no formal comparison between the two existed. The consistent and widespread pattern of comments from health professionals indicated that, on the balance of probability, Vifor representatives had proactively raised the safety profile of Monofer in order to imply differences between the products. Pharmacosmos referred to the six recent examples cited above which had formed the basis of Pharmacosmos' recent exchanges with Vifor.

Pharmacosmos again referred to the anecdotal nature of the reports and restated that it was not making specific allegations for each example cited but wished to portray them as part of the overall picture giving credence to its concerns of a pattern of behaviour of misleading statements.

On 11 March 2016, Pharmacosmos found out about a medical information email sent by Vifor to a specialist nurse who stated that she did not request the letter. For now, Pharmacosmos relied upon the letter as evidence that Vifor had misled health professionals about the safety profile of Monofer. Pharmacosmos noted that it was unlikely that the nurse knew about, or requested information about, a report conducted by a pharmacovigilance body in the Netherlands. Pharmacosmos alleged that Vifor provided the letter proactively. The medical information letter stated that a named regional business manager had asked for the letter to be sent. Since the health professional stated that she did not request the letter, this was at least one example of a representative who had proactively communicated the safety profile of Monofer in a misleading manner. The medical information letter stated:

> 'Thank you for your enquiry on Ferinject (ferric carboxymaltose: FCM). I understand from my colleague, [named], that you have requested a copy of the Lareb report. The Netherlands Pharmocovigilance Centre, Lareb, has received concerns from multiple Dutch hospitals in relation to iron isomaltoside after the switch from iron carboxymaltose (FCM). Doctors and nurses reported an increase in the severity and incidence of allergic reaction. The report has not mentioned any specific safety concerns with FCM.'

This letter was clear evidence that Vifor had tried to compare the safety profiles of Ferinject and Monofer in a misleading manner. On the balance of probability, the six other examples cited above were also therefore likely to be true. Pharmacosmos considered that an appraisal of the material used to train Vifor representatives would corroborate its concerns because it was likely to draw attention to Monofer's adverse event profile in a misleading manner. Pharmacosmos alleged that the training material would link the dextran-derived nature of the Monofer molecular structure to a higher (alleged) propensity for adverse events, which was misleading.

Further, this raised doubts about the quality of investigations undertaken by Vifor and the effectiveness of the recent direction given to representatives with regard to product safety profile comparisons (in response to Pharmacosmos' concerns raised in inter-company dialogue).

Pharmacosmos alleged there was a clear pattern that Vifor representatives had proactively raised concerns about the safety profile of Monofer, which was misleading because there were no head-to-head comparisons and the EMA's review of data concluded that there was no evidence to indicate differences between the available products.

Pharmacosmos concluded that whilst it had hoped that Vifor had adequately and appropriately addressed the six alleged cases of disparaging and misleading claims highlighted during inter-company dialogue, it was shocked and concerned to learn that this activity

had continued, as outlined in the nurse's first-hand account. The EMA had stated that anxiety of clinical staff could increase the incidence of adverse events and given the nature of Vifor's alleged activities this was likely to have a direct impact on staff's confidence with Monofer and therefore put patients' lives at risk.

Pharmacosmos informed the Panel that it had cited an incorrect reference in its original response. Pharmacosmos referred to the EMA in relation to a review which linked clinical staff's anxiety in administering intravenous (IV) irons to an increased reporting of adverse events. Pharmacosmos stated that reference should have been made to the guideline article by Rampton *et al* (2014) which identified anxiety (patients or staff) as a factor increasing risk and/or severity of hypersensitivity reactions in patients given iron infusions.

In response to a request for further information, Pharmacosmos stated that the referenced incidents of alleged disparaging and misleading claims by Vifor representatives had all been raised verbally to Pharmacosmos by health professionals. To provide further context to what and how the information was shared with Pharmacosmos the relevant members of the Pharmacosmos team were asked to provide written statements, copies of which were provided. For completeness, Pharmacosmos provided statements to each case referenced in its complaint and noted that it had anonymised the names of the health professionals as it did not have their permission to identify them. Pharmacosmos further stated that it was its interpretation that 'information from [named] Hospital' related to Grant *et al* that described an audit of Monofer at that hospital.

RESPONSE

Vifor stated that it was committed to adhering to the Code and was disappointed to receive a complaint from Pharmacosmos. Vifor noted that Pharmacosmos refused to cooperate with the industry's self-regulated complaints process in Case AUTH/2694/1/14 and made it very clear that it had never considered that it was included on the list of those companies that agreed to comply with the Code. Vifor was concerned that a company that had clearly, and publicly, stated it would not agree to abide by the ethical regulations of the Code operated in its therapeutic area as a competitor.

Notwithstanding this situation, Vifor accepted that compliance with the Code was of critical importance to the successful relationship between industry, health professionals and the public as a whole and accepted that it had a responsibility to uphold the highest standards at all times.

Vifor submitted that it appreciated the seriousness of any such allegations and had thoroughly investigated the points detailed in the complaint. All representatives gave full accounts (copies provided) of each of the examples that Pharmacosmos, without substantiation, alleged took place. Vifor noted that Pharmacosmos alleged that it had breached Clauses 7.2 and 8.1 and responded as such.

Vifor noted some inaccuracies in Pharmacosmos' complaint which covered selected parts of the recent Code and regulatory authority discussions between the two companies. Firstly, Vifor strongly disagreed with Pharmacosmos' interpretation of the EMA report. The EMA concluded that any differences in safety in relation to hypersensitivity could not be established because some IV iron products did not have sufficient clinical data for meaningful comparative analysis. The statement that the EMA 'concluded that there were no meaningful differences in the safety profiles…' was incorrect. To confirm this, all IV iron marketing authorization holders throughout Europe were required by the EMA to conduct studies to gather safety data to confirm if any differences did exist.

Secondly, the reference to several past Code cases appeared to be an attempt to give credence to Pharmacosmos' submission that it had had long-running concerns about the activities of Vifor's representatives. Vifor noted that reference to these cases showed Pharmacosmos' inaccurate understanding of the reasoning behind the breaches ruled. Pharmacosmos' interpretation of Case AUTH/2422/7/11 was incorrect: Vifor was not ruled in breach for claims that dextran-induced hypersensitivity reactions were common with Monofer, but for claims solely in relation to Ferinject. The content of Case AUTH/2589/3/13, which was not upheld by the Panel, also reflected Pharmacosmos' lack of understanding of Case AUTH/2422/7/11. Vifor queried why not being found in breach should be cited as an illustration of a pattern of non-compliant behaviour.

Vifor assumed that Pharmacosmos was trying to negatively influence the Panel's view of Vifor by citing past cases and an ongoing case which was the subject of PMCPA review and inter-company dialogue and in so doing, disparaged Vifor. Vifor noted that there had also been several past (and ongoing) complaints against some of the promotional activities of Pharmacosmos but Vifor did not consider that these were relevant to the facts of this case.

Vifor had invested much time and resource into building a compliant culture and referred to the 'Compliance at Vifor' section from its new-starter training slides which showed the emphasis it put on maintaining that culture within the organisation. Not only did Vifor instil a compliant culture from the outset, but maintained it and regularly monitored compliance activities with internal audits, best practice sharing, discussion around recent Code cases (both in head office and the field), a compliance newsletter and a dedicated compliance website. Each of Vifor's regional sales teams had a regional compliance liaison member, volunteers were appointed to ensure the best possible sharing of good Code practice. Vifor submitted that the PMCPA was fully aware of the compliance activities Vifor undertook and the seriousness with which it took compliance with the Code and these had only been strengthened since the PMCPA audited Vifor's procedures in relation to the Code in October 2012.

With respect to the six exchanges by Pharmacosmos, Vifor submitted that the hospitals at issue were covered by four representatives, three of whom had passed the ABPI Examination.

In order to respond to the alleged breaches. Vifor appreciated that Pharmacosmos had not made specific allegations for each example cited but it considered that by responding to each in turn with specific details rather than unsubstantiated allegations, the PMCPA could be confident that there was no pattern of behaviour of disparaging or misleading comments as alleged.

Hospital 1

Vifor stated that representative 1 provided a thorough account of all activity on territory since joining Vifor (both face-to-face calls and meetings). The majority of discussions with health professionals focused solely on Ferinject. The one instance where a discussion about Monofer took place, the TAM used the relevant, fully certified SPC Comparator tool.

With regard to the alleged quotations, the TAM stated:

> 'The only explanation I can think of is that I have discussed Ferinject safety data and compared the safety data of Monofer with the SPC comparator reactively which states that due to limited data on Monofer the mentioned undesirable effects are primarily based on safety data for other parenteral iron solutions. This may have led to the health professional coming to the conclusion that there may be more side effects with Monofer based on the SPC Comparator.
>
> With regard to the dextran complaint – following my discussions around Ferinject's carbohydrate shell, some of my health professionals have initiated the question about dextran, and I have reactively answered more around the differences in the carbohydrate shells. I'm not sure which customers this complaint relates to.
>
> I would like to add that I have not knowingly disparaged and compared Ferinject vs Monofer. All my discussions have been based on company information and have been factual.'

Vifor noted that evidence of the above call records were available on request.

Hospital 2

Vifor stated that representative 1 provided a thorough account of all activity on territory since joining Vifor (both face-to- face calls and meetings). All of the discussions with health professionals focused solely on Ferinject. There was no instance recorded in the customer record management (CRM) system where a discussion about Monofer took place.

The same statement from the TAM applied here as it did above.

Hospital 3

Out of the four hospitals in this trust, representative 3 had only ever visited one while employed at Vifor.

The TAM in question researched all call reports and meetings in the CRM system and checked business mileage logs between January 2015 and February 2016 to establish when, if any, calls were made against customers of this trust in this time period.

The TAM stated:

> 'The last recorded call (face:face) in … against a customer in this trust was 24th February 2015, (well before the time period that Pharmacosmos are looking at), when 2 consultant haematologists and a transfusion practitioner was also seen. Discussions centered around the ongoing Ferinject formulary submission. There was no discussion about Monofer as they were solely about Ferinject and its current formulary application status at that time.'
>
> The last known date of travel to the … Hospital was .. August 2015 when the TAM stated 'No calls were recorded on this day in …. (CRM system) as I did not see anyone at the trust. An unsuccessful day in work terms.'

The search revealed that no meetings (departmental, stand or otherwise), in any therapy area, had ever been held by the TAM at the trust.

With regards to contacts with health professionals from the trust at other meetings, the TAM stated that between January 2015 and February 2016, there had been three large scale meetings where customers might have been in attendance:

- In June 2015, one consultant from the hospital visited the Vifor stand at the Digestive Disorders Federation Congress in London.
- At a stand meeting in July 2015, one specialist registrar attended (but had since rotated to another hospital).
- The TAM attended a regional meeting in October 2015 although no meeting contacts were recorded for anyone from the trust. Discussions at these meetings were about ensuring the appropriate use of Ferinject.

Vifor submitted that the TAM did not initially recognise the description of the 'publication in Gut regarding Monofer' but after conducting an internet search realised he/she knew of it by another name. The TAM was not aware it was published in Gut and had not presented the details of this publication to any health professional. The TAM stated:

> 'As stated above, there was no mention of Monofer as a product at [named] Trust, yet alone a discussion around a publication from Gut, in the time that I have been responsible for this trust and in the small number of calls made with health professionals from there. If it refers to any other Gut publication regarding Monofer then I don't know what the publication is.'

The TAM stated that the information given clearly demonstrated that this was a false allegation.

Hospital 4

Representative 3 for this trust was surprised and denied Pharmacosmos' claims.

The trust was not a target account for Vifor and so the TAM had never visited the hospital whilst employed by Vifor. Neither had the TAM spoken to any of the doctors or nurses at the trust about Ferinject or any IV iron product.

Looking back at all meetings in 2015, there was one consultant from the trust who attended a meeting in another hospital in November 2015 where the TAM was present. The TAM did not speak to the consultant at that meeting, nor did the TAM give a presentation to the group. Any conversations with other health professionals present centered around Ferinject and the current status (at the time) of the formulary application. There was no conversation about side-effects of any medicine, so it would be impossible for this health professional to have even overheard a conversation about side-effects.

The TAM did not recall any other discussions with a consultant from the hospital at any other venue.

