CASE AUTH/2868/8/16

JANSSEN-CILAG v SANOFI GENZYME

Promotion of an unlicensed medicine

Janssen alleged that at The European League Against Rheumatism (EULAR) Congress of Rheumatology held in London, in June 2016, Sanofi Genzyme had promoted its forthcoming interleukin-6 (IL-6) receptor blocker (sarilumab) prior to the grant of its licence.

Janssen noted that Sanofi Genzyme had several activities related to IL-6, these included a large exhibition stand that highlighted its importance in rheumatoid arthritis using claims, interactive videos and handouts, a sponsored symposium which discussed those benefits and included information about sarilumab and posters presenting the results of sarilumab studies. Janssen noted that in January 2016 Sanofi Genzyme announced that the US Food and Drug Administration accepted the licence application for sarilumab for review with a target action date of 30 October 2016; the EU licence application was accepted for review in July 2016.

Janssen considered that this case was an important precedent as it distinguished the difference between legitimate scientific exchange (for example the presentation and discussion of new data at a congress symposium) from the outright promotion of specific scientific activity (such as the promotion of the importance of a specific cytokine such as IL-6, when a company had an unlicensed IL-6 receptor blocker).

Janssen stated that it had not complained about the posters or the symposium *per se*, but that the overall conference activity, focussed specifically on IL-6 and its importance in rheumatoid arthritis, especially the exhibition stand, encouraged attendees to ask questions about sarilumab before the grant of its marketing authorization.

Janssen also alleged a breach for failing to maintain high standards.

The detailed response from Sanofi Genzyme is given below.

The Panel noted that Janssen's complaint was about information about IL-6 presented on Sanofi Genzyme's exhibition stand at the Congress. Although there was no complaint about other activities at the conference, the Panel agreed with Janssen's submission that the materials etc on the exhibition stand had to be viewed in the context of Sanofi Genzyme's other activities about IL-6 at the conference. Sanofi Genzyme's medicine, sarilumab, blocked IL-6 and was being developed as a possible treatment for rheumatoid arthritis. When the EULAR Congress was held, sarilumab did not have a marketing authorization although a licence had been applied for in the US and an EU licence application was about to be made.

The Panel noted that although the Code prohibited the promotion of a medicine prior to the grant of its marketing authorization, the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that this did not constitute promotion which was prohibited by the Code. The PMCPA Guidance about Clause 3 further stated that companies must ensure that such activities constituted a genuine exchange of information and were not promotional. Documents must not have the appearance of promotional material. It should be borne in mind that it would be a breach of the Code if non-promotional information on products or indications that were not licensed was used for a promotional purpose.

Promotion was defined as any activity undertaken by a pharmaceutical company or with its authority which promoted the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines.

The Panel noted that in addition to having the exhibition stand at the EULAR Congress, Sanofi Genzyme had sponsored a scientific symposium entitled 'IL-6 as a driver of joint destruction in rheumatoid arthritis: translating complex science into patient benefits'; one speaker would give an overview of the management of joint damage in rheumatoid arthritis, including the effectiveness of IL-6 inhibition. The graphics used on the symposium invitation, although different to those used on the exhibition stand, were not wholly dissimilar.

The exhibition stand appeared to be, from the photographs supplied by Janssen and the plans provided by Sanofi Genzyme, typical of those used by pharmaceutical companies at large conferences. One corner of the stand was designated as the medical corner. The statement 'As IL-6 elevates, the effects go beyond the joints' could be seen on what appeared to be the front and the back of the stand. Material on the stand was exclusively about IL-6 and its role in rheumatoid arthritis. One video for use on the stand was entitled 'IL-6 and articular manifestations of rheumatoid arthritis' and concluded that persistently elevated IL-6 might play a central role in the articular manifestations of rheumatoid arthritis, resulting in pain and disability in patients. A second module was entitled 'The role of IL-6 signalling in rheumatoid arthritis' and concluded that elevated IL-6 signalling in rheumatoid arthritis might lead to the disruption of homeostasis in many cell types and physiologic processes. Two key opinion leader videos on IL-6 in rheumatoid arthritis concluded with invitations for the viewer to review the relevant monographs which were available on the stand. Interactive touch screen panels detailed the role of elevated IL-6 levels in the articular and systemic manifestations of rheumatoid arthritis.

