Case AUTH/2795/9/15

ANONYMOUS, NON-CONTACTABLE NHS WHISTLEBLOWER v NAPP

Promotion of Remsima

An anonymous, non-contactable 'NHS whistleblower' complained about the promotion of Remsima (infliximab) by Napp Pharmaceuticals at a two day meeting for UK health professionals held in Norway. Also at issue was a Remsima leavepiece which advocated switching from Remicade to Remsima. Remsima was a biosimilar of Remicade (marketed by Merck Sharp & Dohme) and both were anti-tumour necrosis factor (anti-TNF) medicines and could be used in the treatment of psoriasis, Crohn's disease and ulcerative colitis.

The meeting held in Norway was entitled 'Norway IBD [inflammatory bowel disease] exchange'. The complainant stated that he/she was extremely concerned that two colleagues who were implementing a wholesale switch of their patients to the new medicine, had been invited by Napp to a four day 'scientific meeting' in Norway. Seemingly as a reward for switching patients to Remsima. Given recent newspaper headlines about pharmaceutical companies taking NHS decision makers overseas on junkets, it beggared belief that this activity was still so blatantly pursued by the UK pharmaceutical industry.

The complainant summarised his/her complaint by stating that this type of activity did nothing for the reputation of either Napp or the UK pharmaceutical industry as a whole. More worrying was the effect that this negligent and unethical behaviour would have on patients. [This comment was taken by the Panel to apply equally to the meeting and the leavepiece.]

The detailed response from Napp is given below.

The Panel noted that the agenda for the meeting stated that the focus of the event was to share best practice in the treatment of IBD in both the UK and Norway, to facilitate discussion about the standard of care in Norway compared with the UK and to identify areas of best practice in both countries. It was further stated that discussions would also focus on the introduction of biosimilars for the treatment of IBD including clinician and patient experience in Norway. The front cover of the agenda stated 'This meeting is organised by Napp Pharmaceuticals. Discussion of Napp Pharmaceuticals' products will take place at this event'. Prescribing information for Remsima was included.

The meeting had been developed in response to feed-back from pre-launch advisory boards that real world evidence and experience from clinicians who had used Remsima was important. Remsima had been available in Norway since January 2014 but not launched in the UK until February 2015. Biosimilar infliximab in Norway had a 63% market share. One of the stated aims of the meeting was to allow key opinion leaders to share real world experience with Norwegian clinicians who used Remsima in IBD given that clinical data in IBD patients and practical experience in the UK of using biosimilar infliximab was very limited. In the Panel's view the meeting was organised specifically with a focus on Remsima and to promote switching from Remicade to Remsima in IBD.

In the Panel's view, the sales force briefing about the meeting, which listed the criteria for inviting potential delegates, further emphasised the importance of Remsima to the meeting for Napp as opposed to sharing best practice as stated on the agenda. The potential delegates appeared to have been chosen for their ability to influence decisions about the use of Remsima.

The Panel noted that the meeting agenda included tours of the gastroenterology clinics of two local university hospitals. Napp had submitted that such tours were so that delegates could see how the biosimilar infliximab was delivered in a real-life clinical setting and speak to clinicians and specialist nurses at the hospitals who had actually administered the product. The Panel noted from the leavepiece at issue below however, that in terms of switching from Remicade to Remsima, it was claimed, *inter alia*, that 'Your clinic won't need to change how it does things' and that there was 'no need for new staff training'. In the Panel's view, although the UK delegates would have a professional interest in seeing the Norwegian clinics, such tours were not integral to the main focus of the meeting. In the agenda given to delegates both hospital tours appeared to be identical in that both would include an overview of the clinic, standards of care and best practice with anti-TNF therapy, patient flow through the system, consultations, infusion procedure, capacity planning and the efficient running of clinics. In the briefing given to the chair and co-chair of the meeting, each of whom would host one of the hospital tours, less detail was given in that it was stated that during the tours it would be 'good if some of the clinic nurses are available, to hear their perspective and views on such things as the infusion procedure, capacity planning, and information that is given to patients to support them'. Overall the Panel considered that it would have made much more logistical sense to have the two Norwegian clinical experts visit the UK to discuss their experiences and relevant patient case histories with their UK counterparts. Alternatively, the Panel queried whether the meeting could have been conducted on-line. It appeared that the two hospital tours had been included to help justify the meeting being held in Norway. Given the lack of a clear and cogent reason to hold the meeting outside the UK, the Panel ruled a breach of the Code.

The Panel noted that the delegates had been invited to a two day meeting in Norway, the primary objective of which appeared to be to allay their concerns about switching IBD patients from Remicade to Remsima. The average total cost of hospitality, to include air fares, was £799.73 per person. The Panel considered that in and of itself, the hospitality had not been excessive although two evening meals each of just over £61 per head was on the limits of acceptability bearing in mind the relevant requirements of the Norwegian Code. Nonetheless, the Panel considered that hosting UK delegates for a two day promotional meeting in Norway, in circumstances where the Panel did not consider that there was a clear and cogent reason for holding the meeting outside the UK, was an inducement to prescribe or recommend Remsima. A breach of the Code was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel noted that the supplementary information to Clause 2 stated that, *inter alia*, an inducement to prescribe was likely to be in breach of Clause 2. The Panel noted its comments above and considered that holding the meeting in Norway was such as to bring discredit upon and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Upon appeal by Napp, the Appeal Board noted its submission that Remsima was the world's first monoclonal antibody biosimilar of infliximab and that the process by which biosimilars were granted a marketing authorization meant that health professionals were confused and lacked confidence about using them. Napp submitted that there was a significant and legitimate educational need relating to the clinical use of biosimilar infliximab in the UK. The evidence required for Remsima's licence was to show that it and the reference medicine (Remicade) were essentially the same biological substance and clinical studies were only confirmatory. Napp submitted that in the case of infliximab the clinical studies were not in gastroenterology but that extrapolation from rheumatology studies to IBD was possible based on the overall evidence of comparability. Thus there was less direct data on the clinical efficacy and safety of Remsima in gastroenterology than would have been available for Remicade. When Remsima was launched in the UK (February 2015), clinical data in IBD and practical clinical experience with biosimilar infliximab was extremely limited. The Appeal Board further noted Napp's submission that Norwegian clinics, however, had used Remsima since early 2014; the position by June 2015 was that Remsima was used for all new IBD patients nationally and several IBD centres had switched to 100% Remsima.

The Appeal Board noted that apart from the originator medicine, Remicade, which had been on the UK market for 15 years, there were now two biosimilar infliximabs available, Remsima and Inflectra. The Appeal Board noted Napp's submission that planning for the October meeting had started in June when only one or two UK centres were using Remsima. In that regard, however, the Appeal Board noted that a National Institute for Health and Care Excellence report, 'Introducing biosimilar versions of infliximab: Inflectra and Remsima', published 31 July 2015 and provided by Napp, stated that between April and June 2015 one UK hospital had switched 150 IBD patients from Remicade to Inflectra. The Appeal Board thus noted that shortly after starting to plan the meeting in question, there was published data which referred to relevant experience of switching gastroenterology patients to biosimilar infliximab in the UK, albeit short-term data compared with the longer term use of a biosimilar infliximab in Norway.

The Appeal Board noted that the meeting delegates had toured the two Norwegian hospitals in groups. The tours of the two hospitals lasted in total 3.5 hours. In the newer hospital the group size was ten with smaller groups touring the older hospital. In that regard the Appeal Board queried whether the group sizes and the relatively short time spent in each hospital were compatible with the delegates being able to observe and absorb meaningful, relevant details about service provision, patient flow, logistics etc.

In the Appeal Board's view, given the evidence required for Remsima's marketing authorization that there was no difference in the use, dose or preparation of Remicade and Remsima, and there was UK experience of switching IBD patients from Remicade to a biosimilar infliximab, there was no clear and cogent reason for the UK delegates to travel to Norway for the meeting. That was not to say that some way could not have been found of incorporating the Norwegian experience into a meeting held in the UK. Nonetheless, the Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on that point was unsuccessful.

The Appeal Board noted that UK delegates had attended a two day meeting in Norway, which had been paid for by Napp. The Appeal Board considered that although the level of subsistence had not been excessive, hosting UK delegates for the two day promotional meeting in Norway, where there was no clear and cogent reason for holding that meeting outside the UK, was an inducement to prescribe or recommend Remsima. The Appeal Board thus upheld the Panel's ruling of a breach of the Code. The appeal on that point was unsuccessful.

The Appeal Board noted its rulings above and considered that high standards had not been maintained and it upheld the Panel's ruling of a breach of the Code. The appeal on that point was unsuccessful.

The Appeal Board noted that biosimilars were emerging therapies the regulatory process for which meant that, as with Remsima, direct clinical data might not be available in all therapy areas. Health professionals in therapy areas where the direct clinical data might be lacking needed to understand and have confidence in that process. In that regard the Appeal Board considered that whilst the location of the meeting was unacceptable, the aim of the meeting was not unreasonable. The Appeal Board noted its

rulings and comments above and decided that on the facts of this case, a ruling of a breach of Clause 2 would be disproportionate. On balance, the Appeal Board ruled no breach of Clause 2. The appeal on that point was successful.