More generally, with regards to alleged claims that the TAM claimed 'Monofer has a higher rate of adverse drug reactions than Ferinject' the TAM clearly stated that he/she would not make that statement as he/she did not know how many side-effects Monofer had. The TAM stated:

> 'It is the TAM's job to talk about Ferinject and that is the knowledge that I have. I am aware of Ferinject's tolerability profile and incidence of side effects, as described by Vifor Pharma. As I am unaware of the relative incidence of side-effects between the two products, it would not be possible for me to make the claim as suggested by Pharmacosmos.'

Vifor noted that evidence of the above call records were available on request.

Hospitals 5 and 6

Vifor submitted that these two allegations referred to alleged incidents that occurred in Ireland. The Irish country manager who in turn reported directly into the vice president & general manager, Vifor UK. Vifor was surprised that Pharmacosmos had included these incidents in its complaint. While Vifor accepted that compliance with the relevant country Code was critically important (in both the UK and Ireland) and was confident that its interviews with relevant staff had revealed that Pharmacosmos' unsubstantiated allegations were groundless, it would not be appropriate for Vifor to respond to the PMCPA about activities in Ireland. However, if necessary, Vifor would provide statements from the relevant staff about their activities in the centres in question.

Medical Information email sent to a nurse

Vifor submitted that this was currently the subject of Case AUTH/2828/3/16. The content of the response was also the subject of current inter-company dialogue with Pharmacosmos.

In Case AUTH/2828/3/16 the nurse asked for the TAM's business card and both verbally (supported by the account from a second Vifor employee present) and by email requested details of comparative safety data. A copy of these accounts plus the subsequent email correspondence were provided.

Vifor explained that following these requests, an email was sent to its medical information team requesting a copy of the Lareb report be sent to the complainant, which it subsequently was. Vifor stated that this report was the most appropriate document to send in light of the request for comparative safety data and the absence of any direct head-to-head clinical trial data on Ferinject and Monofer. This report came from a highly respected information source, The Netherlands Pharmacovigilance Centre, Lareb. Lareb collected and analysed reports of adverse reactions to medicines and vaccines. Health professionals, patients and also manufacturers could report an adverse reaction. Anonymous copies of reports were sent to the EMA and the World Health Organisation.

The specific report in question was entitled 'Intravenous iron preparations and allergic reactions'. It compared Ferinject, Monofer and Diafer and was not specific to only Monofer. It provided objective, factual line listing reports of allergic reactions to the three products. Vifor considered the report to be of good standing and relevant to health professionals. The report concluded that 'special attention should be given to the comparison of the safety profile of the different intravenous iron-containing medicines and in particular to the safety profile of iron isomaltoside'. The request by the Vifor representative to medical information specifically referred to 'Lareb' rather than 'intravenous iron preparations and allergic reactions' for ease of writing. Vifor representatives were aware of the existence of this report.

In addition to the responses above related to the instances cited by Pharmacosmos, Vifor highlighted the following:

- Vifor representatives were highly experienced and aware of the need to provide a balanced view to enable health professionals to make up their own minds on the therapeutic value of a medicine. Vifor submitted that they had not just acquired this knowledge through experience but this point was also made in Vifor's one day training session on adherence to the Code. Vifor noted that the relevant slide set listed the qualities that all promotional material must fulfil and made it clear that the Code applied to both written and verbal communication and that information provided should be sufficiently complete to allow recipients to make up their own minds about the value of a medicine.

- Vifor representatives received limited training on competitor products from the medical advisor during the initial training course (ITC). The training took the form of a workshop, with no materials other than SPCs. During this training they were verbally briefed not to discuss competitor products in detail beyond the SPC. This briefing included the instruction that for non-Vifor products, representatives had to refer a customer to the product's SPC. Vifor produced an SPC Comparator

and a Differentiator tool for use by representatives. Otherwise the customer was advised to contact the medical information department of the product market authorization holder. The representatives were instructed that the Vifor medical information department could not provide information on competitor products, only on Vifor products, unless there was comparative information which included Vifor products. The competitor SPC workshop took place for only two hours on day 9 of the 4 week ITC. This was compared to the ABPI compliance component of the ITC, which was one full day and included a quiz on individuals' knowledge of the Code.

- Vifor's Intravenous Iron Differentiator tool and the SPC Comparator were the only materials available to the representatives that mentioned Monofer. The slide on the comparison of dosing was based on the relevant products' SPCs. The Ferinject SPC was provided and Vifor stated that the Monofer SPC was available on Pharmacosmos' website. The contents of that slide and tool were fully substantiable from those SPCs and were certified for Vifor representatives to use. The tool was certified and first used in January 2016 so was up-to-date.

- Ferinject was the market leader in IV iron therapy and promotional tools and briefing materials provided an accurate and balanced view of the product. As evidenced in 'Questions and Answers, reactive responses to competitor messages', a document which was briefed to Vifor representatives at the sales and marketing conference on 19 January 2016, the last slide instructed all to 'Be professional, never disparage the competition', and 'Discuss the facts in an accurate and balanced way'. This briefing was part of the introduction to the Intravenous Iron Differentiator tool.

- During an open questions and answers session at the December 2015 sales conference, representatives were specifically reminded not to discuss the safety of competitor products. If a customer requested comparative safety data, they were briefed to inform the customer that the representative could not discuss such matters and offer a referral to medical information.

- Following the original inter-company dialogue that resulted in Case AUTH/2830/4/16, in the spirit of the Code, and as a reassurance to Pharmacosmos, an email was sent from the senior managers at Vifor to all representatives to reiterate what was stated at the December sales conference and confirming their obligations in relation to questions on the comparative safety of Ferinject.

Taking into account all of the above, Vifor denied breaches of Clauses 7.2 or 8.1.

Vifor submitted that it found no evidence from any representative that any negative statements about Monofer, particularly in relation to its safety, had been made.

Vifor did not know why Pharmacosmos had cited unsubstantiated anecdotal evidence from anonymous health professionals who coincidentally provided not just consistent but identical quotations across four of the six related examples. Vifor stated that it also did not know why Pharmacosmos had referred to past cases as well as ongoing inter-company dialogue. Furthermore, Vifor submitted that it was concerned about Pharmacosmos' apparent lack of knowledge of the Code and its misleading interpretation of the conclusions from the EMA report.

Vifor appreciated the opportunity to respond to Pharmacosmos' concerns and concluded that the weight of evidence showed there was no basis for any breach of the Code.

In response to a request for further information, Vifor submitted that Grant *et al* was included with an overview of all relevant papers in the 'Clinical papers' session of the ITC. A summary of that session was provided; no slides for the session existed. Vifor noted that the aim of including that information was to educate Vifor employees on the place Ferinject's data held within the broader context of other products. The emphasis was on Ferinject and representatives were instructed not to use the competitor data with customers unless the data contained information on a Vifor product.

Vifor explained that Grant *et al* was published as an abstract in Gut in September 2013. A medical update was provided at the December 2013 sales conference which included information on recent publications for Ferinject and Monofer and included, *inter alia*, Grant *et al*. The training session was for information only as stated on the cover slide (copy provided).

During inter-company dialogue in March 2014, Pharmacosmos queried whether Vifor representatives had used Grant *et al*. Vifor had no evidence that any representative had referred to the publication and concluded that the December 2013 conference had successfully addressed the article. In the spirit of inter-company cooperation, Vifor decided to brief all new representatives not to use the publication as it did not include information on Ferinject. The briefing took place during the clinical paper session of the ITC. Vifor submitted that its representatives had never used the article with health professionals.

Vifor submitted that it should have been clearer in its initial response; representatives were briefed to avoid discussing comparative safety data beyond the SPC. At the 2015 sales conference, as part of normal practice, representatives were again specifically reminded not to discuss the safety of competitor products; if health professionals asked for comparative safety data, representatives were briefed to refer them to medical information.

Vifor submitted that further evidence of this was that it only included safety information relating to the respective products' SPCs and Public Assessment Report (PAR) in the Q&A document (ref UK/FER/15/0274f). The PAR provided the

scientific discussion around the products' marketing authorizations and SPC contents. The Q&A document was confidential, for personal use only as indicated by the statement on the first slide, 'Confidential. Internal use only. Do not share or distribute.' It provided information that representatives might need to be able to reactively discuss facts in an accurate and balanced way by drawing on information from the respective products' SPCs. In addition to safety, the document also referred to price, clinical trial data, and a statement on the EMA IV iron report. There was no further briefing associated with the document.

Vifor explained that the SPC comparator was an app which could only be viewed on certain devices. The app was updated the week commencing 16 May due to some minor updates to several of the SPCs contained within it. It could still be appreciated how it would be used by a representative and viewed by a customer but the content might differ to that of the printed version provided.

Vifor also provided the briefing document for the differentiator tool.

PANEL RULING

The Panel noted that in 2014 Pharmacosmos UK had declined the offer to join the PMCPA list of non-member companies and no longer wished to accept the jurisdiction of the Authority but stated that it would continue to be fully committed to the ethical promotion of its products.

The Panel noted the comments from both parties regarding Cases AUTH/2422/7/11, AUTH/2589/3/13, and AUTH/2422/7/11 and noted that each case was considered on its own particular merits.

Turning to the current case, the Panel noted Pharmacosmos' allegation that Vifor representatives had disparaged Monofer in promotional calls in breach of Clause 8.1 and had provided misleading information in respect of Monofer safety in breach of Clause 7.2 by implying there was a difference in the safety profiles of Monofer and Ferinject when no formal comparison between the two products existed. Pharmacosmos provided six anecdotal examples and Vifor responded to each with specific details. The Panel did not consider these examples *per se* when making its ruling as Pharmacosmos had not made specific allegations for each example but had cited them to substantiate its concerns of a pattern of disparaging comments.

The Panel noted that in addition Pharmacosmos provided a medical information email it alleged was sent proactively (not in response to a request) by Vifor to a specialist nurse at a named hospital as evidence that Monofer had been disparaged. The medical information email was the subject of Case AUTH/2828/3/16. The medical information email stated:

> 'Thank you for your enquiry on Ferinject (ferric carboxymaltose: FCM). I understand from my colleague, [named], that you have requested a copy of the Lareb report.
>
> The Netherlands Pharmocovigilance Centre, Lareb, has received concerns from multiple Dutch hospitals in relation to iron isomaltoside after the switch from iron carboxymaltose (FCM). Doctors and nurses reported an increase in the severity and incidence of allergic reaction. The report has not mentioned any specific safety concerns with FCM.'

The Panel noted that the latter statement was untrue as the report detailed 7 reports of hypersensitivity/anaphylactic reactions associated with the use of Ferinject.

The Panel noted Pharmacosmos' disbelief that a typical UK health professional would be aware of the Lareb report, which was a specific pharmacovigilance assessment of Monofer made by the Dutch pharmacovigilance authority. Pharmacosmos had also submitted that it was difficult to understand why a health professional would proactively raise a request to receive a copy of that specific pharmacovigilance assessment. Pharmacosmos considered the provision of the Lareb report most likely occurred following a representative visit which included comments about the safety profile of Monofer.

The Panel noted Pharmacosmos' statement that an appraisal of material used to train Vifor representatives would corroborate its concerns because it was likely to draw attention to Monofer's adverse event profile.

The Panel noted Vifor's submission that during initial training, representatives were briefed not to discuss competitor products in detail beyond the SPC. This briefing included the instruction that for non-Vifor products, representatives had to refer a customer to the product's SPC. The Panel noted Vifor's submission that the Intravenous Iron Differentiator tool and the SPC Comparator were the only materials available to the representatives that mentioned Monofer. Otherwise the customer was advised to contact the medical information department of the product market authorization holder.

The Intravenous Iron Differentiator tool (ref UK/FER/15/0274a) was a slide set which specifically differentiated Ferinject from Monofer and which was according to the briefing material (ref UK/FER/15/0274e) designed to be used proactively in threatened accounts that were considering switching to Monofer and in accounts that had switched to Monofer. Two slides specifically compared the side-effects and contraindications of Ferinject and Monofer. The briefing regarding these two slides referred to confidence with Ferinject and in that regard implied a lack of confidence with Monofer. The briefing material stated, in summary, that 'The Ferinject proposition is strong, be confident, we have the best treatment'. In the Panel's view the briefing material was at odds with Vifor's submission that it did not permit representatives to discuss comparative safety in a promotional environment. The Panel noted Vifor's submission that the slide on the comparison of dosing was based on the relevant products' SPCs. The Panel noted that the slide also stated that the way in which the Monofer dose was calculated (the Ganzoni formula) was 'inconvenient,

prone to error, inconsistently used in clinical practice, and it underestimates iron requirements'. The briefing on this slide referred to Ganzoni-based dosing as being problematic.