Briefing material reminded all staff (none of whom were from sales or marketing) attending the EULAR Congress that sarilumab was an investigational, unlicensed product in Europe and must not be pro-actively discussed with congress attendees. Although the term 'investigational' was not defined, the Panel queried whether a product for which a marketing authorization had been applied for in the US and would, within 5 weeks, be applied for in Europe, could be considered to be an 'investigational molecule' as stated in the briefing material or as being 'in development' as stated by Sanofi Genzyme in its response. In the Panel's view, health professionals were likely to view sarilumab as a pre-licence product. The briefing material continued by stating that if attendees wanted more information about sarilumab or IL-6 inhibitors then they should be referred to scientific advisers (medical scientific liaison (MSLs)) or medical personnel in the medical area of the stand. In the Panel's view, it was reasonable to assume that, on the balance of probabilities, many of the stand visitors would ask about IL-6 inhibition in general and/or Sanofi Genzyme's interest in the area in particular; a virtual reality presentation on the stand invited questions about IL-6 and rheumatoid arthritis. The briefing material had prepared staff for such questions and a discreet area on the stand in which to answer questions about sarilumab had been provided. Through possible US press activity, some visitors to the stand might have already known about Sanofi Genzyme's forthcoming product. The briefing material stated that delegates from every continent would be at the EULAR Congress. The symposium had discussed the effectiveness of IL-6 inhibition in the management of rheumatoid arthritis. In the Panel's view, given the content of the stand and the messages about the role of elevated IL-6 in rheumatoid arthritis, such questions could not take the benefit of personal, unsolicited requests for information referred to at Clause 1.2 of the Code. In the Panel's view the exhibition stand, within the context of Sanofi Genzyme's other activities about IL-6 at the conference, would prepare the market for the introduction of a new medicine for rheumatoid arthritis which would decrease IL-6 levels and solicit questions about the same; Sanofi Genzyme had a commercial interest in one such medicine. Given that that medicine was unlicensed, a breach was ruled. In that regard the Panel considered that high standards had not been maintained and a further breach was ruled. These rulings were upheld on appeal by Sanofi Genzyme.

Janssen alleged that at The European League Against Rheumatism (EULAR) Congress of Rheumatology held in London, in June 2016, Sanofi Genzyme had promoted its forthcoming interleukin-6 (IL-6) receptor blocker (sarilumab) prior to the grant of its licence. Janssen had raised its concerns with Sanofi Genzyme at the congress but inter-company dialogue had failed to resolve the companies' differences.

Sarilumab was developed jointly by Sanofi Genzyme and Regeneron. Regeneron, a US company, had a European head office in Ireland but as far as Janssen was aware did not have a specific UK presence. When advised of the complaint by the Authority, Regeneron declined to join the list of non-member companies that had agreed to comply with the Code and accept the jurisdiction of the Authority.

COMPLAINT

Janssen noted that Sanofi Genzyme had several activities related to IL-6; its importance in rheumatoid arthritis was highlighted by claims on its exhibition stand, interactive videos and handouts. Janssen noted that in January 2016 Sanofi Genzyme announced that the US Food and Drug Administration (FDA) accepted the biologics licence application for sarilumab for review with a target action date of 30 October 2016. The regulatory submission was indicated as being planned in the EU in quarter 3, 2016. Janssen stated that the EU licence application had since been accepted for review. Janssen provided copies of the press release issued by Sanofi Genzyme on 1 August 2016 which confirmed those dates.

Janssen accepted that companies could engage in legitimate scientific exchange; however, it considered that the nature and content of Sanofi Genzyme's congress activities exceeded the boundaries set in the supplementary information to Clause 3.1. Information was provided in such a manner as to promote the importance of IL-6 in rheumatoid arthritis. Janssen noted that in Case AUTH/2651/11/13, Merck Sharp & Dohme highlighted the risks of such linkage and implied that the promotion of the receptor activity for a specific indication/treatment would, in itself, constitute a breach of the Code. Janssen alleged that the nature of the activity at the congress promoted sarilumab and would have encouraged health professionals to ask questions about the product. This was underlined by the fact that the prominent promotion of IL-6 activity coincided with what would otherwise be legitimate scientific exchange about sarilumab (scientific posters and a symposium) but each would have propagated interest in the other.

Janssen explained that Sanofi Genzyme's activity included a large exhibition stand that promoted the benefits of addressing the cytokine IL-6, a sponsored symposium which further discussed those benefits and included information about sarilumab and posters presenting the results of sarilumab studies.

Janssen considered that this case was an important precedent as it distinguished the difference between legitimate scientific exchange (for example the presentation and discussion of new data at a congress symposium) from the outright promotion of specific scientific activity (such as the promotion of the importance of a specific cytokine such as IL-6, when a company had an unlicensed IL-6 receptor blocker).

Janssen stated that it had not complained about the posters or the symposium *per se*, but that the overall conference activity, especially the exhibition stand, encouraged attendees to ask questions about sarilumab before the grant of its marketing authorization. Janssen alleged that this constituted promotion of an unlicensed medicine in breach of Clause 3.1.