The complainant provided a copy of a leavepiece entitled 'Your guide to changing treatment Remicade → Remsima' which explained the process for switching treatments. The complainant was concerned that the industry continued to pursue such an aggressive stance on switching between treatments with little concern for patients, or patient safety. There was no reference in the leavepiece to the conditions which either medicine was used to treat and it was even suggested that there should be no safety concerns associated with switching to Remsima, despite being a recently licensed medicine with limited safety information. The complainant submitted that this type of irresponsible action by the industry put patient's safety, and indeed lives, at risk.

The Panel noted that the leavepiece was a guide to changing treatment from Remicade to Remsima. The leavepiece explained that Remsima was a biosimilar of Remicade. It was stated that patients currently on Remicade could therefore be changed to Remsima treatment providing they were eligible. In that regard the Panel did not consider that it necessarily had to be stated in the main body of the leavepiece which conditions patients would be treated for; in any event, the prescribing information listed the licensed indications for Remsima. The Panel noted that the leavepiece listed those patients who would not be eligible for Remsima treatment (eg those who had discontinued Remicade therapy due to intolerance or lack of efficacy) and those who would be eligible (ie those who currently responded well to or remained stable on Remicade). In addition it was stated that any switch should always be done on a case-by-case basis. Having listed which patients might or might not be eligible for a switch, the leavepiece described how the switch should be carried out and what to expect after switching. On the back of the leavepiece was a highlighted box of text with additional safety information about the risk of tuberculosis during and after treatment with [Remsima].

The Panel did not consider that the leavepiece suggested that there were no safety concerns with Remsima as alleged. The Panel considered that on the basis of the information before it, there was nothing to show that the leavepiece had not encouraged the rational use of the medicine; the eligibility or otherwise of patients had been made clear. The Panel did not consider that the information in the leavepiece was misleading. No breaches of the Code were ruled.

The Panel noted its rulings above and did not consider that high standards had not been maintained. No breach of the Code was ruled. Given its rulings above, the Panel also ruled no breach of Clause 2.

An anonymous, non-contactable complainant who described him/herself as an 'NHS whistleblower' complained about the promotion of Remsima (infliximab) by Napp Pharmaceuticals Limited. At issue was a two day meeting for UK health professionals held in Norway and a Remsima leavepiece (ref UK/REMS-15078) which advocated switching from Remicade to Remsima. Remsima was a biosimilar of Remicade (marketed by Merck Sharp & Dohme). Both Remsima and Remicade were anti-tumour necrosis factor (anti-TNF) medicines and could be used in the treatment of psoriasis, Crohn's disease and ulcerative colitis.

A Meeting held in Norway, 11-13 October 2015

The meeting was entitled 'Norway IBD [inflammatory bowel disease] exchange'.

COMPLAINT

The complainant stated that he/she was extremely concerned to discover that two colleagues in a named hospital who were implementing a wholesale switch of their patients to the new medicine, had been invited by Napp to a four day 'scientific meeting' in Norway in November. This 'meeting' seemed to be to reward those who were switching to using Remsima which the complainant described as a new version of infliximab. Given recent headlines in The Telegraph about pharmaceutical companies taking NHS decision makers overseas on junkets, it beggared belief that this activity was still so blatantly pursued by the UK pharmaceutical industry.

The complainant summarised his/her complaint by stating that this type of activity did nothing for the reputation of either Napp or the UK pharmaceutical industry as a whole. More worrying was the effect that this negligent and unethical behaviour would have on patients. [This comment was taken by the Panel to apply equally to the meeting and the leavepiece at issue at Point B below.]

When notified of the complaint, Napp was asked to respond in relation to Clauses 2, 9.1, 18.1 and 22 of the Code.

RESPONSE

Napp explained what a biological medicine was and stated that NHS England's recent publication, 'What is a Biosimilar Medicine?', defined a biosimilar medicine as:

> 'a biological medicine which is highly similar to another biological medicine already licensed for use. It is a biological medicine which has been shown not to have any clinically meaningful differences from the originator biological medicine in terms of quality, safety and efficacy.'

Napp submitted that health professionals, patients and the public often misunderstood what a biosimilar was. Biosimilars were large, complex proteins up to one thousand times larger than small chemical molecules eg aspirin. In contrast to generic versions of small molecules all biological medicines including biosimilars were manufactured within living cells, and so no two batches were ever identical. Instead the regulators accepted a reference range of batch-to-batch variation through a comparability exercise. Napp referred to the European Generic and Biosimilar

Medicines Association brief internet video on 'Biosimilar Medicines: An Opportunity for Healthcare'. The guideline from the European Medicines Agency (EMA) on biosimilars stated that a biosimilar had to demonstrate such comparability by head-to-head, state-of the-art, physico-chemical analysis; biological testing, and limited clinical trials such that there were no clinically meaningful differences to the originator.

It followed that the originator monoclonal antibody infliximab (Remicade) had many 'versions' over the 15 years since it was first licensed as a result of batch-to-batch variation and manufacturing changes. 'Virtually all monoclonal antibodies have been subject to several changes after authorization – a fact that is not well known by clinicians and that is rarely explicitly communicated'. (Schneider 2013).

The confusion by health professionals about the comparability of biosimilars with the originators had arisen from statements like 'similar but not the same', a problem which had been highlighted by several expert European regulators. An expert rheumatologist wrote:

> '**Similar but not the same – comparability**
> There was extensive experience in comparability studies that controlled the safety and efficacy of biologicals after manufacturing changes. Current methods to analyse physicochemical and structural differences were extremely sensitive. Analysis of manufacturing batches of the originator (reference) products had revealed differences after a change in the manufacturing process between the pre- and post-change batches. In these cases, no clinical studies were performed. These differences were similar to those that had raised a lot of concerns when observed between a biosimilar and its reference product. Thus, the slogan "Similar but not the same" applied to originator products at the time of licensing and today!' (Kurti 2014).

Napp submitted that Remsima was the world's first monoclonal antibody biosimilar of infliximab approved by the EMA in July 2013, though 12 biosimilars had been approved in Europe over the past 10 years. Remsima was infliximab just as much as the many batches of originator Remicade were infliximab, and was described as such within the summary of product characteristics (SPC) as Remsima (infliximab). The EMA stated that Remsima was highly similar to the originator and had not shown any clinically meaningful differences as part of its submission.

Napp submitted that the complainant was thus mistaken to describe Remsima as a new version of infliximab. Remsima was no more a new version than were the multiple batches of Remicade. Remicade patients over the past 15 years had effectively received several 'versions' of infliximab – though all falling within a tightly controlled and acceptable reference range.

With regard to the meeting at issue, Napp confirmed that a two day meeting would take place in Oslo from arrival on Sunday afternoon 11 October 2015, to departures after lunch on Tuesday, 13 October (a copy of the agenda was provided). Napp stated that it interpreted 'scientific meeting' as used by the complainant as a means to draw attention to an ironic or inaccurate use, in this case a junket rather than a truly scientific and educational meeting. Napp submitted that the agenda and the speaker briefings showed that the meeting had an extremely high scientific and educational content. The meeting had been certified as a promotional meeting which was not solely focused on switching between infliximab brands. Napp firmly believed that high standards had been maintained at all times and noted that it had applied the question given in the supplementary information to Clause 22, 'would you and your company be willing to have these arrangements generally known?'. The following approval documents were provided:

- The certified Napp organised Meeting/ Accommodation and Internal Hospitality Proposal Form (ref UK/INM-14009(1)). This detailed the type of meeting, including meeting aims, justification, the agenda, dining arrangements, hotel details, subsistence costs and travel arrangements. Napp noted that dinner costs in the proposal form had been approved as £65/head on Sunday and £70/head on Monday. These were finalised and confirmed as £61.26 and £61.64, respectively. [This form also referred to a similar meeting held in March 2015]
- The certified Napp customer invitation brochure (ref UK/INM-14009(1)a). The front page made it clear that this was a promotional meeting as prominently highlighted by the words: 'This meeting is organised by Napp Pharmaceuticals Limited. Discussion of Napp Pharmaceuticals' products will take place at this event'. The inside of the invitation described the faculty members and the focus of the meeting as well as the agenda. The next page provided contact details and introduced the Napp team. The final page contained the Remsima prescribing information
- The certified Napp internal briefing document which explained the delegate selection criteria (ref UK/INM-14009(1)b). The delegates from each region of the UK, were hospital health professionals (doctors with an interest in gastroenterology medicine or specialist inflammatory bowel disease (IBD) nurses) who cared for patients with IBD, ulcerative colitis or Crohn's disease – both licensed indications for infliximab
- The certified Napp internal speaker agreement proposal form which provided detailed explanations of the agenda, the aims of the meeting and full speaker briefings and biographies for the faculty (ref UK/INM-14009(1)c). The slide sets were currently undergoing review by Napp prior to final certification
- Napp also provided pictures of the conference facilities at the hotel and a spreadsheet detailing all final costs associated with subsistence, accommodation and travel.