A briefing document approved in January 2016 (Questions and Answers. Reactive responses to competitor messages, ref UK/FER/15/0274f) listed the comments and messages from customers regarding Monofer and stated 'What we need to do is reactively discuss the FACTS in an accurate and balanced way, to allow the customer to make an informed decision'. It was stated on one slide that one of the benefits of Ferinject, in an implied comparison with Monofer, was confidence because it was the market leader. The document included an explanation that the misconception of the competitor claim 'Reformulation, old Monofer had [adverse events], new formulation is better' suggested that Pharmacosmos acknowledged Monofer had a problem with adverse events as the only reformulation Vifor was aware of was Diafer which was simply half strength Monofer. The final message of the briefing document was again 'The Ferinject proposition is strong, be confident, we have the best treatment'.

In the Panel's view, there was no doubt that Vifor was specifically targeting Monofer sales and that the representatives had been briefed to discuss the comparative safety of Ferinject vs Monofer.

The Panel noted Vifor's submission that Grant *et al* was included with an overview of all relevant papers in the 'Clinical papers' session of the ITC. A summary of that session was provided; no slides for the session existed. Vifor noted that the aim of including that information was to educate Vifor employees on the place Ferinject's data held within the broader context of other products. The emphasis was on Ferinject and representatives were instructed not to use the competitor data with customers unless the data contained information on a Vifor product.

The Panel noted Vifor's explanation that Grant *et al* was published as an abstract in Gut in September 2013. Grant *et al* was an audit of case notes of 40 patients who had received Monofer. The authors concluded 'Utilisation of Monofer in our clinical practice has shown a sub-optimal attainment of Hb target. Furthermore, the frequency of adverse reactions was much higher than expected from those reported in the product SPC or previous studies in renal patients. In light of these observations we no longer use Monofer'.

A medical update was provided at the December 2013 sales conference which included information on recent publications for Ferinject and Monofer and included, *inter alia*, Grant *et al* and the authors' conclusion as stated above. The slide set for the session stated on the first slide that it was for internal use for training purposes. The cover slide did not state, as submitted by Vifor that the training session was for information only. The Panel considered that the slides contained material which Vifor would expect its representatives to use. No context had been given to the results from Grant *et al*.

The Panel disagreed with Vifor's submission that it only included safety information relating to Ferinject and Monofer in the Q&A document (ref UK/FER/15/0274) given that such comparisons appeared in the Intravenous Iron Differentiator tool and in the SPC Comparator tool. With regard to the latter, the Panel noted that the Ferinject and Monofer SPCs were being used by Vifor for a promotional purpose. The Panel noted that the briefing material stated that the tool had been designed to help representatives to directly compare different sections of the SPCs for the most prescribed IV irons including Ferinject and Monofer, it was to be used when asked specific questions about Vifor IV irons and those of its competitors. The briefing also stated that 'You can also project this from your iPad for use with multiple HCPs [healthcare professionals] at meetings'. There was no information on how to use the information provided in the tool and how to present the comparisons to a customer. The Panel noted Vifor's submission that representatives were briefed not to discuss competitor products in detail beyond the SPC. In the Panel's view, providing a tool which directly compared SPCs, implying that such direct comparisons of data were valid, went beyond that. The Panel also considered that the SPC Comparator tool went beyond the reminder given in December 2015 that representatives were not to discuss the safety of competitor products and that if a customer requested comparative safety data the request should be forwarded to medical information.

The Panel considered that on the balance of probabilities, given the strident tone and content of the sales materials and briefings, Vifor representatives had disparaged Monofer in promotional calls as alleged. A breach of Clause 8.1 was ruled. The Panel further considered that on the balance of probabilities, Vifor representatives had provided misleading information with regard to the safety of Monofer as alleged. A breach of Clause 7.2 was ruled.

APPEAL BY VIFOR

Vifor appealed the Panel's rulings of breaches of the Code.

Vifor reviewed the Panel's rulings, the material submitted as part of the complaint and also the additional evidence from Pharmacosmos that was not provided to it until after the rulings. Vifor submitted that despite requests that it do so, the PMCPA had not confirmed that Pharmacosmos would bear administrative charges if its complaint was unsuccessful. Nor had it provided Vifor with all the information requested in its notice of appeal, namely the Protocol of Agreement referred to in the introductory section of the Code [provided to Vifor on 11 August 2016] that set out the relationship between the ABPI and the PMCPA. Vifor requested sight of the Protocol of Agreement since it might help inform whether a non-member pharmaceutical company that had not submitted to the jurisdiction of the PMCPA – indeed one that had refused to accept a PMCPA ruling and had walked away from the self-regulatory scheme – could bring a complaint under the PMCPA process (and not be responsible for any

administrative charges). Vifor was unaware of this issue ever having been addressed specifically in a prior appeal. Vifor's notice of appeal referred to the 1997 Code of Practice Review because this was when the Protocol of Agreement first entered into force and the Review made clear that 'it is available on request'. The PMCPA did not provide Vifor with the Protocol of Agreement. Instead, it suggested that everything it needed to confirm the independence of the PMCPA was in Paragraph 1 of the Constitution and Procedure and the Introduction to the Code. However, these documents referred to the Protocol of Agreement which, unreasonably, had not been provided.

Nevertheless, Vifor gave its detailed grounds of appeal below and reserved its right to update or amend them as new material became available. Vifor's primary case was that the case preparation manager should not have presented the case to the Panel for review since Pharmacosmos did not have standing to bring a complaint through the Constitution and Procedure (see Ground 1: Pharmacosmos lacks standing). The Appeal Board's determination on this point would also be relevant to ABPI members and other non-members that had agreed to submit to the jurisdiction of the PMCPA. However, the fact that Vifor had raised the issue of standing should not be interpreted as implying that it did not wish to defend its position. If the Appeal Board found that Pharmacosmos did have standing, then Vifor appealed on the basis that the process conducted to date had been manifestly unfair given that key evidence from Pharmacosmos was disclosed to it only after the ruling was made (see Ground 2: Fairness). Regardless of these points, on the evidence submitted (and that Vifor had had an opportunity to respond to), Vifor argued that Pharmacosmos had failed to discharge the burden of proof (see Ground 3: Burden of proof).

Finally, Vifor submitted that, as noted in its notice of appeal, certain passages in the internal documents concerned were highly confidential and could not be shared with Pharmacosmos (although Vifor had provided redacted versions that could be shared). Vifor noted from the PMCPA's letter of 29 July '… the general principle is that anything which the respondent company wishes the Appeal Board to consider has to be made available to the complainant'. Whilst Vifor generally agreed (since this supported its appeal against the Panel's decision under Ground 2), this was subject to issues of confidentiality. As the documents in question were internal company documents that revealed commercial strategies of Vifor *vis-à-vis* Pharmacosmos, there was a presumption that such documents were confidential and should not be disclosed. Since these documents were not themselves subject to the specific allegations of breach, Vifor failed to see what value (other than competitive value) these documents could be to Pharmacosmos' case.

Vifor fully expected that Pharmacosmos would not object to the redactions. If, notwithstanding this, the Director had considered that she could not determine the matter and that she needed to seek the involvement of an independent referee, Vifor wished to understand who would bear the administrative cost for that given that the issue of administrative charges was a key plank of its argument under Ground 1. Also, given that Pharmacosmos had already refused to accept the findings of the Panel and had turned its back on the self-regulatory scheme, Vifor asked what safeguards would be put in place to ensure that Pharmacosmos kept the information confidential since there was nothing at all to bind Pharmacosmos to an independent referee's decision (this again went to Ground 1).

Grounds of Appeal

Ground 1: Pharmacosmos lacks standing

Vifor understood that Pharmacosmos was neither an ABPI member nor a non-member that had agreed to submit to the jurisdiction of the PMCPA. Indeed, it was a company that had previously flouted a Panel ruling. Vifor submitted, therefore, that the Constitution and Procedure must be interpreted as meaning that such pharmaceutical companies could not benefit from the ABPI's independent adjudication process and the benefits that went with it. Rather, on receiving information about Vifor's activities from Pharmacosmos, the PMCPA case preparation manager should have checked whether Pharmacosmos was willing to re-engage with self-regulation and submit to the jurisdiction of the PMCPA and if not, the company should have been advised to take the complaint up with the Medicines and Healthcare products Regulatory Agency (MHRA), or indeed the applicable Irish authorities in relation to some of the points raised.

Context of the standing position

As previously stated, Vifor had assumed that since Pharmacosmos lodged a complaint, that it was a non-member company that had voluntarily agreed to comply with the Code and accept the jurisdiction of the PMCPA. However, the Panel's ruling on this point was not clear. The Panel merely noted 'that in 2014 Pharmacosmos had declined the offer to join the PMCPA list of non-member companies and no longer wished to accept the jurisdiction of the Authority but stated that it would continue to be fully committed to the ethical promotion of its products'.

Vifor understood that if a pharmaceutical company wished to complain or respond to a complaint through the PMCPA process, that it had to be either a member of the ABPI, or a non-member that had submitted to the jurisdiction of the PMCPA. Vifor fell under the second category.

Vifor noted, in particular, that the PMCPA had considered in previous cases involving Pharmacosmos whether Pharmacosmos had accepted the jurisdiction of the PMCPA (Case AUTH/2694/1/14). The Panel's ruling in that case was disturbing. Pharmacosmos UK accepted the rulings of breaches of the Code but decided that it no longer wished to accept the PMCPA's jurisdiction or give the undertaking the PMCPA had requested. The PMCPA noted that Pharmacosmos had previously agreed to be on the list of companies abiding by the Code and accepting the PMCPA's jurisdiction and that it

would be required to report the company to the Appeal Board. However, Pharmacosmos UK argued that its parent company, Pharmacosmos A/S, had agreed to comply with the Code and that, because the UK subsidiary was not on the list, it was not possible to remove it and there was no basis for a referral to the Appeal Board. This was notwithstanding that, as the PMCPA noted, 'both in terms of complaints received **and complaints submitted** and in that regard both [Pharmacosmos UK and Pharmacosmos A/S] appeared to consider themselves effectively, if not formally, on the non-members list' (emphasis added).

Vifor noted that in a letter dated 25 July 2016, the PMCPA stated that its:

> 'Constitution and Procedure allows complaints to be submitted from any source … The position remains that Pharmacosmos was entitled to submit a complaint and the Authority acted within its Constitution and Procedure in accepting it.'

Vifor submitted that the assertion that the Constitution and Procedure allowed complaints to be submitted by any pharmaceutical company source was misguided as, in fact, there was no clear reference to this in the Constitution and Procedure. Rather, information received must be processed by a case preparation manager in accordance with Paragraph 5.1 of the Constitution and Procedure and that case manager 'determines whether a case should go before the Panel'. That determination did not benefit from unfettered discretion. The case preparation manager should not put a case before the Panel if the complaint was from a pharmaceutical company that was not a member of the ABPI or that had not agreed to submit to the PMCPA jurisdiction. This position was also supported by the Memorandum of Understanding between the ABPI, PMCPA and MHRA, which stated:

> 'Compliance with the Code is a condition of membership of the ABPI and, in addition, about 60 pharmaceutical companies that are not members of the Code have agreed to comply with the Code and submit to the jurisdiction of the PMCPA. Members of the ABPI and **non-members of the ABPI who have agreed to comply with the Code should send their complaints to the PMCPA**' (emphasis added).

Vifor submitted that this passage clearly implied that non-members which had not agreed to comply with the Code should refer their complaints to the MHRA. The fact that the memorandum also stated that the MHRA and PMCPA 'deal with complaints whatever their source' simply meant that with respect to companies such as Pharmacosmos, the PMCPA's case preparation manager should refer the matter to the MHRA.