Janssen explained that rheumatoid arthritis was a chronic, multisystem, multifactorial autoimmune disease. Although the aetiology was still not clear, it appeared that rheumatoid arthritis had strong correlation with environmental and genetic factors. Cytokines, such as IL-6, carried out many crucial biological processes like cell growth, proliferation, differentiation, inflammation, tissue repair and regulation of the immune response. However, in addition to IL-6, examples of other cytokines were TNF-alpha, IL-1, IL-4, IL-7, IL-10, IL-12, IL-13, IL-17, IL-18, IL-21, IL-23, IL-27, IL-32, IL-33, and IL-35. There were already treatment options to inhibit some of those cytokines and there were others under development.

Janssen submitted that although many pathogenetic elements were responsible for rheumatoid arthritis, it was concerned that all of Sanofi Genzyme's activities at EULAR focused specifically on IL-6 and its importance in rheumatoid arthritis. The exhibition stand was a Sanofi Genzyme and Regeneron branded stand and the two companies had a specific partnership to develop sarilumab. Given the status of the licence applications in the US and EU it was difficult to see it as anything other than the promotion of a forthcoming product prior to the grant of a licence by soliciting enquiries about that product.

As evidence of the pre-licence promotion, Janssen provided images of the large, purpose-built exhibition stand (typical of those at international congresses and measuring approximately 100m^2) and the accompanying video screens and materials that were distributed from it. Janssen clarified that it had not complained about each aspect of the stand individually but the overall nature of the combined activities. Janssen also provided a diagram of the exhibition hall to show the location of the stand.

Janssen noted that the majority of the stand was dedicated to the importance and contribution of IL-6 in the context of rheumatoid arthritis, with bold claims and consistent associated imagery. The stand contained bold statements such as: 'In rheumatoid arthritis (RA), as IL-6 elevates, the effects go beyond the joints'. The statements were in capitals and 'IL-6' and the inference of benefits was in larger font to highlight the benefits of IL-6 inhibition. Further, the claims on IL-6 extended across the entire exhibition stand, even beyond the allocated 'medical corner'. Janssen alleged that this activity would solicit enquiries about sarilumab prior to the grant of its marketing authorization.

Janssen stated that the associated imagery was directly aligned with the claims about the effects of IL-6 in the manner of promotional material, for instance the red inflammation areas on the female model correlated with the colouring of the font in the claims and also extended around the stand linking the video screens and the displays of the 'medical' handouts (educational monographs).

Janssen noted that the interactive videos displayed on the stand bore consistent imagery with that on the stand itself. The content of the videos highlighted the specific importance and contribution of the IL-6 cytokine. The titles of the videos included:

- A Review of the Dual Signalling Mechanism of IL-6
- Contributions of IL-6 to Disease Manifestations of RA
- The Contributions of IL-6 to Bone Resorption in RA
- The Roles For IL-6 in both Innate and Adaptive Immunity.

Janssen further noted that several 'educational monographs' (medical handouts) were available from the stand which was highlighted as part of the stand itself, as in the image provided, and linked with the 'inflammation' graphics. In that context, Janssen alleged that the handouts also promoted the importance and contribution of IL-6. By consistently highlighting the importance of IL-6 in rheumatoid arthritis and indeed the negative consequences of a persistently elevated IL-6 in rheumatoid arthritis, there was an inference on the benefit that inhibiting IL-6 in rheumatoid arthritis would provide. Janssen alleged that this was in a manner that breached Clause 3.1 and would solicit enquiries about the forthcoming Sanofi Genzyme IL-6 receptor blocker.

Photographs of the monographs were provided; their titles were similar to those of the videos listed above.

Janssen alleged that the nature of the exhibition stand (and associated stand materials) in itself constituted promotion of a product prior to the grant of its marketing authorization on the grounds that it was likely to solicit enquires about the associated product, an IL-6 receptor blocker, sarilumab. Janssen's concerns were further increased by Sanofi Genzyme's additional associated activity.

Janssen explained that at the same conference, the Sanofi Genzyme sponsored symposium discussed IL-6 and specifically referred to sarilumab and highlighted the MOBILITY study, one of the key studies cited in Sanofi Genzyme's press releases and pivotal to the sarilumab licence application. Janssen respected the right of companies to engage in legitimate scientific exchange and in that context did not express any particular concerns about the symposium itself. However, the symposium directly linked sarilumab with IL-6, and thus increased the likelihood of questions about the product at the exhibition stand and effectively promoted the product through the stand's focus on the importance of addressing IL-6.

To further underline the link between IL-6 and sarilumab, several posters were presented at the conference which highlighted results with sarilumab. Again, Janssen did not express any particular concerns about the posters directly, but submitted that those posters obviously linked the product and the intense promotion of the importance of the associated IL-6 cytokine in rheumatoid arthritis at the exhibition stand.