Napp stated that it could be seen that that the delegates were not selected based on any form of 'reward' to those switching to Remsima (ref UK/INM-14009(1)b). Each representative could invite up to 3 delegates for a maximum of 20 available places. Twenty seven delegates could be invited and then head office medical and marketing teams decided on the final 20 based upon the documented selection criteria.

Napp noted that the final delegate number was 21.

A list of the invitees and their organisations/hospitals was provided. Of the 21 delegates, only 1 invitee (a specialist nurse) had begun switching and 2 were considering switching. Thus 95% of the delegates (20/21) had not switched IBD patients to Remsima contrary to the complainant's allegation.

The purpose of the promotional meeting was fully described in the 'type of meeting' section of the Napp speaker agreement proposal form (ref UK/INM-14009(1)c). The meeting was not developed to focus primarily on switching patients to Remsima but was in response to feedback from pre-launch key opinion leader advisory boards that sharing real world evidence and experience from clinicians who had used Remsima was important. As described in the background section above, the regulatory process for biosimilars focussed heavily on comparability exercises to demonstrate that the biosimilar was highly similar to the original, and clinical studies were only confirmatory. In the case of biosimilar infliximab, the clinical studies conducted under this pathway included patients with rheumatoid arthritis and ankylosing spondylitis only. Extrapolation to IBD was possible based on the overall evidence of comparability provided from the comparability exercise and due to the conserved pathological mechanism across the diseases. However, this meant that when the medicine was launched in the UK, clinical data in IBD patients and practical clinical experience with biosimilar infliximab was extremely limited. The meeting was held in Norway because it was one of the first European countries to have access to Remsima. Norwegian clinicians began treating patients with Remsima in early 2014, one year before its availability (February 2015) in the UK due to differences in patent expiry dates. Norwegian gastroenterologists had since gained significant practical clinical experience in both new and switched IBD patients. One question could be why the Norway experts could not visit UK to share their insights and experience.

The programme had been designed such that UK delegates could see how biosimilar infliximab was delivered in a real-life clinical setting and speak to clinicians and specialist nurses at the hospitals who had actually administered the product. Furthermore, Napp hoped that by exposing UK health professionals to how IBD was managed in Norway, patient care in the UK would be enhanced. Napp stated that there were visits to two hospitals to experience at first hand the gastroenterology facilities and infusion clinics where infliximab was delivered. Both of these hospitals were key centres for the treatment of IBD in Norway and the two Norwegian professionals who hosted the hospital tours were international key opinion leaders in the field of IBD. There were also meetings with clinic staff and sharing of clinical methods and patient management in a different healthcare setting.

In summary, Napp had organised the promotional Norway IBD exchange to:

- Share real world experience of using Remsima to treat IBD patients in Norway
- Share best treatment practice of IBD in the UK and Norway
- Facilitate learning of IBD treatment in Norway by visiting two key clinical centres of excellence in Oslo
- Facilitate discussions about the standards of care in Norway compared with the UK to identify areas of best practice in both countries.

In view of the information provided, Napp refuted any breach of Clause 18.1, as there had been no gift, pecuniary advantage or benefit offered connected to the promotion of Remsima or as an inducement to prescribe. The meeting arrangements and hospitality were fully aligned to all aspects of Clause 22 and Napp refuted a breach of this clause. Napp had maintained high standards at all times by ensuring the meeting arrangements met all aspects of the Code; it had not brought discredit upon, or reduced confidence in the pharmaceutical industry. Napp denied breaches of Clauses 9.1 and 2.

In response to a request for further information Napp stated that the meeting was promotional; the delegates did not attend as consultants to Napp therefore they were not remunerated and no contractual agreements were put in place. The meeting joining instructions which were sent to delegates prior to the event were provided.

All slide sets used at the meeting were provided as well as feedback from the March and October IBD exchange meetings. Napp submitted that the agendas for the March and October meetings were not identical but were very similar. Details were provided of three amendments made to the October agenda as a result of feedback from the March meeting.

Napp stated that once registration was opened for the October meeting, a much higher proportion of specialist nurses applied to attend than had applied to attend the March meeting. In order to maintain relevance to the audience, an IBD nurse specialist from one of the Norwegian hospitals was included as an additional faculty member. The nurse specialist did not present a distinct session and the agenda was not modified; she was instead asked to contribute her clinical experience to the existing planned sessions and on one of the hospital tours. The agenda for the March meeting was provided. The speakers were essentially the same. Sixteen delegates attended the March meeting; fourteen consultant gastroenterologists and two IBD specialist nurses.

Napp submitted that there had been no particular follow up with any of the delegates of the March or October meetings by Napp head office staff. Napp promotional staff had not been specifically asked to follow up with attendees although it was likely that some or all of the delegates would have met Napp promotional staff as part of routine promotional activities since the meetings occurred but any activity of this type had not been recorded or audited over and above routine promotional call recording.

Napp submitted that two of the delegates had been contracted to provide services to Napp since attending the March exchange meeting; one had attended an advisory board regarding biosimilar infliximab uptake in London in July 2015 and the other authored a Remsima promotional advertorial which was

published in a journal and attended an advisory board regarding biosimilar infliximab uptake in London in July 2015. None of the delegates from the October meeting had provided services to Napp yet since returning from the meeting although two might do so in the near future; there was provisional plans for both to speak at a Napp promotional meeting. A list of the March and October delegates with the above delegates highlighted was provided.

Napp submitted that it routinely monitored Remsima sales to UK hospitals. No additional methods to monitor Remsima use had been implemented in hospitals where Norway exchange meeting delegates were employed. Neither had any exercise been undertaken to specifically correlate sales data against hospitals where Norway exchange meeting delegates were employed.

Napp submitted that in the planning and certification of the meeting arrangements the most recent 2014-2015 Norwegian 'Rules for Marketing of Medicinal Products' was taken into consideration (copy provided). Point 9.04 of this guidance outlined acceptable costs for meetings and stated that 'As a general rule, it shall not exceed what healthcare professionals would have paid if they were to pay it themselves'. There was also specific guidance on the rates that must be adhered to for lunch and dinner under Section 9.04A. This stated that the currently established dinner and lunch rates per person that shall not be exceeded were NOK 822 (£63.22) for dinner and NOK 172 (£13.23) for lunch.

Napp submitted that two dinners were organised during the meeting. The total cost for dinner on Sunday, 11 October at the conference hotel was £4,244.67, which consisted of 27 three course meals at £44.97 each, and four snacks for late arrivals at £7.61 each. The total cost of dinner at a restaurant on Monday, 12 October was £1,620.71 for 30 people including Napp staff and delegates. The cost per head was therefore £54.06. Unfortunately one delegate had to leave unexpectedly at the end of the first day hence only 30 heads for dinner. Receipts for these two dinners were provided. Two lunches were organised; one on Monday, 12 October and the other on Tuesday, 13 October. Both took place at the conference hotel and were part of the day delegate rate charged by the hotel that included room hire; technical equipment and AV hire; support from the hotel staff with AV throughout the meeting; water, tea and coffee refreshments at the break; and hotel pen and paper. A limit was set for the lunch provision by the hotel of £13.23. Relevant correspondence from the hotel was provided. The receipt from the hotel outlined the total cost of 60 day delegate rates for 30 delegates including Napp staff for 2 days as £3,345.56. The cost per head, per day was therefore £55.76 of which the lunch subsistence was £13.23.

Napp submitted that the meeting formally concluded at 13:15 on Tuesday, 13 October, lunch was arranged at the hotel until 14:00. All but two delegates departed by 17:15 or earlier on that day; one delegate departed at 18:40 in order to return to a different UK airport and another departed at 21:25 for personal reasons; Napp did not consider it unreasonable. A table of the delegates' return flights was provided.

Napp confirmed that the two hospital tours undertaken during the visit were to different hospitals and the transfer times were therefore different. On Monday, 12 October the group toured Akershus University Hospital. The transfer time from the hotel was approximately 30 minutes. The tour itself lasted 60 minutes, followed by a 30 minute discussion. There was then a 30 minute transfer back to the hotel. On Tuesday, 13 October the group toured Oslo University Hospital. The transfer time from the hotel was approximately 15 minutes. The tour lasted 90 minutes followed by a 30 minute discussion and a 15 minute transfer back to the hotel.

Napp submitted that Remsima and Inflectra were both the biosimilar infliximab manufactured by Celltrion in South Korea. Inflectra was sold worldwide by Hospira, which was recently acquired by Pfizer. Both Remsima and Inflectra received centralised EU marketing authorizations in September 2013 meaning the product was simultaneously authorised for sale in all European Economic area countries. However, the product was not able to launch immediately in any European territory due to ongoing patent protection of Remicade. Due to differing patent legislation between EEA countries, Remsima and Inflectra were subsequently able to launch in Poland, Norway, Finland, Hungary and some other smaller Eastern European countries in approximately January 2014, whilst the originator patent protection remained in force in all other EU markets until February 2015. Therefore, there was significantly greater experience of biosimilar infliximab use in these four countries than in any other EU country, and these four countries constituted the initial list for a potential exchange visit.