Consequences of allowing Pharmacosmos to participate in the complaints process

(a) Gaming the system

The standing position of Pharmacosmos was vitally important for Vifor (and it assumed other companies in its position, as well as ABPI members). If the PMCPA allowed pharmaceutical companies which were not members and which had not accepted the jurisdiction of the PMCPA (or refused to abide by its findings) to complain, this could clearly lead to a gaming of the self-regulatory system to the detriment of ABPI members and companies like Vifor (which paid the associated administrative charges and so forth) – gaming that Pharmacosmos had shown it was quite comfortable with.

Vifor firmly believed in self-regulation and compliance with the Code, but the rules had to be respected by all pharmaceutical companies which wished to participate in the PMCPA complaints process and the benefits that went with that system of self-regulation, in particular ensuring a level playing field in terms of the rules and the speed of determining complaints. Vifor noted in particular the following comments from the Chairman of the Appeal Board, in the PMCPA Annual Report 2008:

> '… one of the strengths of the current procedure is that cases **are resolved relatively speedily**. That is as it should be; justice delayed is justice denied… Every effort is made to complete consideration of cases as quickly as possible and publish the outcomes. **Transparency and openness are key requirements to maintain confidence**. The detail given in the published case reports serves the industry well and **demonstrates that the system operates without fear or favour**' (emphasis added).

From Vifor's perspective, this meant that Pharmacosmos could lodge complaints about companies subject to the framework with the *quid pro quo* that Vifor was itself subject to the framework when complaints were made against it (and hence all parties benefited from consistent decision-making using a relatively quick adjudication process). For example, Vifor could complain about another company's use of promotional aids or its disclosure of transfers of value (and expect complaints in return if a competitor had a cause for concern). Conversely, companies like Pharmacosmos could similarly complain to the PMCPA without fear of challenge in return since those rules were entirely voluntary (ie, promotional aids were still legally acceptable provided they were inexpensive and there was no obligation to disclose further transfers of value).

Vifor further submitted that the system of administrative charges (which could be quite significant for non-member companies) could deter companies from making frivolous complaints. When Vifor asked how the administrative charges would be applied to Pharmacosmos, it was dismayed at the PMCPA's lack of transparency and openness in its answer ('[the] imposition [of administrative charges] is not relevant to the consideration of the merits of a case' – letter from PMCPA of 26 July 2016). This non-response went against the spirit of transparent decision-making that the Chairman referred to above. Also, the PMCPA fundamentally missed the point. Vifor could appreciate why the imposition of administrative charges might not be relevant to the merits of a specific case, but the failure to address this point meant that Vifor was no longer confident that the PMCPA operated 'without fear or favour'.

Vifor noted that, as stated by the PMCPA, administrative charges were a contribution towards the general running costs of the Authority. If companies like Pharmacosmos could make a series of complaints that were unsuccessful, the cost of those complaints was borne by ABPI member companies and non-member companies who submitted to the jurisdiction of the PMCPA. That was simply unfair and Vifor could not imagine the ABPI Board would fully support that without debating the issue amongst its membership. The situation was completely different of course for complaints from outwith the industry, ie from health professionals, ex-employees, patient groups, the media, etc, since it was quite right that legitimate complaints from such groups should be covered. Indeed, this was why pharmaceutical companies paid administrative charges and those from outwith the industry did not.

For the avoidance of doubt, Vifor did not advocate that Pharmacosmos be deprived of any or all regulatory recourse in instances where it had a complaint about a competitor company. In fact, Pharmacosmos had such recourse at its disposal in that it could complain to the MHRA which administered UK law on behalf of the Health Ministers.

(b) Procedural safeguards during the PMCPA adjudication process

Vifor was also very concerned that a pharmaceutical company complainant which did not submit to the jurisdiction of the PMCPA would not be obligated to comply with the rules of the complaints procedure some of which were more subtle than what was written in the PMCPA Constitution and Procedure. For example, the Panel had made clear that 'Self-regulation relie[s] upon a full and frank disclosure of the facts' (Case AUTH/236610/10). For the reasons mentioned above regarding Pharmacosmos' precarious status as a complainant, it was impossible to guarantee that Pharmacosmos' complaint and documentation sent to the PMCPA was based on a full and frank disclosure of events, nor was Pharmacosmos bound to deliver as such nor were there any consequences should it not do so.

Vifor was also very concerned about documents that it had submitted in response to this complaint being sent to Pharmacosmos without any clear confidentiality undertakings being in place. Indeed, as set out above, Vifor still did not have any assurance from the Panel or from Pharmacosmos that it would respect the decision of an independent referee in deciding which of its documents were confidential or not (nor did it know who would bear the administrative cost of that procedure). [Vifor was informed that the costs of referring matters to an independent referee were paid by the PMCPA].

Ground 2: Fairness

Vifor stated that during a telephone discussion on 19 July 2016, it became clear that the Panel had not shared evidence in support of Pharmacosmos' complaint with Vifor prior to the Panel's ruling. On 21 July, the PMCPA disclosed the additional information, which comprised emails from individuals within the company that purported to provide an account of what health professionals had told Pharmacosmos about Vifor's conduct in various parts of the country.

Vifor was extremely concerned that the Panel ruled against Vifor on the balance of probabilities without giving the company an opportunity to review and, if necessary, comment and respond to that evidence. This was manifestly unfair, particularly in proceedings of this kind and was best characterised by Lord Denning in one of the leading cases in this area that the accused person:

> 'must know what evidence has been given and what statements have been made affecting him; and he must be given a fair opportunity to correct or contradict them ... **It follows, of course, that the judge or whoever has to adjudicate must not hear evidence or receive representations from one side behind the back of the other. The court will not inquire whether the evidence or representations did work to his prejudice, sufficient that they might do so. The court will not go into the likelihood of prejudice. The risk of it is enough**' (emphasis added).

Vifor submitted that in not making available the specific allegations and the evidence purporting to support those allegations, the Panel had breached a fundamental principle of natural justice that provided a party a right to respond to the charges (Vifor referred to Tudor v Ellesmere Port & Netson Borough Council (1987) Times, 8 May). Moreover, the process had frustrated Vifor's ability to provide a 'complete response' to the complaint, in accordance with Paragraph 5.2 of the Constitution and Procedure.

Vifor submitted that this position was also true in the criminal context. The Court of Appeal had made clear that being deprived of the opportunity of producing further evidence was fundamental and 'is not a matter of mere procedural nicety' (Musone v R [2007] EWCA Crim 1237).

Vifor submitted that had this information been disclosed during the proceedings, it would have commented upon and corrected such evidence and responded to it with its own evidence, including call reporting records and, if necessary, statements from company representatives corroborated with a statement of truth.

Ground 3: Burden of proof

Vifor submitted that the Panel found it in breach of Clauses 8.1 and 7.2 on the basis that the material provided by Pharmacosmos evidenced a 'pattern' of disparaging comments about Monofer. This decision was irrational since all of Pharmacosmos' evidence was anecdotal and Vifor had fully rebutted all but one point (and this was a point already accepted to some extent in Case AUTH/2828/3/16, in which Vifor had accepted that the manner in which the Lareb report was distributed and the manner in which the content of the report was described could have been better. Vifor had since changed the relevant processes and the manner in which it described the Lareb report).

Vifor submitted that a 'pattern' of behaviour must, on any sensible interpretation, mean more than an isolated incident. It suggested a company-wide pattern of non-compliance which could not be further from the truth. The Panel referred to three previous PMCPA cases in support of its conclusion that there was a 'pattern' of inappropriate behaviour. However, two of the cases the Panel cited were over 5 years old and the more recent case did not result in a finding of breach. Vifor did not accept that this evidenced a 'pattern', as the Panel suggested.

Vifor stated that it was committed to adhering to the Code. Vifor accepted that compliance with the Code was critically important to the successful relationship between industry, health professionals and the public and it was Vifor's responsibility to uphold the highest standards at all times.

Vifor submitted that the PMCPA was fully aware of the company's compliance activities and the seriousness with which Vifor took compliance with the Code and these had only been strengthened since the PMCPA audited Vifor's procedures in relation to the Code in October 2012. Vifor had invested much time and resource in building a compliant culture and many key staff, attached a great importance in maintaining this. Vifor stated that the Panel's comments about the requirements of Clause 15.4 had already been incorporated into its Field Force meetings SOP as this was under review when Vifor received the comments. Specifically, Vifor had:

- Code of Practice training for all new starters
- Regular review of SOPs
- Internal audits
- Regular 'Lunch and Learn' sessions covering PMCPA cases
- Regional compliance liaisons (an individual from each regional team who worked closely with compliance and ensured effective communication of compliance-related information)
- Quarterly 'Getting it Right' compliance newsletter
- Vifor Code compliance site
- Advanced Code training for Marketing and Medical
- Final signatories forum
- Externally led training sessions for key staff
- Electronic training system.

With this in mind, Vifor simply did not understand how the Panel arrived at a decision that suggested there was a pattern of non-compliance behaviour. The decision should therefore be set aside on the basis that Pharmacosmos had failed to discharge the burden of proof on the balance of probabilities. The evidence in support was not supported by verifiable evidence and based on anecdotal hearsay; further the Panel's interpretation of Vifor's documents provided in response to the complaint was flawed. In Case AUTH/2824/2/16, the Panel had to determine whether there was sufficient evidence to substantiate the allegation that representatives went to a named location contrary to the terms of a verbal undertaking. The Panel found there was no evidence to substantiate the complainant's allegations that the representatives visited the named location and therefore no breaches were ruled. The essence of this case was to demonstrate the difficulty of substantiating an event where there was competing anecdotal or hearsay evidence. Allegations should be substantiated. Such allegations were not substantiated in Case AUTH/2824/2/16 nor were they substantiated in this case. Examples included:

- Two of the cases relied on by the Panel were from Ireland and, therefore, irrelevant to the issue before the Panel but yet the decisions were quoted at length in purported reliance on them and as evidence of a 'pattern' of UK behaviour. Vifor Ireland was a separate, independent company with its own country manager and these components should have been disregarded from the outset, as had been requested by Vifor.

- In two of the cases, Vifor's documented call records and representative statements confirmed that no Vifor calls were made in the institutions mentioned within the relevant time period. In Case AUTH/2824/2/16 the Panel confirmed the acceptability of representative call records as evidence of non-activity. The Panel ignored this material evidence in favour of uncorroborated, anecdotal hearsay from a company not bound by the rules of full and frank disclosure.

- In another two cases, Vifor had found no evidence from the one representative concerned that he/she made any negative statements about Monofer, particularly in relation to its safety. The accounts of this representative were provided.

- One case related to the distribution of the so-called Lareb report. The company had already accepted a ruling in relation to the medical information process of sending the Lareb report in a parallel case (Case AUTH 2828/3/16) brought by the health professional concerned. But the Appeal Board would also be aware that Vifor was also appealing all other rulings in that case and it had its own unique set of facts. In any event, a single isolated incident (which must be taken in context) could not on any reasonable view support a finding of a 'pattern of behaviour.

Vifor submitted that the Panel appeared to have placed significant weight on the balance of representative briefing documents which it suggested had led to a pattern of behaviour that would lead representatives to denigrate Monofer. In doing so, the Panel reproduced a number of allegations by Pharmacosmos, without ever checking their accuracy or plausibility. The Panel restated Pharmacosmos' assertion that 'an appraisal of the material used to train Vifor representatives would corroborate its concerns because it was likely to draw attention to Monofer's adverse event profile in a misleading manner. Pharmacosmos alleged that the training material would link the dextran-derived nature of the Monofer molecular structure to a higher (alleged) propensity to adverse events, which is misleading'. Yet none of Vifor's briefing materials (all of which had been provided to the Panel) referred to dextran, the nature of the Monofer molecular structure or a higher propensity to adverse

events. Rather than simply appearing to accept this allegation for which no evidence whatsoever was found, the Panel should have weighed this inaccurate statement when determining whether Pharmacosmos had discharged its burden of proof and indeed whether the complaint might in some respects be vexatious.

However, Vifor submitted that it had been at pains to emphasise that its representatives were briefed not to discuss comparative safety data beyond the SPC. The SPC held key information approved by the regulatory body and the information contained within the SPC was, therefore, accurate, balanced, fair, objective and unambiguous and based on an up-to-date evaluation of all the evidence. Vifor did not draw any of its own conclusions from the SPC comparison but presented the data side-by-side (as in the SPC comparator) to allow health professionals to make their own decisions. Vifor was therefore perplexed by the Panel's ruling that the SPC comparison tool was misleading. It was merely a side-by-side restatement of the terms of the products' approved SPCs to be used as a basis for discussions with health professionals and to assist in responding to their questions. Vifor had not extracted portions of either SPC or presented them in a promotional manner.

In relation to the iron differentiator, Vifor submitted that it provided an accurate, balanced and up-to-date reflection of the evidence in this document. Vifor had summarised every Phase 3 and 4 trial in the listed therapy areas for each product and presented each in the same way so that health professionals could judge the clinical trial data for themselves. The date of last update was included on the overview slide to demonstrate that it was up-to-date. The differentiator tool acknowledged in a number of places that there were no head-to-head comparisons of the two products. The information about dosing and infusion was referenced to the product SPCs. The statement about the Ganzoni formula was clearly referenced to an independent, expert group. The sections on tolerability – undesirable events and contraindications – were referenced solely to the product SPCs. All of this information was factual, verifiable and fully substantiable.

Vifor therefore encouraged the Appeal Board to read all of its briefing material and not merely the statements selected by the Panel which had been misinterpreted and taken out of context to suggest a culture of non-compliance within the company when the opposite was true.

Vifor submitted that given the briefing materials, the Panel's decision was not reasonable and it encouraged the Appeal Board to read the materials at issue in full. The Panel appeared to have focussed almost exclusively on the phrase 'The Ferinject proposition is strong, be confident, we have the best treatment'. This phrase was found at the very end of one of many extensive briefing documents (ranging from 14 to 26 pages in length) and so needed to be read in context of the document as a whole and previous historical briefing documents.

Vifor submitted that UK/FER/13/0201 dated back to 2013 but it gave an objective overview of changes to the SPCs for both Ferinject and Monofer and recent clinical studies within the relevant therapy area and concluded (without any mention of Monofer) with the fact that '… we have the most documented evidence …'.

Vifor submitted that UK/FER/15/0015b was created in mid-2015 to introduce the SPC comparator, which was a simple factual re-representation of the SPCs of all the products in this therapy area. It did not edit or comment upon the content and the representatives were simply directed to '…use when asked specific questions about the [Vifor] irons and those of our competitors…' which again illustrated the objectivity of the material provided. Vifor remained perplexed as to why the Panel took exception to the instruction '…you can also project this from your iPad for use with multiple HCPs at meetings …' as this was common practice within the industry.

Vifor noted that the Panel ruling commented on a briefing document UK/FER/15/0279 which stated:

> 'Five accounts had switched from Ferinject to Monofer. No reason was stated for the switch but it was reasonable that representatives would assume that it was to do with safety and tolerability given that was the heading to the slide.'

Vifor submitted that it was appropriate to share information and knowledge about events and developments in the market with its representatives. All of the content on the briefing slide in question was factual and accurate. The representatives invariably discussed occurrences such as this between themselves. The purpose of providing this sort of update was to prevent inappropriate use of such knowledge. The briefing document did not state why the cited accounts had switched from one product to another, nor did it instruct the representatives to proactively use this information with health professionals.

Vifor submitted that UK/FER/15/0274a, Ferinject Differentiation from Monofer slide set, and its accompanying briefing document (UK/FER/15/0274e) were created in January 2015 [sic, it was certified in January 2016] for use at a sales conference. These covered in depth randomised clinical trials in the relevant therapy area and the respective products' SPCs. The associated briefing document was objective and factual and whilst it instructed that the slides were designed to be used in accounts that were considering, and in accounts that had switched to, Monofer nothing in either the slides or briefing document was inconsistent with the facts of either the clinical trials or SPCs of the products in question and representatives were encouraged '…if additional information is requested, complete the Medical Information request form' (the Panel's comments on the statement '… The Ferinject proposition is strong, be confident, we have the best treatment …' were addressed below). Vifor supported its statement that the Ganzoni formula used to calculate the Monofer dose was '…recognised as

inconvenient, prone to error, inconsistently used in clinical practice, and it underestimates iron requirements …The briefing on this slide referred to Ganzoni-based dosing as being problematic …'. Ganzoni-based dosing was problematic and it was not misleading to say so, as substantiated by the citation supporting this conclusion.

Vifor submitted that the briefing document UK/FER/15/0274f was also created for the January 2015 [sic, it was certified in January 2016] sales conference and was a pivotal document in both the PMCPA's interpretation of the actions Vifor had allegedly encouraged its representatives to take and in Vifor's defence. It was important to read this document in full. The heading of the briefing was 'Reactive Responses to Competitor Messages'; the first slide of the document was headed 'Customer Reported Monofer Messages' and listed below the headline were 10 comments that prior to the conference Vifor representatives had informed the company that customers had reported to them as being told to them by Monofer representatives and requested clarity upon.

Vifor submitted that the first slide of the deck clearly stated '…what we need to do **reactively** is to discuss the **FACTS** in an accurate and balanced way, to allow the customer to make an informed decision …' (bold not added). The remainder of the briefing document then covered each one of the 10 reported misinformation topics and presented the facts regarding this misinformation in a clear, objective, fully compliant appropriate way. The summary slide should also be considered in full. It stated:

- Be professional, never disparage the competition
- Discuss the facts in an accurate and balanced way
- If the customer wants extra information on Ferinject, offer the Medical Information service
- Following this advice will build the customers credibility and respect for you
- The Ferinject proposition is strong, be confident, we have the best treatment.'

Vifor submitted that the single, final summary statement could not render all of its briefing materials as 'strident' or disparaging of Monofer. This final statement was simply the logical progression of all the previous information; it reinforced to the representatives that if they concentrated on the facts in an accurate and balanced way and acted professionally they would build credibility and respect with their customers, not disparage the competition and have confidence that their customers would choose Ferinject because the facts would illustrate that Vifor had the best treatment. The statement itself was purely motivational for internal use and appeared in no promotional materials. If the Appeal Board considered that this type of statement could not be included in context in its internal communications, it would appreciate a thorough explanation in the case report for transparency purposes. Statements such as these were commonly used in the industry (and by the ABPI itself) to motivate the salesforce or employees more generally by instilling belief in the company, the product or services. An appropriate and every-day analogy would be where motivational speeches or 'pep-talks' were given on staff appreciation or away-days. It was important to note that neither the statements such as the ones complained of nor the analogous examples offered here prevented or precluded representatives from discussing comparative safety in a promotional environment. The statement did not directly or indirectly advocate either directly or indirectly any course of action which would be likely to lead to a breach of the Code.

Given the above, Vifor did not consider, that Pharmacosmos had discharged the burden of proof with respect to its allegations. In fact, by the Panel's own admission, Pharmacosmos had provided 'anecdotal examples' to 'substantiate its concerns'. Vifor submitted that anecdotal, unsubstantiated examples could not be given weight over verified, documented evidence.

Vifor submitted that the Panel acknowledged in its ruling that the appropriate standard was the 'balance of probabilities'. Vifor noted the burden of proof in the civil litigation context where 'the standard to be attained in most cases was that the court must be satisfied "on a balance of probabilities"' that the client's allegation was correct. In Miller v Minister of Pensions [1947] 2 All E.R. 372, QBD, Denning J. explained this as (at page 374):

> 'If the evidence is such that the tribunal can say "we think it more probable than not", the burden is discharged, but if the probabilities are equal, it is not.
>
> In essence, in order to satisfy the judge that one party's version of the events is the version to be accepted, the judge has to be convinced that this version is more likely than not to be true-that the balance of evidence is tilted in the client's favour. If this were to be expressed in simple mathematical terms, at least a 51 per cent probability in favour of the client must be demonstrated, as suggested by Lord Simon in Davies v Taylor [1974] A.C. 207, HL (at p.219). If, on the other hand, the client's version is just as probable as the opponent's version, the client has failed to discharge the burden of proof.'

Vifor submitted that at worst, its version of events was just as probable as that put forward by Pharmacosmos. In any event, Pharmacosmos had not demonstrated its evidence discharged the burden of proof on the balance or probabilities assessment, nor was the Panel entitled to rule as such.

Vifor noted that in Case AUTH/2572/1/13 the Appeal Board had had to consider the burden of proof and it indicated that where 'it is not always clear how/whether the material supported the complainant's allegation … the Appeal Board [had] to decide how much weight to attach to this evidence'. In that case, the Appeal Board considered that extracts from emails and excerpts from published papers were insufficient evidence and did not provide a 'fair and balanced reflection of the evidence available at the time'. The Appeal Board made it clear that where the

complainant failed to marshal sufficient evidence to discharge the burden of proof, there should not be a ruling of a breach.

> '[where] there is insufficient provided by the complainant …. The Appeal Board considered that the complainant had not discharged its burden of proof and it upheld the Panel's ruling of no breach ...'

Vifor submitted that this reflected a general and widely-acknowledged strand in the law of evidence that 'the weight of evidence depends on the rules of common sense' (R. v Madhub Chunder (1874) 21 W.R Cr. 13 at 19 (Ind) per Birch J).

Vifor submitted in conclusion that it was impossible, on a common sense view, to make a finding against it based on Pharmacosmos' evidence.

COMMENTS FROM PHARMACOSMOS

Pharmacosmos noted Vifor's appeal in relation to alleged disparaging and misleading claims about Monofer. In summary:

- Pharmacosmos agreed with the Panel's ruling. Vifor promoted Ferinject in a manner that was both misleading and disparaging;

- Pharmacosmos understood that there was a need for greater clarity in the process and it commented below in respect of Vifor's appeal submission.

The following sections addressed key considerations.

1 Panel's ruling

Pharmacosmos stated that in essence, the Panel determined that Vifor had presented the comparative safety profiles of Ferinject vs Monofer in an inappropriate manner that was disparaging and misleading.

Pharmacosmos stated that it had initiated inter-company dialogue because reports from health professionals indicated a centrally-driven message being disseminated by Vifor representatives. Such central messaging was difficult for a competitor to prove as most complaints relied on the written sales material. In an increasingly digital age such evidence was difficult to obtain. Pharmacosmos first attempted to resolve the matters by inter-company dialogue with Vifor leading to Pharmacosmos' initial acceptance of the actions communicated. (For further comments in relation to the inter-company exchanges see Section 2, below).

Pharmacosmos subsequently escalated its concerns to the PMCPA. Pharmacosmos did not make specific allegations concerning the examples cited in its previous correspondence with Vifor as it accepted that the PMCPA did not consider anecdotal reports *per se*. As stated, the allegation was that there was a pattern of similar activities, and it was important to demonstrate how Pharmacosmos had attempted to resolve matters through meaningful inter-company dialogue in the first instance as well as why it concluded that inter-company dialogue had failed.

When Pharmacosmos received the report from the nurse, in March 2016, it concluded that, on the balance of probability, it was unlikely that the three Vifor employees named (the representative, the regional business manager and the person from medical information), would have acted in the way they did if the supposed communication from senior Vifor directors to their teams less than two weeks earlier had been effective. As a consequence, Pharmacosmos lost confidence in previous statements made during inter-company dialogue.

Thus Pharmacosmos had urged the PMCPA to look at Vifor's training material. The PMCPA subsequently uncovered both training material and promotional material that directly and misleadingly compared Ferinject and Monofer. It was important to note the nature of the evidence cited by the Panel in ruling breaches of Clauses 7.2 and 8.1:

- Vifor's Intravenous Iron Differentiator tool
- Vifor's SPC Comparator tool
- The existence of these documents despite Vifor's submission that representatives did not discuss relative safety profiles
- Vifor's lack of clear briefing in how to use these tools appropriately
- Vifor's use of these documents specifically in accounts 'threatened' by Monofer
- That representatives were specifically targeting Monofer sales and had been specifically briefed to compare the side-effect profiles
- Vifor's failure to instruct sales representatives not to use material and information that had been provided to them (eg Grant *et al*)
- The 'strident tone' of Vifor's sales materials and briefings.

Pharmacosmos noted that Vifor's appeal stated that it could not recognise the pattern of non-compliant behaviour cited by Pharmacosmos owing to Vifor's credible compliance programme. Pharmacosmos alleged that this, perhaps, missed the point. Pharmacosmos merely argued that the pattern of attacks against Monofer's safety profile suggested central coordination and that this specific activity was non-compliant; the Panel's findings confirmed its allegation. It must be up to the authorities to decide whether Vifor's compliance system was effective or not.