As of June 2015, uptake, and therefore clinical experience, of biosimilar infliximab in Hungary and Finland was relatively poor compared with Norway and Poland. The final decision to use Norway was made on the following basis:

- Norway operated an exclusive single national tender system for biologic medicines. This tender to market biosimilar infliximab (Remsisa) was won in 2014 and 2015 by Orion Pharmaceuticals Limited, which marketed Remsima on behalf of Celltrion in Scandinavian countries. All biosimilar infliximab used in Norway was specifically Remsima. This was in contrast to Poland where much of the biosimilar infliximab used was Inflectra (marketed by Alvogen in Poland on behalf of Hospira)
- The Norwegian Medicines Agency had conducted a government sponsored 500 patient, randomised, double-blind trial to assess the safety and efficacy of switching from originator infliximab to Remsima (called NOR-SWITCH study). This ongoing study had received publicity in the UK and Napp believed the delegates would value the opportunity to meet with some of the study investigators and discuss their experiences with Remsima as part of this trial
- The Norwegian healthcare system was similar in structure to the NHS, ie exclusively publicly funded in contrast to the Polish healthcare system which was a public-private hybrid system. Napp believed that more valuable discussions and insights would be obtained from meeting international colleagues

working in a similarly organised healthcare system hence the reason for selecting Norway as the location to share best practice.

Napp submitted that as a similar biosimilar, Remsima was granted a marketing authorization on the basis of a relatively new and little understood regulatory pathway. Biosimilars were biological medicinal products that were developed as copies of already existing biological medicines ie they could be conceptualised as being 'generics' of biological medicines. However, due to the high complexity and heterogeneity of biological medicines it was not possible to develop a chemically identical copy of a biological medicine, as could be done for a traditional 'small molecule' chemical medicine. Biosimilars could not therefore be authorised via a generic regulatory pathway which clinicians were familiar with, yet authorisation of these products required extensive physicochemical and *in vitro* characterisation rather than the extensive clinical trial data package that was a prerequisite for the grant of marketing authorization for a new medicine. Consequently, a 'hybrid' licensing pathway was developed for biosimilar products, whereby limited clinical data was required for the grant of a marketing authorization for all of the same therapeutic indications as the originator biological medicine by extrapolation.

With regard to Remsima, the regulatory authorities advised Celltrion that pivotal clinical trials of the product were undertaken only in the rheumatology conditions of rheumatoid arthritis (RA) and ankylosing spondylitis (AS), as the clinical endpoints as clinical markers of improvement were well defined and validated.

In the UK most infliximab was administered intravenously in hospital as a day case in inflammatory bowel diseases such as Crohn's disease (CD) and ulcerative colitis (UC). Rheumatologists in the UK mainly used subcutaneously administered biological therapies to treat RA and AS for greater patient convenience as this did not require hospital attendance. As outlined above no controlled clinical trials were required or conducted in CD and UC. Remsima was thus launched in the UK in a completely unprecedented position; as a 'new' biological medicine that lacked any clinical data in the most common gastroenterology indications of CD and UC. Dissemination of real-world evidence and peer-to-peer sharing of real-world experience of use of Remsima in CD and UC was critical in providing gastroenterologists with the knowledge and confidence to use it for these conditions. The necessity of sharing this real-world experience was made very clear to Napp in pre-launch advisory boards for Remsima. Napp provided the excerpts from a gastroenterologist and specialist gastroenterology nurse advisory board to illustrate the point.

PANEL RULING

The Panel noted that the agenda for the meeting at issue, which was sent to delegates, stated that the focus of the event was to share best practice in the treatment of IBD in both the UK and Norway, to facilitate discussion about the standard of care in Norway compared with the UK and to identify areas of best practice in both countries. It was further stated that discussions would also focus on the introduction of biosimilars for the treatment of IBD including clinician and patient experience in Norway. The front cover of the agenda stated 'This meeting is organised by Napp Pharmaceuticals. Discussion of Napp Pharmaceuticals' products will take place at this event'. Prescribing information for Remsima was on the back outside cover.

The meeting proposal certified by Napp stated that the meeting had been developed in response to feed-back from pre-launch advisory boards that real world evidence and experience from clinicians who had used Remsima was important. Remsima had been available in Norway since January 2014 but was not launched in the UK until February 2015. Biosimilar infliximab in Norway had a 63% market share. One of the stated aims of the meeting was to allow key opinion leaders to share real world experience with Norwegian clinicians who used Remsima in IBD given that clinical data in IBD patients and practical experience in the UK of using biosimilar infliximab was very limited. The Panel noted Napp's submission that the meeting was promotional; the agenda showed that two presentations on the first morning were specifically about initiating or switching treatment with Remsima. The Panel further noted Napp's submission that the Norwegian Medicines Agency had conducted a government sponsored 500 patient, randomised, double-blind trial to assess the safety and efficacy of switching from originator infliximab to Remsima (the NOR-SWITCH study). As the study had received some publicity in the UK, Napp believed the delegates would value the opportunity to meet with some of the study investigators and discuss their experiences with Remsima as part of this trial. Notwithstanding tours of two university hospital gastroenterology clinics included on the agenda, in the Panel's view the meeting was organised specifically with a focus on Remsima and to promote switching from Remicade to Remsima in IBD.

In the Panel's view, the sales force briefing about the meeting, which listed the criteria for inviting potential delegates, further emphasised the importance of Remsima to the meeting for Napp as opposed to sharing best practice as stated on the agenda. The potential delegates appeared to have been chosen for their ability to influence decisions about the use of Remsima. Delegates had to fulfil the following criteria:

'Secondary care healthcare professionals with an interest in gastroenterology medicine from each region who fulfil the following criteria:

- Will benefit from the educational agenda at the Norway IBD Exchange
- Are recognised as a national or regional opinion leader
- Will be involved in early education or decision making in relation to the use of Remsima and would benefit from understanding about the real world usage of Remsima in Norway

And who also fulfils one of the following additional criteria;

- Have training and education responsibilities at a national or regional level

- Have presented at local, regional or national meetings and congresses
- Have a history of producing key publications in gastroenterology
- Have a history of commissioning in gastroenterology.'

With regard to follow-up of the March delegates, the Panel noted Napp's submission that two had provided services to Napp since the exchange meeting; one had attended an advisory board regarding biosimilar infliximab uptake in London in July 2015 and the other authored a Remsima promotional advertorial which was published in a journal and attended an advisory board regarding biosimilar infliximab uptake in London in July 2015. With regard to the October delegates, Napp had provisional plans to ask two of them to speak at future promotional meetings but nothing was confirmed to date. The Panel noted that Napp's submission on this point appeared contrary to its statement that there had been no particular follow up with any of the delegates of the March or October meetings by Napp head office staff and Napp promotional staff had not been asked to follow up with attendees. In that regard the Panel also noted Napp's submission that of the 21 delegates at the October meeting, only 1, a specialist nurse had begun switching and 2 were considering switching.

The Panel noted that the supplementary information to Clause 22 stated that meetings organised by pharmaceutical companies which involved UK health professionals at venues outside the UK were not necessarily unacceptable. There had, however, to be valid and cogent reasons for holding meetings at such venues. These were that most of the invitees were from outside the UK and, given their countries of origin, it made greater logistical sense to hold the meeting outside the UK or, given the location of the relevant resource or expertise that was the object or subject matter of the meeting, it made greater logistical sense to hold the meeting outside the UK. As with meetings held in the UK, in determining whether such a meeting was acceptable or not, consideration must also be given to the educational programme, overall cost, facilities offered by the venue, nature of the audience, subsistence provided and the like. As with any meeting it should be the programme that attracted delegates and not the associated hospitality or venue.

The Panel noted that the meeting in question was the second of its kind. The first Norway IBD Exchange had been held in March 2015. The October 2015 meeting proposal form submitted by Napp indicated that due to the excellent feedback from March it had been decided to repeat the event. That feedback from a meeting was positive did not mean, by that very fact, that it was appropriate to take UK health professionals outside the UK or that the meeting otherwise complied with the Code. The Panel noted that the feedback form from the March meeting asked the delegates (questions 9 and 10) to rate the two hospital tours; everyone thought they were, good, very good or excellent. Similar feedback was obtained from the October meeting. Question 11 was 'After what you have heard discussed at the meeting, has this helped reassure you about using biosimilars in your own clinical practice?'; everyone from the March meeting answered 'Yes' and some specifically referred to switching. Similar responses were given by those attending the October meeting. All but one of the delegates indicated that they thought the March meeting would have an impact on how they managed their IBD patients (question 12). Two delegates from the October meeting did not think the event would change how they managed patients. Again, some of the respondents from both meetings referred to switching.

Turning to the meeting at issue (the October Norway IBD Exchange) the Panel noted that it was wholly for UK health professionals; the delegates comprised 10 specialist nurses, 10 consultant gastroenterologists and one IBD Fellow. Three hospitals each had two delegates at the meeting. In addition six Napp staff attended. The speaker panel consisted of two UK clinicians and two Norwegian professors.

The Panel noted Napp's submission that the meeting allowed key opinion leaders to share real world experience with Norwegian clinicians who used Remsima in IBD given that clinical data in IBD patients and practical experience in the UK of using biosimilar infliximab was very limited. The Panel considered that this submission was at odds with Napp's explanation about the comparability of biosimilars and that 'Remsima was infliximab just as much as the many batches of originator Remicade were infliximab'. The Panel further noted Napp's submission that the EMA had stated that Remsima was highly similar to the originator and had not shown any clinically meaningful differences as part of its submission.