Pharmacosmos noted that Vifor's appeal relied at least in part on explaining the specific circumstances surrounding the individual anecdotal health professional comments cited. However, Pharmacosmos submitted that was not the point; the main issue was that, in addition to the anecdotal reports, the material provided by Vifor was inappropriate and thus likely to directly lead to comments like those cited. Even if the dates cited did not exactly match the call reports of Vifor representatives, the simple truth was that Vifor representatives disseminated messages issued by Vifor's central office. Pharmacosmos made it clear in its complaint that it was more concerned with the pattern of disparaging and misleading behaviour than with the actions of individual representatives. The Panel's identification of the existence and use of

the Intravenous Iron Differentiator tool and the SPC Comparator tool confirmed its suspicions that Vifor representatives were directed centrally to compare the products in a misleading and disparaging manner. This was especially true given that these two tools had been issued and used in contradiction to the 'briefing' issued to Vifor representatives in 2015 that questions regarding comparative safety were to be referred to its medical information department. The accounts from the representatives interviewed by Vifor confirmed that they actively used the SPC Comparator and the Intravenous Iron Differentiator tools and also identified concerns with Monofer, rather than solely promoting the merits of their own product *per se*.

Pharmacosmos alleged that Vifor's appeal addressed the direction that Vifor representatives should be confident because they 'had the best treatment'. Pharmacosmos agreed that this was a motivational statement, however, Vifor failed to recognise that without substantiating evidence it was also misleading those representatives. As stated in the appeal:

> '… customers will choose Ferinject based on the facts as the facts will illustrate that we have the best treatment.'

Pharmacosmos alleged that this degree of belief in the product was admirable. However, if Vifor could not recognise the lack of comparative evidence (facts) to prove this point, then it was clear that the representatives were being instilled with a similar perception that did not recognise the relative merits of the clinical data that existed individually for the two products.

Pharmacosmos alleged that as it highlighted in its appeal, Vifor seemed not to understand that a side-by-side comparison of two SPCs was not a relevant clinical comparison. In fact, as the Panel indicated, Vifor clarified that it had not instructed its representatives in how to use the SPC Comparator tool – it simply asked them to show the SPCs and 'allow health professionals to make their own decision'. This was at the crux of the matter and appeared to be a key point in this case. Vifor did not recognise that the provision of information in this context was a promotional activity; or that clinical comparisons were necessary to promote clinical conclusions about the differences between products.

Pharmacosmos stated that further, the single example of the use of the Lareb report was not to be dismissed as Vifor suggested, but should be regarded as an example of the type of approach being employed by Vifor. In its appeal, Vifor clarified that it would continue to use the document, albeit in an amended form; thus issuing the Lareb report was not an isolated incident as Vifor contended.

Pharmacosmos alleged that Vifor's response to the Panel seemed to suggest that in the absence of head-to-head data, Vifor was entitled to selectively provide the Lareb report in order to build a perception of comparative differences between Monofer and Ferinject:

> 'This report was the most appropriate document to send in light of the request for comparative safety data and the absence of any direct head to head clinical trial data on Ferinject and Monofer'.

Pharmacosmos was concerned about the provision of the Lareb report in isolation because the data lacked context and failed to acknowledge the existence of contradictory reports from other health authorities, such as a Swiss Medic report which highlighted a high incidence of adverse drug reactions when Ferinject was introduced as new alternative IV iron in Switzerland.

Pharmacosmos also noted that when the Vifor representative wrote to the Vifor medical information department, the request was specifically for the provision of the Lareb report; it was not a request for the wider comparative safety data requested by the health professional. This was important because it showed that:

- Vifor representatives knew enough about the Lareb report to request it specifically
- Vifor medical information was not surprised to receive a request for this specific report, which implied it was not an unusual occurrence
- the Vifor representative concerned had deliberately requested a document that presented an unbalanced view of Monofer.

Pharmacosmos submitted that Vifor's provision of the Lareb report was clearly not in line with its inter-company commitment that requests for data about Pharmacosmos' products would be redirected to Pharmacosmos' medical information.

2 Inter-company dialogue

Pharmacosmos submitted that it had lost faith in the value of Vifor's commitments made during inter-company dialogue. The PMCPA was aware that, in the spirit of inter-company dialogue, Pharmacosmos had written to Vifor (16 February 2016) concerned about claims allegedly made by Vifor representatives in relation to the respective safety profiles of Monofer and Ferinject. The specific concerns were based on a number of incidents proactively brought to Pharmacosmos' attention by health professionals, and it had therefore strong reason to believe that disparaging and misleading claims were being made about Monofer by at least some Vifor representatives. In its response to Pharmacosmos dated 3 March 2016, Vifor stated that all its representatives:

> '…have been trained to forward any questions relating to the safety of Ferinject that go beyond the Summary of Product Characteristics or the comparative safety of Ferinject to our Medical Information Department.'

Vifor continued:

> 'As my colleague, [named] has stated in previous communications with the Pharmacosmos UK Medical Team, if we were to receive any questions relating to the comparative safety of Monofer

through Medical Information, the enquirer would be asked to contact Pharmacosmos Medical Information in relation to Monofer as there are currently no comparative data.'

Pharmacosmos alleged that however, it was clear from the evidence in this case that representatives had directed Vifor's medical information team to provide specific comparative data and had specifically requested the Lareb report. However, the Lareb report was not designed to provide comparative evidence.

Pharmacosmos alleged that with the information and materials exchanged between Vifor and the PMCPA as well as the communication by the medical information at Vifor it furthermore appeared that, contrary to Vifor's statement in inter-company dialogue that:

- Vifor intentionally briefed and enabled its sales team to make comparative claims between Ferinject and Monofer using its SPC Comparator tool and Intravenous Iron Differentiator tool;

- Vifor's medical information department made no attempt to refer enquirers to Pharmacosmos' medical information for information about Monofer. Instead the Vifor medical information officer proactively communicated safety information about Monofer to the named nurse, which was cherry-picked to be intentionally disparaging and completely ignored the specific safety reports related to Ferinject:

  'The Netherlands Pharmocovigilance Centre, Lareb, has received concerns from multiple Dutch hospitals in relation to [Monofer] after the switch from [Ferinject]. Doctors and nurses reported an increase in the severity and incidence of allergic reaction. The report has not mentioned any specific safety concerns with [Ferinject].'

Pharmacosmos submitted that these two points contradicted an inter-company confirmation that a communication from two senior Vifor directors was:

'… sent to all Vifor Pharma representatives in both the UK and Ireland confirming their obligations in relation to questions on the comparative safety of Ferinject.'

Pharmacosmos stated that another example of Vifor's seeming failure to adhere to commitments made in inter-company dialogue related to the continuous use of the GUT abstract by Grant *et al*. The PMCPA was aware that Vifor confirmed during inter-company dialogue in February/March 2014 that Vifor representatives would neither proactively nor reactively communicate this abstract. This had been agreed because the abstract, based on a single hospital audit, did not represent the balance of evidence. Despite its commitment, Vifor confirmed in its letter to the PMCPA dated 23 May 2016 that the company had continued to systematically introduce the abstract as part of its ITC for all new sales representatives. In the letter Vifor explained:

'The Grant *et al* publication in Gut is included with an overview of all relevant papers in the "Clinical Papers" session within the Vifor Pharma UK (VPUK) Initial Training Course (ITC) […]. Please note that the aim of including this information is to educate VPUK employees on the place Ferinject's clinical data holds within the broader context of other products.'

Pharmacosmos noted that anxiety amongst health professionals administering IV iron was a known risk factor for developing an adverse drug reaction. Rampton *et al* reported in 'Hypersensitivity reactions to intravenous iron: guidance for risk minimisation and management' that anxiety amongst either patient or staff was one of the 'factors increasing risk and/or severity of hypersensitivity reactions (HSRs) in patients given iron infusions'. According to Vifor's own briefing document the SPC Comparator tool and the Intravenous Iron Differentiator tool were designed 'to be used proactively in threatened accounts that were considering switching to Monofer and in accounts that had switched to Monofer' and which according to the PMCPA's ruling contained content that 'referred to confidence with Ferinject and in that regard implied lack of confidence with Monofer'. By causing anxiety amongst health professionals, particularly nursing staff responsible for the IV administration of Monofer, Vifor might have been responsible for increased incidence and/or increased severity of hypersensitivity reactions with Monofer. The following statements were extracted from the nurse's letter to hospital colleagues:

'… [named Vifor employee] and his colleague became very 'aggressive' and in their manner/talk and started to tell me that this 'new' drug is very dangerous and it's not safe and how do I know that it will be safe to our patients' (quotation by named health professional).

'I too had one of these unannounced visits from them [Vifor Pharma], and totally agree that they were scare mongering' (quotation by named health professional's colleague)

'… they were also trying to discredit the drug in quite an intense way. Referring to big centres that had swapped from ferrinject to monofer and had big reactions scaring a bit more of the infusion team than anything else' (quotation by named health professional's colleague).

Pharmacosmos noted that in its appeal Vifor submitted that the two anecdotal reports from Ireland were not relevant to this case as they were not managed by Vifor:

'Two of the cases relied on by the Panel were from Ireland and, therefore, irrelevant to the issue before the Panel but yet the decisions are quoted at length in purported reliance on them as evidence of a 'pattern' of UK behaviour. Vifor Ireland was a separate, independent company with its own country manager and these components should have been disregarded from the outset, as had been requested by Vifor.'

Pharmacosmos, however, noted that:

- Vifor had an open position for country manager Ireland listed on its website on 13 February 2016. The position reported to the general manager for UK and, to its knowledge, was a newly created position at that time (Pharmacosmos understood that Ireland was previously managed directly from the UK, as the following points would suggest);
- Vifor appointed [named] as Country Manager Ireland who would not take position until May 2016, ie months after the cited Irish reports;
- Vifor had open positions for national sales director and medical science advisor listed on its website in September 2015. Both positions had responsibility for UK and Ireland;
- Vifor's Ferinject website for Ireland (www.ferinject.ie) automatically redirected to its Ferinject website for the UK (www.ferinject.co.uk).

Pharmacosmos submitted that all of these factors indicated a considerable involvement by Vifor in its operations in Ireland. This might be underlined by the fact that the inter-company dialogue in relation to the two reports of alleged misleading and disparaging claims in relation to Monofer was not redirected to the Ireland office for management when Pharmacosmos raised its concern in its letter dated 16 February 2016.

3 The complaint process

Pharmacosmos noted that there had clearly been much interchange between Vifor and the PMCPA in respect of this case and in that regard it commented on points made in Vifor's appeal in relation to the Constitution and Procedure and corrected some points about Pharmacosmos' approach to compliance, its supposed 'lack of standing' and the allegation that it 'turned its back on the self-regulatory scheme'.

Pharmacosmos' position with regard to the PMCPA

Pharmacosmos stated that it fully accepted the jurisdiction of the PMCPA in relation to complaints from 2010 (when Pharmacosmos established its UK subsidiary) until April 2014. During this time, Pharmacosmos and Vifor were party to a number of shared cases - initiated by either by company and at all times acknowledged the rulings of the PMCPA. In 2014, Pharmacosmos started to receive anonymous complaints through the PMCPA from alleged health professionals characterised by having particularly detailed knowledge of the Code, the IV iron market in Europe and of Pharmacosmos. The cases resulted in a significant workload for Pharmacosmos without any risk or potential downside to the complainant; the opportunity for inter-company dialogue, that would normally precede a PMCPA complaint, was bypassed. As a result of this potential misuse of the self-regulatory scheme Pharmacosmos declined in April 2014 a formal invitation from the PMCPA to join its non-members list. Despite this Pharmacosmos was always fully committed to ethical promotion and to following the principles outlined in the Code.

Since opting out of the self-regulatory system Pharmacosmos submitted that it had not received any complaints – anonymous or otherwise – from any party other than from Vifor. Pharmacosmos had always responded duly in inter-company matters, and when reference had been made to the Code, Pharmacosmos always related to the specific rules in question.

Pharmacosmos strongly objected to Vifor's allegation that it was 'gaming the system'. On the contrary, Pharmacosmos accepted the fact that decisions of the MHRA could be far-reaching and have serious consequences and it submitted to its authority directly.

For clarity, Pharmacosmos submitted that it would never hide behind anonymity and should it bring an unfounded complaint to the PMCPA it would pay the requisite administration charge. Indeed, Pharmacosmos hoped never to have to complain to either the PMCPA or MHRA, but that relied on the proper activities of its competitors. In that regard Pharmacosmos operated transparently and without fear or favour. As such, it was disappointed that the language used in Vifor's appeal implied that Pharmacosmos would do anything other than give a full and frank disclosure in any dealings with the PMCPA or the MHRA. As Vifor, the PMCPA and the MHRA were aware, Pharmacosmos had responded comprehensively on all complaints from named persons or named organisations.

Pharmacosmos accepted that there were some aspects of the Code that went beyond the MHRA's Blue Guide and yet it reassured the Authority that it still followed the principles of the Code itself; including, for example, the fact it had disclosed transfers of value in accordance with the Code's requirements, albeit on its website as it was not permitted to access the central platform. Nor did Pharmacosmos issue promotional aids other than those permitted by the Code. However, Vifor made important points in this regard as matters covered solely by the Code did not in fact have an enforcement mechanism beyond the PMCPA itself. Such aspects were not directly relevant to the rulings in this case, but they were important constitutional points to be considered.

Constitution and Procedure

Pharmacosmos stated that it would not comment on Vifor's views about the Panel's integrity or that the complaints procedure had been inappropriately applied by the PMCPA (including the reference to comments from Lord Denning from a case against the Malayan government 55 years ago). That said, Pharmacosmos considered that the quotation of legal rulings in this matter was misguided.

Pharmacosmos noted that the ruling in Tudor v Ellesmere Port & Neston Borough Council essentially rested on the fact that the Crown Court made a decision without giving the appellant the right to defend herself against a decision made based on evidence the appellant had not seen. Pharmacosmos submitted all the evidence to the PMCPA and, so far,

as it knew everything pertinent was passed on to Vifor. Additionally, the Masone case quoted by Vifor was largely about procedural errors in a criminal case and was not relevant here.

Pharmacosmos noted Vifor's summary that in its view Pharmacosmos had failed to establish the burden of proof. Vifor extended the discussion to encompass material that might be considered by the Appeal Board. Vifor had failed to understand that proof did not have to be provided solely by the complainant, but that the ruling was made on the balance of probability based on a combination of the complaint and the response. By centrally driving representatives to raise concerns about Monofer's side-effect profile, Vifor had disparaged a licensed product. Pharmacosmos would have no problem with the presentation of a clinical head-to-head study showing that one product or the other had fewer side-effects, however Vifor's strategy was to selectively raise doubts about Monofer based on a biased comparison of the two products – as indicated in the material it submitted to the Panel.

Pharmacosmos noted that Vifor had highlighted two further legal cases to explain the meaning of the balance of probability in civil cases. Combined, these cases indicated that if the tribunal (PMCPA) was satisfied that one version of events was the more likely, then the ruling could be made; if the situation was not clear then a ruling of 'no breach' should be given. The simple truth was that the PMCPA found evidence that representatives were instructed to target Monofer accounts and to raise doubts about the safety profile of Monofer using materials provided by head office and backed up with inappropriate materials issued by medical information. The probability that Monofer was disparaged in a misleading manner would therefore appear to be somewhat beyond the 51% required in the civil test as cited in the legal cases highlighted by Vifor.

In conclusion, Pharmacosmos believed that the Panel's rulings were correct. Vifor's centrally created materials and briefings had created a situation where competing products had been compared in a manner that was misleading and disparaging.

FURTHER COMMENTS FROM PHARMACOSMOS

The discussions regarding confidentiality of documents meant that some of Vifor's material was provided at different time points. On each occasion Pharmacosmos was given the opportunity to supplement its response to the appeal set out above.

Pharmacosmos alleged that the additional Vifor material supported the Panel's ruling which found Vifor in breach for:

- disparaging Monofer in promotional calls (in breach of Clause 8.1 for the pattern of behaviour).
- providing misleading information in respect of Monofer safety (in breach of Clause 7.2 for the pattern of behaviour).

Pharmacosmos alleged a consistent pattern of misleading and disparaging promotion of Ferinject with respect to Monofer in absence of comparative data. The pattern was evidenced in all of Vifor's promotional materials and internal briefings that had been shared with Pharmacosmos.

Pharmacosmos reiterated that the alleged misleading and disparaging conduct by Vifor's representatives had, in recent years, been the key point in a series of inter-company dialogues and Code cases between Pharmacosmos and Vifor. In some of the Code cases the Panel had ruled in support of Pharmacosmos and in others, where there had been insufficient evidence for Pharmacosmos to have made its case conclusively, the Panel had ruled in support of Vifor. Vifor had in these instances consistently argued that its representatives were clearly instructed, in the absence of comparative data, not to discuss competitor products and to refer health professionals who asked for comparative information to its medical information department, which in turn, Vifor had consistently argued, had been instructed to refer health professionals to Pharmacosmos' medical information department, when queries related to Monofer.

Pharmacosmos alleged that the Vifor materials provided in this case clearly showed that representatives were systematically being trained to focus promotional activity on attacking Monofer, rather than simply promoting Ferinject, despite the absence of comparative data. This resulted in misleading and disparaging comments about Monofer because the company's training material and promotional content was misleading.

At the core, Pharmacosmos was deeply concerned with the description of a Vifor culture that demonstrated a clear disrespect for the self-regulatory system and the Code; and which seemingly had taken no fundamental learnings from past rulings of serious Code breaches and subsequent audits by the Authority (the Appeal Board ruled in Cases AUTH/2411/6/11 and AUTH/2422/7/11 that Vifor should be audited by the Authority; Vifor was audited in November 2011, March 2012 and October 2012).

Pharmacosmos presented some examples from the Vifor material in evidence of this case that further supported the Panel's ruling that there was a pattern of misleading and disparaging promotion by Vifor representatives with respect to Monofer; there were a large number of additional points Pharmacosmos could cite, all based on a detailed analysis of the Vifor material.

The relevant briefing document advised representative's that they 'could also project [the SPC comparator tool] from your iPad for use with multiple HCPs at meetings'. This showed the tool was clearly designed to be used at meetings, as the Panel indicated in its ruling, thus it was not for reactive use only. It, furthermore, showed that Vifor briefed its representatives to discuss competitor products, despite the company's promises to the contrary in inter-company dialogue.

The Briefing Document Competitor Update December 2015 clearly identified the Lareb report as a marketing tool. This showed that Vifor's argument that its representatives were not briefed to discuss the Lareb report was not correct.

The Description of Clinical Data Sessions showed that Vifor representatives spent at least 4 hours studying Monofer clinical papers. This confirmed that Vifor had deliberately sought to focus on perceived Monofer shortcomings rather than Ferinject achievements. It, again, showed that Vifor briefed its representatives to discuss competitor products, despite both the absence of comparative data and the company's promises to the contrary in inter-company dialogue.

The Ferinject Differentiation from Monofer Slide Set UK was, by its omissions of key Monofer clinical data and incomplete description of Monofer's clinical proposition, both disparaging and misleading. Examples of this were:

- The name of the job bag for the material: 'Ferinject Differentiation from Monofer Slide Set UK' on the ZINC approval cover page identified Monofer as the target. This undermined and contradicted Vifor's consistent reassurance in inter-company dialogue that its representatives were trained to refer all health professional questions about Monofer to its medical information department.

- In the section entitled 'Breadth of clinical experience', the following key controlled trials on Monofer had been partly or completely omitted although published in peer reviewed journals: Wikstrom *et al* (2011) (nephrology); Hildebrandt *et al* (2010) (cardiology); Reinisch *et al* (2015) (gastroenterology; mentioned in brackets, but not as a separate publication); Birgegard *et al*, 2016 (in oncology) and Dahlerup *et al* (2016) (gasteroenterology).

Pharmacosmos considered that Vifor might argue that its selection criteria (randomised controlled trials) would exclude some of these Monofer trials. However, Wikstrom *et al* and Hildebrandt *et al* were pivotal regulatory Phase 3 trials in the Monofer approval process in Europe and they represented important and relevant studies. Indeed, safety was the primary objective in these two studies and so their absence gave Vifor representatives (and health professionals) a misleading and incomplete picture of Monofer safety data.

Pharmacosmos further noted that in its promotional materials for health professionals, Vifor only presented four Monofer clinical trials but trained its representatives in nine – as evidenced in Description of Clinical Data Sessions. For the studies that had been included, the presentation of study data included several data omissions and/or misleading data representations with respect to Monofer clinical trials publications. The consequence was cherry-picking of data in training and/or misleading promotion.

Pharmacosmos submitted that Vifor might also argue that Wikstrom *et al* and Dahlerup *et al* were published after the document was released in November 2015. However, Vifor was obliged to ensure that documents were revised when new studies were published. It was difficult to imagine that Vifor would delay such revision if a Ferinject study was published.

Pharmacosmos alleged, overall, the above omissions of key Monofer clinical data in the section titled 'Breadth of clinical experience' was misleading. Furthermore, the Monofer clinical data was presented such as to encourage health professionals to draw misleading conclusions on the comparative efficacy and safety of Monofer in the absence of comparative data.

The section titled 'Determination of the cumulative iron dose' suggested that only Ferinject offered simplified dosing for all patients which was not so. The Monofer dose could be determined by either using a simplified dosing table or the Ganzoni formula. The Ganzoni formula was used for particular patient groups where extra caution might be advisable. However, this was a recommendation only, and it remained up to the prescriber's clinical judgement as to whether to determine the dose using the Ganzoni formula or the simplified dosing table.

Pharmacosmos alleged that the information on the slide was structured to imply that 'Monofer equals the Ganzoni formula' and that 'the Ganzoni formula equals inconvenient, prone to error, inconsistently used in clinical practice, and underestimated iron requirements' (repeated on slide 24). Pharmacosmos noted that the phrase 'in other patients simplified dosing can be offered' was Vifor's own wording and not from the Monofer SPC. Pharmacosmos was concerned that Vifor insinuated that appropriate dosing recommendations for specific patient groups implied risk when using Monofer.

The section 'Ferinject and Monofer infusion' contained a call-out box with the subheading 'What does this mean in clinical practice?', which pretended to provide a complete description of the different patient scenarios based on two parameters used for determining iron need, ie the patient's haemoglobin level (Hb) and body weight (kg). However, this presentation was misleading because it failed to recognise the large group of patients with Hb ≥ 10g/dl and 75-100kg, which according to the simplified dosing table required 1,500mg iron. This group was a core component of the simplified dosing table for both products. For these patients Monofer offered treatment in one administration compared with two administrations with Ferinject. Pharmacosmos alleged that it was cherry-picking when clearly pretending to describe relevant scenarios from clinical practice and omitting a patient segment that was common in the UK. Instead, Vifor implied that the only area where Monofer had fewer (one) administrations compared with Ferinject (two) was for patients with a body weight above 100kg. Pharmacosmos was very concerned with the potential serious risks to patients that a misrepresentation of the dosing information of products could pose.

The section 'Undesirable events' underlined the attempt to cast doubt on the safety data for Monofer. The statement about Monofer was accurately quoted from the Monofer SPC, but was unreasonable. When the document was approved in January 2016, Monofer had been studied in more than 1,500 patients across more than 10 clinical studies, and post-marketing data included more than 3 million treatments worldwide. In essence, the slide implied that the risk-benefit profile of Monofer was questionable whereas that of Ferinject was not. This approach was continued on two subsequent slides.

The section 'Contraindications' whilst factually correct, implied that decompensated liver cirrhosis and hepatitis was not a risk factor with Ferinject, despite the fact that the condition was described under Special Precautions in its SPC. Failure to inform health professionals about an important special precaution might pose serious risk to patients.

The 'Medical Update 12 December 2013' Pharmacosmos noted that the section 'SPC Updates' on slides 3-9 informed the representatives of the recent EMA's 'Assessment Report for: Iron containing intravenous (IV) medicines products' ('Article 31 Updates'), which triggered a harmonisation of the SPCs for IV iron product (including Monofer and Ferinject) with regards to the risk of severe hypersensitivity reactions. Pharmacosmos alleged that the statement on slide 7 that 'Insufficient data meant that there was no way of differentiating between any IV iron' was not a fair representation of the situation. In its assessment report, the EMA stated:

> '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.'