The Panel noted that the meeting agenda included tours of the gastroenterology clinics of two local university hospitals. Napp submitted that such tours were so that delegates could see how the biosimilar infliximab was delivered in a real-life clinical setting and speak to clinicians and specialist nurses at the hospitals who had actually administered the product. The Panel noted from the leavepiece at issue in Point B below however, that in terms of switching from Remicade to Remsima, it was claimed, *inter alia*, that 'Your clinic won't need to change how it does things' and that there was 'no need for new staff training'. In the Panel's view, although the UK delegates would have a professional interest in seeing the Norwegian clinics, such tours were not integral to the main focus of the meeting. In the agenda given to delegates both tours of the hospitals appeared to be identical in that both would include an overview of the clinic, standards of care and best practice with anti-TNF therapy, patient flow through the system, consultations, infusion procedure, capacity planning and the efficient running of clinics. In the briefing given to the chair and co-chair of the meeting, each of whom would host one of the hospital tours, less detail was given in that it was stated that during the tours it would be 'good if some of the clinic nurses are available, to hear their perspective and views on such things as the infusion procedure, capacity planning, and information that is given to patients to support them'. Overall the Panel considered that it would have made much more logistical sense to have the two Norwegian clinicians, and the IBD nurse specialist from Oslo, visit the UK to discuss their experiences and relevant patient case histories with their UK counterparts. Alternatively, the Panel queried

whether the meeting could have been conducted on-line. It appeared that the two hospital tours had been included to help justify the meeting being held in Norway. Given the lack of a clear and cogent reason to hold the meeting outside the UK, the Panel ruled a breach of Clause 22.1.

The Panel noted that the delegates had been invited to a two day meeting in Norway, the primary objective of which appeared to be to allay their concerns about switching IBD patients from Remicade to Remsima. The average total cost of hospitality, to include air fares, was £799.73 per person. The Panel considered that in and of itself, the hospitality had not been excessive although two evening meals each of just over £61 per head was on the limits of acceptability bearing in mind the relevant requirements of the Norwegian Code. Nonetheless, the Panel considered that hosting UK delegates for a two day promotional meeting in Norway, in circumstances where the Panel did not consider that there was a clear and cogent reason for holding the meeting outside the UK, was an inducement to prescribe or recommend Remsima. A breach of Clause 18.1 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that the supplementary information to Clause 2 stated that, *inter alia*, one activity likely to be in breach of Clause 2 was an inducement to prescribe. The Panel noted its comments above and its ruling of a breach of Clause 18.1 and thus considered that holding the meeting in question in Norway was such as to bring discredit upon and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

During its consideration of this matter the Panel was concerned to note that the presentation on initiating and switching treatment with Remsima appeared to refer to a dose of Remsima which was not in accordance with the particulars listed in the SPC. Slide 10 referred to a dose of 300mg Remsima in a patient who weighed 50kg. An asterisk beside the patient's weight took the reader to a statement which read 'The licensed posology for Remsima in moderate to severe [Crohn's disease] is 5mg/kg'. The Panel noted that the supplementary information to Clause 7.2 stated that claims must be capable of standing alone; in general, claims should not be qualified by the use of footnotes and the like. The Panel queried the acceptability under the Code of referring to a 6mg/kg dose of Remsima and requested that Napp be advised of its concern in this regard.

APPEAL BY NAPP

Promotional nature of the meeting

Napp noted that the Panel had highlighted that the meeting was promotional in nature and concluded that 'Notwithstanding tours of two university gastroenterology clinics included on the agenda, in the Panel's view the meeting was organised specifically with a focus on Remsima and to promote switching from Remicade to Remsima in IBD'.

Whilst Napp agreed that the meeting was promotional it strongly disagreed with the Panel's conclusion that the trip was specifically focused only on Remsima and switching from Remicade to Remsima. There was a much larger content of non-Remsima related education exchanging the clinical management, service delivery and healthcare organisation of IBD in Norway and UK.

The timings were as follows:

- 9.25 hours total meeting agenda (excluding breaks and travel time)
- 1.5 hours (~16%) on two presentations on the clinical use of Remsima in both new and switch patients by Norwegian expert gastroenterology professors
- 7.75 hours (~84%) spent on IBD clinical management and practical visits to the two hospitals.

Furthermore, Napp submitted that the two hospital tours, which were carefully planned and an integral component of the visit rather than an afterthought as suggested by the Panel, comprised 3.5 hours (38%) of the meeting. If it had not been possible to tour the two national IBD centre hospitals in Oslo then the meeting would not have been held.

Napp agreed that this was a promotional meeting but with a highly predominant (~84%) educational and practical discussion on all aspects of the management of IBD patients, contrasting the practices in UK and Norway.

Napp submitted that it made it clear in its response above that the agenda was conceived as having clear educational content (as per Clause 22.1 supplementary information) and organised by the medical department. However because Remsima would be discussed, as well as other biosimilar and originator products, Napp viewed it as a promotional meeting and so all related materials were certified as promotional, and included all obligatory information in accordance with Clause 4.2.

Selection of delegates

The Panel stated that criteria for delegate selection '… further emphasised the importance of Remsima to the meeting for Napp as opposed to sharing best practice as stated on the agenda.' and 'The potential delegates appeared to have been chosen for their ability to influence decisions about the use of Remsima'.

Napp agreed that one of the selection criteria for health professionals was their ability to influence decisions about the use of Remsima. Of equal importance was that they were recognised as a national or regional opinion leader and would benefit from the educational agenda, which included sharing best practice. Four further selection criteria were also applied, with delegates having at least one of the following:

- Training and education responsibilities nationally or regionally
- Presented at local, regional or national meetings and congresses

- A history of producing key publications in gastroenterology
- A history of commissioning in gastroenterology.

Napp submitted that these criteria ensured that the delegates were appropriate health professionals to educate their peers and implement service improvements after the IBD exchange meeting. The speaker faculty included two recognised UK gastroenterology key opinion leaders who presented UK IBD best practice, whilst two eminent Norwegian professors of gastroenterology, presented Norwegian IBD practice. There were no promotional presentations given by Napp staff. Napp therefore disagreed with the Panel's conclusion that the meeting was predominantly about promoting Remsima.

Napp understood that the Code did not prohibit companies selecting health professionals to be promoted to, based on their ability to influence decisions about the use of specific products. This was indeed the daily activity of the pharmaceutical industry promoting to health professionals.

Subsequent delegate 'follow-up' and consultancy

Napp noted that the Panel ruling discussed the fact that two of the March meeting delegates had subsequently provided consultancy services to Napp, and that Napp had provisional plans to approach two further delegates to provide consultancy services. The Panel ruling then noted that '… Napp's submission on this point appeared contrary to its statement that there had been no particular follow up with any of the delegates …'.

Napp submitted that there had been no particular follow up with any of the delegates. Napp made this submission in response to the first of three questions (see below) as part of the Panel's request for further information:

> '4. What follow up has there been with attendees of the Norway IBD exchange meetings? Have any of the delegates been contracted to present or provide any other services on behalf of Napp Pharmaceuticals following their attendance at one of the Norway IBD exchange meetings? Was there any follow up on or monitoring of Remsima use following these exchange meetings?'

Napp submitted that this request for further information consisted of three distinct questions, which it interpreted as mutually exclusive and not directly connected when answering them. Napp's response to the first question was that there had been no particular 'follow up' which it interpreted to mean specific 'visit' to delegates post Norway trip. Napp's response to the second question stated that two of the March delegates had subsequently acted as consultants, and that Napp was considering similarly approaching two of the October delegates. These activities would have occurred irrespective of whether the health professionals involved had attended Norway or not, since they were consultant gastroenterologists with relevant sub-specialty expert knowledge of IBD. Napp apologised if its response appeared contradictory on this point, and hoped its reasoning was now clear.

The Panel also noted that the meeting in October was the second to be held in Norway and commented 'That feedback from a meeting was positive did not mean, by that very fact, that it was appropriate to take UK health professionals outside of the UK …'. The second meeting in October was not held simply due to positive feedback from the March delegates. Commercial (IMS market share) data in July 2015, when it was decided to conduct another Norway trip, highlighted that Remsima usage was very low (1% of UK infliximab market) and feedback from clinicians was that there was still an educational need to understand biosimilars. Napp took the feedback from the March meeting into account insofar that 100% of the delegates confirmed the meeting had helped to reassure them about using biosimilars in their own clinical practice. With all of this information Napp considered that repeating the Norway meeting was appropriate. Finally, when the meeting was arranged there were no UK hospitals with significant experience of treating patients with biosimilar infliximab, and therefore no associated clinical service changes.

Acceptability of meetings outside the UK

The Panel detailed the criteria by which it might be considered acceptable for a pharmaceutical company to organise a meeting outside of the UK. The Panel quoted directly from the supplementary information to Clause 22.1 'There had, however, to be valid and cogent reasons for holding meetings at such venues [outside the UK]. These were that … given the location of the relevant resource or expertise that was the object or subject matter of the meeting, it made greater logistical sense to hold the meeting outside the UK'.

Napp reiterated that it carefully considered this meeting in relation to the supplementary information to Clause 22.1; in its view, given the location of the relevant resource and expertise, there were valid and cogent reasons for conducting this meeting in Norway.

Legitimacy of the educational need regarding biosimilars (I)

Napp noted that the Panel had noted its submission that the meeting allowed key opinion leaders to share real world experience of use of Remsima in IBD, given that clinical data in IBD patients and practical experience of using the product in the UK was very limited. The Panel further noted that Remsima and Remicade were highly similar medicines with no clinically meaningful differences between the two. Napp submitted that the ruling then stated that the Panel considered these two submissions to be 'at odds', ie it implied that learning about practical use of Remsima could not be an adequate justification for the meeting when the practical use of Remsima was apparently identical to that of Remicade.

Napp submitted that the introduction of the world's first monoclonal antibody biosimilar (Remsima) to gastroenterologists who had had no previous experience with other biosimilars and also with no clinical data in IBD brought with it significant educational and practical considerations. Napp submitted that the Panel was correct that gaining both educational and practical experience of the use

of biosimilar infliximab (Remsima) in IBD was an objective of the meeting, but not the main one. The Panel was also correct to note that Remicade and Remsima were highly similar biological medicines. However the high similarity of Remicade to Remsima did not preclude the significant need to educate IBD specialists in the practical use of biosimilar infliximab (Remsima). This was further supported by a September, 2015 NHS England publication entitled 'What is a biosimilar medicine' along with several others cited in Napp's original response.

Napp referred to its response above in which it submitted that not only were Remsima and Remicade highly similar (as the Panel had noted), but also that this fact was commonly misunderstood or confused by health professionals, ('What is a Biosimilar', NHS England, Weise *et al*, 2012, Kurki 2015, Van der Plus *et al*, 2015, and Weise *et al*, 2014). Napp referred to statistics from a recent independent survey of European gastroenterologists conducted by the European Crohn's and Colitis Organization (ECCO), (Danese *et al*, 2015).

- The majority of respondents (70%) were aware that a biosimilar was a similar copy, but not equal to the originator, 19% responded that it was a copy of a biological agent, identical to the originator (like a generic), with a further 8% confusing a biosimilar with a different anti-TNF agent, like adalimumab to infliximab. **[ie 30% of gastroenterologists did not have a basic conceptual understanding of what a biosimilar was.]**
- The responders ranked as the main issue of biosimilars a different immunogenicity pattern than the originator (67%), while only 6% of respondents stated that there were no additional issues. **[Increased immunogenicity of a biosimilar product compared to its corresponding reference product would strictly preclude authorisation, therefore 67% of gastroenterologists were mistaken in this belief]**
- When asked if they would feel confident in prescribing biosimilars to their patients, most **(61%) felt little or no confidence in using biosimilars in their everyday clinical practice**, 26% felt confident enough to use biosimilars, 8% were very confident, and 5% were totally confident. **(Emphasis added)**

Napp submitted that the Panel ruling was incorrect with regard to a lack of need for education on biosimilars. Napp submitted that there was a legitimate educational need regarding biosimilar infliximab, and in Norway where there was the relevant resource and expertise not present in the UK when the meeting was organised. The educational legitimacy of the meeting was further substantiated by the results of the delegate feedback which Napp had previously communicated to the Panel. One delegate sent the following unsolicited feedback: 'I found the trip extremely educational – it will certainly change several aspects of my day-to-day practice!' – gastroenterology consultant.

The Panel stated that the leavepiece at issue in point B demonstrated, *inter alia*, that there was no educational need surrounding biosimilars, due to the inclusion of the claims 'Your clinic won't need to change how it does things' and 'no need for new staff training'.

Legitimacy of the educational need regarding biosimilars (II)

Napp submitted that the two abbreviated leavepiece quotations by the Panel were presented out of context. The full quotation made it clear that these statements referred specifically and only to the reconstitution, dilution and intravenous administration of Remsima. It did not follow that there was no educational requirement around biosimilars – it was simply designed to reassure clinicians that the preparation and intravenous administration of Remsima was the same as for Remicade.

Importance of the hospital tours, justification of the location and breach of Clause 22.1

The Panel further stated that '… although the UK delegates would have a professional interest in seeing the Norwegian clinics, such tours were not integral to the main focus of the meeting'. The reasons cited were that the agenda for the two hospital tours appeared to be identical and that the briefing given to the two meeting chairs (and hosts of the two hospital tours), was not sufficiently detailed/prescriptive in terms of the tour contents.

The Panel further stated that 'It appeared that the two hospital tours had been included to help justify the meeting being held in Norway', before concluding that it would have made more logistical sense to bring the two Norwegian clinicians and IBD nurse specialist to the UK, or that the meeting could have alternatively been conducted online. Therefore the Panel did not consider there had been a clear and cogent reason to hold the meeting outside the UK, and ruled no breach of Clause 22.1.

Napp submitted that the agendas for the two hospital tours were both similar, but not identical, because of differences between the hospital facilities, gastroenterology layout and service operations. However, as the hospital tours comprised 3.5 hours (38%) of the entire agenda, Napp strongly disagreed that the hospital tours were 'not integral to the main focus of the meeting', nor 'had been included to help justify the meeting held in Norway'. As detailed above the majority of UK gastroenterologists and IBD specialist nurses had little or no confidence in the practical use of biosimilars.

Napp submitted that in planning the meeting two Napp medical staff twice visited the two Norwegian gastroenterology professors who co-chaired the meeting and hosted the hospital tours to discuss in detail the arrangements and logistics of the agenda and the hospital tours. The first meeting was held on 10 November 2014 where the Napp staff proposed a draft agenda. The hospital tours were always an integral part of the meeting since biosimilar infliximab was administered as an infusion in the hospital setting only. As outlined in the meeting proposal the hospital tours focused on:

- An overview of the gastroenterology clinic set up and facilities
- Standards of care and best practice with anti-TNF therapy in the management of IBD patients at these national centres of excellence in the

management of IBD
- How patients flow through the hospital system
- Patient outpatient facilities and consultations
- Infusion room set up, medicine handling and infusion procedures
- Capacity planning – how was this approached?
- Running clinics most effectively to improve efficiencies.

Napp submitted that it was particularly important that delegates saw how biosimilar infliximab infusions had been incorporated into the Norwegian IBD clinics, how the department managed the aseptic preparation of two brands of infliximab, how the medicine was administered and spoke to clinicians, nurses and patients about their experiences of biosimilar infliximab, providing food for thought and reassurance for the visiting UK health professionals.

Napp submitted that at the initial meeting the professors agreed the hospital tours were a vital element of the agenda and sought permission from their hospital managers that UK delegates could be shown around. Indeed one of the professors stated 'yes we could travel to UK to tell about our experience, having discussions, but showing our department, areas, locations, organisations, nurse led IBD visits - would never been the same'. Napp reiterated that without permission to conduct the tours, the meeting would not have gone ahead.

Napp submitted that on 2 March 2015 the two Napp medical staff visited Oslo to finalise the hospital tour agendas. They spent two hours at each of the hospitals touring each with the professors. They discussed what would be important for the delegates to see as well as who it would be important for the delegates to meet and speak with, including senior and junior gastroenterology clinicians, IBD specialist nurses and patients. Further to these verbal briefings, the speaker contracts for the two professors clearly stated 'when you give the UK clinicians a tour of the clinic', thus confirming the hospital tours were expected to occur.

Napp submitted that there were also several differences in the practicalities of the physical set up and organisation of the gastroenterology services within the UK and also between the two Norwegian hospitals, which were both national centres of excellence. Napp submitted that there was a legitimate educational need for delegates to gain first-hand clinical experience and understanding of the specialised resources and expertise within Norway. When the meeting was held in October there was no such equivalent hospital in UK which could match that found in Norway.

Napp submitted that with regard to visiting two hospitals in Norway, the analogy could be drawn of visiting one hospital in UK and concluding that all hospitals operated the same way without consideration to its surroundings and facilities. At the macro level they might be, but not at the more detailed level of service provision, physical surroundings/facilities, equipment, staffing, resources, capacity planning etc. In the case of the two hospitals they contrasted gastroenterology services at a hospital with old buildings physical surroundings and design, vs a sleek modern state of the art highly automated and digital hospital. Indeed one of the IBD specialist nurses stated 'The 2 hospital visits were very interesting. The new state-of-the-art hospital vs the old fashioned one that I am used to'.