Pharmacosmos alleged that the EMA's statement did not imply the data was insufficient as Vifor suggested. The underlying message intended by Vifor was that more data would show favourable difference between Ferinject and other IV iron products.

Pharmacosmos considered that the Panel's ruling also demonstrated that Vifor representatives were being trained on a local audit (subsequently presented as a poster: Grant *et al*). In previous inter-company dialogue in April 2014, Vifor had indicated that its representatives were neither trained in this audit nor discussed it with health professionals. This was clearly not the case. What was even more worrying was Vifor's admission that, despite the commitment in the inter-company dialogue, the audit was included in the nine studies referenced in 'Description of Clinical Data Sessions'. Pharmacosmos submitted that if representatives were trained on this audit during the ITC, there must be a reasonable expectation that they would use the information in promotional discussions.

Pharmacosmos submitted that the above were just some of the several examples of misleading and disparaging promotion that it had identified in the Vifor material provided. Pharmacosmos was particularly concerned that the material appeared to contradict commitments that had been made during inter-company dialogue:

- representatives were being trained to draw attention to the local audit and the Lareb report and they were directing health professionals to perceived concerns about Monofer
- health professional enquiries about Monofer were not being directed to Pharmacosmos' medical information department.

Pharmacosmos noted that it had raised concerns in inter-company dialogue about the consistent and widespread pattern of comments from health professionals indicating that on the balance of probability Vifor representatives had proactively raised the safety profile of Monofer in order to imply differences between the products. Six recent examples formed the basis of inter-company exchanges with Vifor in early 2016 all of which were characterised by health professionals proactively informing Pharmacosmos that Vifor representatives had stated that 'Monofer has a higher rate of adverse drug reactions than Ferinject'. Pharmacosmos also noted Vifor's statement in an inter-company response to Pharmacosmos dated 3 March 2016:

> 'As per your request, a thorough investigation of the incidents mentioned has been conducted by Senior Management. With the available information, no conclusive evidence has been found that the alleged disparaging and misleading claims have been made.'

Pharmacosmos submitted that a review of Vifor's material suggested that Vifor senior management had failed its obligation to adequately investigate, identify and resolve the systematic training in and provision of promotional material, which contained misleading and disparaging information about Monofer's safety profile.

In conclusion Pharmacosmos' stated that its review of the Vifor material supported the Panel's ruling that Vifor's representatives had disparaged Monofer in promotional calls and provided misleading information about Monofer safety. Pharmacosmos was deeply concerned with the evidence and alleged that Vifor representatives were systematically, and in the absence of comparative data, being trained to focus on attacking Monofer rather than promoting Ferinject.

Pharmacosmos alleged that the evidence gave the impression of a company with clear disrespect for the self-regulatory system and the Code; and which seemingly had taken no fundamental learnings from past rulings of serious Code breaches and subsequent audits by the Authority. Based on the review of Vifor's material referenced above, it respectfully urged the PMCPA to again reconsider its decision to set up an external lawyer confidentiality ring. Pharmacosmos submitted that its review above demonstrated that an external lawyer could not feasibly identify the areas where data was presented in a misleading fashion. To identify the issues required specialist technical

knowledge. In fact, even health professionals that specialised in the therapy area might not identify the manner in which key data had been left out or misrepresented; detailed technical knowledge of the product data set was required to identify such shortcomings. Specialists in law would undoubtedly not have the clinical and data-specific knowledge to appropriately assess the balance of evidence and whether or not the presentation of data in Vifor's material was disparaging, misleading or incomplete. Pharmacosmos was very concerned that not allowing it to review and comment on all relevant materials puts at risk the fair and complete resolution of the case and contradicted the general principles of the PMCPA Constitution.

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After referral to, and a decision by, an independent referee Pharmacosmos was provided with redacted versions of the 'Intravenous Iron Differentiator briefing guide' (only slides 1, 2, 21, 22, and 26) and slide 8 of the 'Competitor update at the December Sales Conference'.

Pharmacosmos alleged that whilst this new material further evidenced the consistent pattern of disparaging and misleading claims with respect to the comparative safety of Monofer, it noted that Vifor had tried to stop Pharmacosmos seeing this material, which arguably damaged Monofer the most:

Slide 8 'Competitor update at the December Sales Conference'.

- The briefing to Vifor representatives evidenced a clear intention to undermine confidence in Monofer safety by stating that '5 accounts have switched back to Ferinject from Monofer'
- The briefing evidences that Vifor representatives were trained in the Lareb pharmacovigilance report which contained Monofer safety reports; Lareb was the Netherlands Pharmacovigilance Centre. Vifor failed to recognise that training its representatives in the Lareb pharmacovigilance report represented an inappropriate provision of selective safety data.

The 'Intravenous Iron Differentiator briefing guide', slides 1, 2, 21, 22, and 26:

- Vifor representatives were trained to use the Intravenous Iron Differentiator tool 'proactively in threatened accounts that are considering switching to Monofer and in accounts that have switched to Monofer'. This confirmed that the tool (as also suggested by the compliance job title: 'Ferinject Differentiation from Monofer Slide Set UK') was intended to make comparative claims despite there being no of appropriate head-to-head studies
- Vifor representatives were instructed to ask health professionals 'what sort of adverse events would be expected with Monofer?' This again demonstrated the clear focus on Monofer in the Ferinject campaign despite Vifor's repeated commitments in inter-company dialogue that representatives were instructed not to discuss Monofer safety and instead refer health professionals to its medical information.
- Vifor stated that 'undesirable effects are primarily based on safety data for other IV irons in the Monofer SPC'. Such a statement, without acknowledging that when the document was approved there were 10 clinical trials with more than 1,500 patients treated with Monofer, created a perception which was not representative of the balance of evidence.
- Vifor made various claims with respect to Ferinject under the headline 'Confidence' which implied that health professionals could not have confidence with Monofer.

In conclusion, Pharmacosmos alleged that that the new materials provided further evidence in support of the Panel's ruling.

The independent referee decided that one document should only be provided to Pharmacosmos via an external lawyer confidentiality ring. Pharmacosmos decided not to join a confidentiality ring. This meant that the document 'Questions and Answers Reactive response to competitor messages' could not be provided to Pharmacosmos via a confidentiality ring. It was provided to the Appeal Board.

APPEAL BOARD RULING

The Appeal Board noted that in 2014 Pharmacosmos UK had declined the offer to join the PMCPA list of companies which were not members of the ABPI but had, nonetheless, agreed to comply with the Code; it stated that it no longer wished to accept the jurisdiction of the Authority but that it would continue to be fully committed to the ethical promotion of its products.

The Appeal Board disagreed with Vifor's submission that as Pharmacosmos was neither a member of the ABPI nor a non-member that had agreed to comply with the Code and accept the jurisdiction of the Authority, it was not in a position to be able to complain under the Code. This point had only been raised by Vifor in its appeal. The Appeal Board noted that the Memorandum of Understanding between the ABPI, PMCPA and MHRA did not exhaustively detail who could submit complaints under the Code, referring only to the position of ABPI member companies and non-members that had agreed to comply with the Code. Paragraph 5.1 of the Constitution and Procedure was clear that the complaints procedure could commence once the Director had received information that certain companies might have contravened the Code. Paragraph 5.1 of the Constitution and Procedure only required the *respondent* company to be either an ABPI member or a non-member company which had agreed to comply with the Code and accept the jurisdiction of the Authority. There was thus nothing in the Constitution and Procedure to preclude Pharmacosmos from submitting a complaint; indeed if there were, the Appeal Board considered that such provision might encourage some companies to submit complaints anonymously. In the Appeal Board's view, the Authority had been correct to allow the complaint to proceed.

The Appeal Board noted that Pharmacosmos had made it clear that, if applicable, it would pay any administrative charges due.

The Appeal Board noted Vifor's concerns that it had not seen certain information in relation to anecdotal reports submitted by the complainant until 21 July, after it was advised of the Panel's rulings on 12 July. Vifor was originally provided with the correspondence between Pharmacosmos and the PMCPA relevant to the merits of the case. The relevant detail of the anecdotal reports was included in Pharmacosmos' letter of complaint and Pharmacosmos was clear in that complaint that it was not making specific allegations for each example, rather portraying them as part of the overall picture to give credence to concerns about a pattern of behaviour of misleading and disparaging statements. The Appeal Board considered that it would have been preferable for Vifor to have been provided with the copies of the emails from Pharmacosmos staff before the Panel made its ruling. In any event, the Appeal Board noted that Vifor now had the information and any remedy in it not being provided sooner lay in Vifor's ability to appeal.

The Appeal Board noted that Pharmacosmos had complained about a pattern of behaviour and had cited a number of anecdotal reports to support its allegations that Vifor had disparaged Monofer and misleadingly implied that there was a difference in the safety profiles of Monofer and Ferinject when no head-to-head comparison between the two existed. In addition, Pharmacosmos also provided email evidence from one hospital which it alleged showed that Vifor had misleadingly compared the safety profiles of Monofer and Ferinject.

The Appeal Board noted that a medical update presentation from December 2013 (ref UK/FER/13/0201) included three slides detailing the results of Grant *et al*, a retrospective case note review of patients who had received Monofer at a particular hospital. The third slide detailed the authors' conclusions ie that the use of Monofer had shown a sub-optimal attainment of Hb target and the frequency of adverse reactions was much higher than expected from those reported in the SPC or previous studies in renal patients, and thus they no longer used the medicine. The concluding slide of a competitor update for the December 2015 conference (ref UK/FER/15/0279) headed 'Safety and Tolerability' referred to these properties as being a key factor in choosing an IV iron. The slide named five hospital accounts which had switched back to Ferinject from Monofer. It also drew attention to the Lareb report and included the quotation 'special attention should be given to the comparison of the safety profile of the different intravenous iron-containing medicines and in particular to the safety profile of [Monofer]'. The slide continued by urging representatives to 'Be proactively reactive' and the instruction that if a customer asked about the detailed safety of Ferinject beyond the SPC then they should be referred to medical information for detailed information. No instructions were given on the slide as to what to do if a customer asked for detailed safety information on Monofer or for a comparison of the safety profiles of Monofer and Ferinject.

The Appeal Board noted that Vifor representatives had clearly been briefed about the outcome of Grant *et al* and the conclusion of the Lareb report as it related to Monofer. There was no written briefing about how, if at all, the representatives were to use either paper. In the Appeal Board's view, briefing the field force about the existence of the papers which were highly critical about the safety of the major competitor was not unacceptable *per se* but without any instructions to the contrary it was likely that the representatives would assume that both could be used to support their promotion of Ferinject. The results of neither paper had been put into context. In the Appeal Board's view, the briefing on the Lareb report with the instruction to be 'proactively reactive' would encourage representatives to look for every opportunity to send the paper out. Further, the Appeal Board was concerned to note that there was no standard medical information letter about either Grant *et al* or the Lareb report nor about the comparative safety profile of Monofer and Ferinject. Email evidence from one hospital showed that medical information had sent out the Lareb report to a customer with a very misleading and factually inaccurate covering letter which clearly undermined the reader's confidence with regard to the safety of Monofer.

The Appeal Board noted, overall, the content of the briefing material, the emphasis on and the lack of context given with regard to Grant *et al* and the Lareb report, the absence of clear, unequivocal instructions to the representatives about the use of those two papers, the lack of a defined company position regarding the safety profile of Monofer alone, and vs Ferinject (as standard medical information letters and representatives' briefing material) and the very poor medical information letter sent to a customer with a copy of the Lareb report. Given all of these factors, the Appeal Board considered that, on the balance of probabilities, it was likely that Vifor representatives had disparaged Monofer as alleged. The Panel's ruling of a breach of Clause 8.1 was upheld. The Appeal Board further considered that on the balance of probabilities, it was likely that Vifor representatives had provided misleading information with regard to the safety of Monofer as alleged. The Panel's ruling of a breach of Clause 7.2 was upheld. The appeal was thus unsuccessful.

Complaint received **1 April 2016**

Case completed **7 December 2016**