Napp refuted the Panel's claim that '… it would have made much more logistical sense to have the two Norwegian clinicians, and the IBD nurse specialist from Oslo visit the UK to discuss their experiences and relevant case histories with their UK counterparts.' '… or be conducted on-line'. If the meeting had only involved a series of educational presentations then Napp would agree. Clearly this would have not been a possibility for the hospital tours due to lack of resources in the UK and the expertise found in Norway. The hospital tours did not consist only of discussions with the two clinicians and IBD nurse specialist, as asserted by the Panel. On the contrary, the hospital tours included:

- Several opportunities for the delegates to meet and converse with a number of IBD clinical staff of varying roles and responsibilities regarding all aspects of their roles
- Direct observation and discussion of the infusion suite facilities, capacity issues, logistics of patient databases and experiences of any clinical issues when infusing originator or biosimilars
- Direct observation and discussion of the medicines dispensing, storage, reconstitution and preparation facilities used for infusions
- Direct observation and discussion of the quality and layout of the endoscopy suites and associated facilities in the two hospitals
- A visit to the outpatient consulting rooms to meet and discuss patient flow and how the IBD specialist nurses run their own patient consultations
- An opportunity for the delegates to meet and talk with IBD patients who had received or were in the process of receiving intravenous biological medicine infusions, including Remsima. This provided reassurance that the biosimilar was tolerated as an infusion just as for the originator medicine, Remicade
- Direct observation and contrasts of the logistics and distribution systems within the two hospitals
- A demonstration of how registry data was captured in an on-line electronic database, which then fed into the national IBD registry (something which the UK IBD community was trying to emulate)
- A meeting in his research laboratory with an eminent scientist at one hospital who discovered and developed one of the primary diagnostic tests used by IBD clinicians (faecal calprotectin). This also was an opportunity for him to discuss some of his more recent research activities
- A meeting with the wider nurse team about how they keep up-to-date and share knowledge with IBD nurse networks across Norway.

Photographs which showed the delegates during the tour of the two hospitals were provided.

Napp submitted that when the meeting was held, the objectives above could not have been met by visiting

a UK hospital because this experience did not exist (both in terms of the amount of biosimilar infliximab usage and long term follow up). Obviously, it would not be possible to transport all facilities, staff, and patients from Norway to the UK for this purpose. Napp submitted that the Panel's suggestion that the meeting could have been conducted online was an unsatisfactory proposal. If this were the case then videoconferencing would have replaced national and international conferences and other multi-participant meetings, which had not happened. The limitations and difficulties of conducting multi-participant teleconferences were well known. In this particular case what could not easily be reproduced was the 360 degree view of each area of the hospital when accompanied by fellow health professionals. This facilitated discussions and observations of room layouts eg of the endoscopy suite and of the infusion suite, where the infusions were prepared. Also even basic observations contrasting the ultra-modern facilities of one hospital with the older hospital. Additional feedback was sought from delegates as a result of this complaint, and Napp provided comments from various delegates to support the importance of the hospital tours. (Napp similarly noted that the PMCPA Guidance on Appeal Procedures Point 7 (Hearing by the Appeal Board), stated that joining an appeal meeting by teleconference was not viable.

In conclusion, the two contrasting hospital tours were highly educational and a practical unique resource in accordance with Clause 22. It would not have been logistically possible to conduct the hospital tours in the UK nor online. Napp therefore strongly disagreed that there was not a 'clear and cogent reason' for conducting the meeting in Norway, and therefore appealed the Panel's ruling of Clause 22.1.

Cost of hospitality

The Panel noted that the cost of '… hospitality had not been excessive although two evening meals each of just over £61 per head was on the limits of acceptability bearing in mind the relevant requirements of the Norwegian Code'.

Napp noted that the figure of '£61 per head' was from its response which preceded the actual visit to Norway when maximal predicted costs were certified. These were then monitored to ensure they did not exceed this limit. As stated previously the cost for dinner on the first night was £44.97 per head, and £54.06 per head on the second night. Napp would respectfully contest the Panel's use of the phrase '… on the limits of acceptability …' in this context. Napp submitted that the use of this phrase seeks to characterise Napp's conduct as unacceptable. The Norwegian Code of Practice asserted a strict quantitative limit (£63) to the cost of a dinner which was clearly not exceeded, therefore no unacceptable conduct had occurred.

Inducement to prescribe and breach of Clauses 18.1, 9.1 and 2

Napp noted that the Panel ruled that as there was no clear and cogent reason for holding the meeting outside the UK, the meeting constituted a breach of Clause 18.1, and consequently a breach of Clause 2.

Napp submitted that it had carefully explained that there were clear and cogent reasons for the meeting to take place in Norway. The meeting was not intended to be an inducement to prescribe, nor was it perceived as such by the delegates or faculty. All hospitality was within established cost guidelines, air travel was economy class, travel within Norway was by group coach or economy class train, the hotel used was not luxurious, there was no scheduled time in the agenda for social or tourist activities other than one dinner outside the hotel, and there was a very busy educational schedule. In fact one delegate commented on how 'jam-packed' the educational agenda was and that he had 'worked extremely hard' during the meeting.

Napp submitted that the meeting was designed and intended to meet a legitimate educational need amongst gastroenterology specialists and IBD specialist nurses regarding the practical experience of implementing biosimilar infliximab into clinical practice. When the meeting was held this could only have been realistically achieved by taking delegates to Norwegian IBD centres of excellence which had already significant clinical experience of Remsima for over a year. Napp therefore appealed the Panel's ruling of Clauses 18.1, 9.1 and 2.

Concluding remarks

Contrary to the complainant's allegations, Napp submitted that it had always upheld the highest standards with respect to the Code, and had provided detailed explanations for its actions. Napp was shocked and upset to receive the anonymous complaint about the Norway meeting. The meeting was not an inducement to prescribe or a reward for switching and certainly not a 'junket'. Napp continued to defend the care and attention in planning and conduct of this highly educational, promotional meeting. Napp considered that the sharing of real-world experience provided important practical evidence of the safety and effectiveness of biosimilars in clinical practice. It also provided a better understanding for clinicians to allay their concerns and those of their patients and give them the confidence to use biosimilars in appropriate patients. Napp submitted that this was a rational and responsible course of action.

APPEAL BOARD RULING

The Appeal Board noted Napp's submission that Remsima was the world's first monoclonal antibody biosimilar of infliximab. Napp further submitted that the process by which biosimilars were granted a marketing authorization posed a unique challenge to clinician understanding, and health professionals were confused and lacked confidence about biosimilars. Napp submitted that there was a significant and legitimate educational need relating to the clinical use of biosimilar infliximab in the UK. The evidence required for Remsima's licence was to show that it and the reference medicine (Remicade) were essentially the same biological substance and clinical studies were only confirmatory. The Appeal Board noted Napp's submission that in the case of infliximab the clinical studies were not in gastroenterology

but that extrapolation from rheumatology studies to IBD was possible based on the overall evidence of comparability. Thus there was less direct data on the clinical efficacy and safety of Remsima in gastroenterology than would have been available for Remicade. When Remsima was launched in the UK (February 2015), clinical data in IBD and practical clinical experience with biosimilar infliximab was extremely limited. The Appeal Board further noted Napp's submission that Norwegian clinics, however, had used Remsima since early 2014; the position by June 2015 was that Remsima was used for all new IBD patients nationally and several IBD centres had switched to 100% Remsima.

The Appeal Board noted that apart from the originator medicine, Remicade, which had been on the UK market for 15 years, there were now two biosimilar infliximabs available, Remsima and Inflectra. The Appeal Board noted Napp's submission that planning for the October meeting had started in June at which time only one or two centres in the UK were using Remsima. In that regard, however, the Appeal Board noted that a National Institute for Health and Care Excellence (NICE) report, 'Introducing biosimilar versions of infliximab: Inflectra and Remsima', published 31 July 2015 and provided by Napp, stated that between April and June 2015 one UK hospital had switched 150 IBD patients from Remicade to the biosimilar infliximab, Inflectra. The Appeal Board thus noted that shortly after starting to plan the meeting in question, there was published data which referred to relevant experience of switching gastroenterology patients to biosimilar infliximab in the UK, albeit short-term data compared with the longer term use of a biosimilar infliximab in Norway.

The Appeal Board noted that delegates to the meeting had toured the two Norwegian hospitals in groups. The tours of the two hospitals lasted in total 3.5 hours. In the newer hospital the group size was ten with smaller groups touring the older hospital. In that regard the Appeal Board queried whether the group sizes and the relatively short time spent in each hospital were compatible with the delegates being able to observe and absorb meaningful, relevant details about service provision, patient flow, logistics etc.

The Appeal Board noted that the supplementary information to Clause 22 stated that meetings organised by pharmaceutical companies which involved UK health professionals at venues outside the UK were not necessarily unacceptable. There had, however, to be valid and cogent reasons for holding meetings at such venues. In the Appeal Board's view, given the evidence required for Remsima's marketing authorization that there was no difference in the use, dose or preparation of Remicade and Remsima, and there was UK experience of switching IBD patients from Remicade to a biosimilar infliximab, there was no clear and cogent reason for the UK delegates to travel to Norway for the meeting. That was not to say that some way could not have been found of incorporating the Norwegian experience into a meeting held in the UK. Nonetheless, the Appeal Board upheld the Panel's ruling of a breach of Clause 22.1. The appeal on that point was unsuccessful.

The Appeal Board noted that UK delegates had attended a two day meeting in Norway, which had been paid for by Napp. The Appeal Board considered that although the level of subsistence had not been excessive, hosting UK delegates for a two day Remsima promotional meeting in Norway, where there was no clear and cogent reason for holding that meeting outside the UK, was an inducement to prescribe or recommend Remsima. The Appeal Board thus upheld the Panel's ruling of a breach of Clause 18.1. The appeal on that point was unsuccessful.

The Appeal Board noted its rulings above and considered that high standards had not been maintained and it upheld the Panel's ruling of a breach of Clause 9.1. The appeal on that point was unsuccessful.

The Appeal Board noted that biosimilars were emerging therapies which due to the way in which they were granted a marketing authorization meant that, as with Remsima, direct clinical data might not be available in all therapy areas. Health professionals in therapy areas where the direct clinical data might be lacking needed to understand and have confidence in that process. In that regard the Appeal Board considered that whilst the location of the meeting was unacceptable, the aim of the meeting was not unreasonable. The Appeal Board noted its rulings and comments above and decided that on the facts of this case, a ruling of a breach of Clause 2 would be disproportionate. On balance, the Appeal Board ruled no breach of Clause 2. The appeal on that point was successful.

B Remsima Leavepiece (ref UK/REMS-15078)

The leavepiece was entitled 'Your guide to changing treatment Remicade → Remsima'.

COMPLAINT

The complainant provided a copy of a leavepiece which explained the process for switching treatments. The complainant was very concerned that the UK pharmaceutical industry continued to pursue such an aggressive stance on switching between treatments with little concern for patients, or patient safety. There was no reference in the leavepiece to the conditions which either of the medicines in question were used to treat, and it was even suggested that there should be no safety concerns associated with switching to Remsima, despite being a recently licensed medicine with limited safety information. The complainant submitted that this type of irresponsible action by the pharmaceutical industry put patient's safety, and indeed lives, at risk.

The complainant summarised his/her complaint by stating that this type of activity did nothing for the reputation of either Napp or the UK pharmaceutical industry as a whole. More worrying was the effect that this negligent and unethical behaviour would have on patients. [This comment was taken by the Panel to apply equally apply to the meeting at issue in Point A above and the leavepiece].

When notified of the complaint, Napp was asked to respond in relation to Clauses 2, 7.2, 7.9, 7.10 and 9.1 of the Code.

RESPONSE

Napp disagreed that switching from an originator biologic to a biosimilar version of infliximab was pursuing an 'aggressive stance on switching between treatments with little care for patients, or patient safety'. The leavepiece in question which promoted a switch was created as a supplementary item in response to health professionals' requests for clarity around how to switch, ie as a practical guide to changing treatment (a copy of the switch leavepiece briefing, (ref UK/REM-15078a) was provided). For example, several health professionals were confused over whether they could use the biosimilar infliximab in patients who had previously had an adverse reaction to the originator infliximab. This was addressed on pages 2 and 3 of the leavepiece when emphasising eligibility criteria. Furthermore, page 3 of the leavepiece highlighted in a grey box that 'the decision to switch should still always be done on a case-by-case basis with the consent of the treating physician and the patient'. Napp submitted that the leavepiece promoted the rational use of Remsima and in that regard the company had not promoted aggressive switching and had carefully considered patient safety.

Napp noted that the front page of the leavepiece stated that 'Prescribing information can be found on the back' which listed all the licensed indications for Remsima. Thus the complainant was incorrect to assert that there was no mention of the conditions which either of the medicines in question were used to treat.

Napp further noted that point 2 on page 4 of the leavepiece also stated clearly and with references that 'The dosing and posology of Remsima is identical to Remicade across all licensed indications'. Furthermore, the leavepiece was left only with secondary care specialist health professionals who were also very familiar with infliximab; Remicade had been licensed in the UK for over 15 years (EMA approval, 13 August 1999).

The complainant stated that the leavepiece even suggested that there should be no safety concerns associated with switching to Remsima, despite it being 'a recently licensed medicine with limited safety information'. Napp assumed that this specifically related to page 6 of the leavepiece headed 'What to Expect after Switching'. The totality of current evidence (as per Clauses 7.2, 7.9 and 7.10) demonstrated the lack of any meaningful difference in clinical safety, efficacy or immunogenicity of biosimilar and originator infliximab. This included extensive regulatory *in vitro*, and controlled clinical trial data and was supplemented with post-marketing *in vitro* and *ex vivo* immunogenicity data, as well as increasing amounts of real-world clinical outcomes data.

Furthermore, the complainant did not explain why switching from an originator to a biosimilar was irresponsible and could 'put patient's safety, and indeed lives at risk'. As discussed above, Napp assumed that the complainant fundamentally misunderstood the concept of biosimilarity.

The overarching regulatory guidance explicitly stated that, 'The ultimate goal of the biosimilar comparability exercise is to exclude *any relevant differences* between the biosimilar and the reference medicinal product' (emphasis added). The EMA position had been further clarified in a publication co-authored by a number of senior employees of the EMA, the Medicines and Healthcare products Regulatory Agency (MHRA) and other European regulatory agencies, which stated, 'Undoubtedly, biosimilars developed in line with EU requirements can be considered therapeutic alternatives to their respective reference products'.

Patient populations had also on many occasions been exposed to changes in the molecular characteristics of their biological medicines that were directly comparable to the differences seen between originator and biosimilar medicines. It was therefore incorrect to suggest that Remsima was an 'irresponsible action by the pharmaceutical industry [which] puts patients safety and indeed lives at risk' implying that there was 'no clinical experience' in these types of changes.

Napp noted the wider European perspective on the switching to biosimilar infliximab from the originator product. Several European medicines regulatory agencies advocated switching to biosimilar infliximab – some (eg Denmark) actively mandated a switch for economic as well as clinical considerations. In some countries large-scale switches had therefore already occurred, resulting in uptake of ~70%, ~90% and ~38% for biosimilar infliximab in Norway, Denmark and Finland respectively. It was therefore misinformed and not credible to suggest that up to 90% of infliximab patients in some European countries had been treated irresponsibly.

Napp further noted the recent document from the NICE, 'Introducing biosimilar versions of infliximab: Inflectra and Remsima', the recent set of documents published by the PrescQIPP organisation about implementation of biosimilar infliximab, and the letter routinely sent from a UK hospital when patients were switched. All three of these authoritative UK organisations addressed the issue of switching from originator to biosimilar medicines and concluded that it was rational and responsible.

Counter to the complainant's proposition that switching a patient was an 'irresponsible action by the pharmaceutical industry [which] puts patient's safety, and indeed lives, at risk', section 4.4 of the NHS England document 'What is a Biosimilar Medicine?' answered the question of switching a patient to a biosimilars as follows:

> **'4.4 Can a patient already established on an originator biological medicine be switched to a biosimilar medicine?**
> There is growing practical NHS experience that demonstrates the safety and efficacy of biosimilars in clinical practice. The evidence regarding interchangeability is still developing. Guidance across some EU Member States currently recommends that switching between a reference product and its biosimilar (and indeed amongst biosimilar medicines) should be managed at the discretion of the individual prescriber in partnership with the patient, with appropriate monitoring in place. Evolving evidence and

treatment guidance should be made available to patients and prescribers to support them in their decision-making.'

In conclusion Napp submitted that the leavepiece complied with Clauses 7.2, 7.9 and 7.10. Napp had not stated that Remsima had no adverse reactions and safety had been qualified to encourage rational use without exaggeration or misleading claims. Napp had maintained high standards by careful consideration of how to promote switching without jeopardising patient safety. Napp submitted that it had not brought discredit upon, or reduced confidence in the pharmaceutical industry. Napp denied breaches of Clauses 9.1 and 2.

PANEL RULING

The Panel noted that the leavepiece at issue was a guide to changing treatment from Remicade to Remsima. In that regard the Panel noted that it was not unacceptable under the Code for a company to promote a simple switch from one product to another; companies could not, however, assist a health professional in implementing a switch. The leavepiece explained that Remsima was infliximab and a biosimilar of Remicade. It was stated that patients currently on Remicade could therefore be changed to Remsima treatment providing they were eligible. In that regard the Panel did not consider that it necessarily had to be stated in the main body of the leavepiece which conditions patients would be treated for; in any event, the Remsima prescribing information on the back of the leavepiece listed the licensed indications for the medicine. The Panel noted that the leavepiece listed those patients who would not be eligible for Remsima treatment (eg those who had previously had to discontinue Remicade therapy due to intolerance or lack of efficacy) and those who would be eligible (ie those who currently responded well to or remained stable on Remicade). In addition it was stated that any switch should always be done on a case-by-case basis. Having listed which patients might or might not be eligible for a switch, the leavepiece described how the switch should be carried out and what to expect after switching. On the back of the leavepiece was a highlighted box of text with additional safety information about the risk of tuberculosis during and after treatment with [Remsima].

The Panel did not consider that the leavepiece suggested that there were no safety concerns with Remsima as alleged. No breach of Clause 7.9 was ruled. The Panel considered that on the basis of the information before it, there was nothing to show that the leavepiece had not encouraged the rational use of the medicine; the eligibility or otherwise of patients had been made clear. No breach of Clause 7.10 was ruled. The Panel did not consider that the information in the leavepiece was misleading. No breach of Clause 7.2 was ruled.

The Panel noted its rulings above and did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled.

Given its rulings above, the Panel also ruled no breach of Clause 2.

Complaint received **18 September 2015**

Case completed **14 March 2016**