Janssen considered that the Sanofi Genzyme exhibition stand was designed to both highlight the importance of IL-6 in rheumatoid arthritis and initiate discussions on it using different mediums and tools. Janssen alleged that the activity would certainly solicit enquiries about sarilumab, a product which was discussed by Sanofi Genzyme

at the same conference, prior to the grant of its marketing authorization.

Janssen alleged that given the nature and content of its material, Sanofi Genzyme had promoted sarilumab prior to the grant of a marketing authorization in breach of Clause 3.1. Janssen also alleged a breach of Clause 9.1 for failing to maintain high standards.

RESPONSE

Sanofi Genzyme submitted that its congress activities included a stand in the exhibition hall on the role of IL-6 in the pathophysiology of rheumatoid arthritis and associated conditions, disease awareness and educational materials on IL-6, available at the exhibition stand, a sponsored symposium entitled 'New findings for IL-6 blockade in Rheumatoid Arthritis', 10 poster presentations relating to rheumatoid arthritis treatment, co-authored with health professionals and 4 peer reviewed abstracts in the conference abstract book.

Sanofi Genzyme submitted that the European Medicines Agency (EMA) accepted the sarilumab marketing authorization application for review on 14 July 2016. EMA records suggested that it would then take an average of 11 months until a marketing authorization was issued but it was too early in the process to offer a realistic estimate as to when it would expect the review of sarilumab to be completed.

Sanofi Genzyme submitted that it and Regeneron were independent companies but had collaborated since 2007 to develop, manufacture and commercialize medicines in a number of therapy areas, including the joint clinical development of sarilumab as a potential treatment for rheumatoid arthritis and other illnesses.

Sanofi Genzyme submitted that the arguments offered by Janssen to support its complaint were not enumerated and did not refer to any specific statements or claims and so it offered a counter-argument and an explanation of its activities.

Sanofi Genzyme corrected two initial factual inaccuracies within Janssen's complaint:

- Sarilumab had no marketing authorization and so Sanofi Genzyme did not market or supply it in the UK as Janssen alleged.
- Sarilumab was still in development so the use of the past tense 'was developed by …' by Janssen was misleading.

Sanofi Genzyme noted that a stand in the exhibition hall at a scientific conference need not necessarily be used for the promotion of specific medicines. Many different companies and organisations used stand space to exhibit a wide variety of products and initiatives. There was, indeed, promotion of specific medicines but there was also corporate promotion, disease awareness projects, promotion of charities and journal subscriptions and promotion of future meetings and events or other related professional organisations and memberships. In reality, in most conference exhibition halls a very wide range of informational, educational and promotional activities took place alongside the promotion of specific medicines. On many pharmaceutical company stands it was not unusual to see the promotion of specific medicines and the provision of medical education or scientific information taking place at different ends of the same stand. Sanofi Genzyme submitted that, therefore, just because an activity took place, or material was made available at an exhibition stand, did not mean that it constituted promotion of a specific medicine.

Clause 1.2 of the Code stated that information related to human health or diseases was excluded from the scope of the Code provided there was no reference, either direct or indirect, to specific medicines.

Sanofi Genzyme submitted that its activities and materials used on its stand consisted of information about a human disease, namely, the role of IL-6 in the pathophysiology of rheumatoid arthritis and did not refer, either directly or indirectly, to a specific medicine. With regard to Janssen's allegation of a breach of Clause 3.1, Sanofi Genzyme noted that no materials used on the stand referred to sarilumab either directly or indirectly, nor was there any mention of the mode of action of sarilumab, nor the mode of action of any potential therapy for rheumatoid arthritis. Claims made in materials and on the exhibition stand were not product claims. Sanofi Genzyme submitted that Janssen appeared to have confused IL-6, a cytokine present naturally in the body, with a pharmaceutical product. No claims were made for sarilumab nor any potential medicine that might target IL-6.

Sanofi Genzyme acknowledged that the materials on its stand focused on IL-6 and submitted that it was a critically important cytokine in the signalling pathway that led to the inflammatory reaction seen in rheumatoid arthritis. Sanofi Genzyme submitted that its collaborative research with Regeneron was focused on IL-6 and its scientific expertise in the area was mainly around the role of IL-6 in the pathophysiology of rheumatoid arthritis and the associated clinical and laboratory signs and symptoms. Sanofi Genzyme considered that it was reasonable to share that scientific expertise and highlight the important role of IL-6 in rheumatoid arthritis with health professionals interested in learning more about the disease. Sanofi Genzyme did not deny that there were components other than IL-6 in the complex pathophysiology of rheumatoid arthritis but nor did the materials used at the stand deny it. Sanofi Genzyme acknowledged that it had a medicine in development that inhibited IL-6 and it submitted that it intentionally focussed its materials and presentations on IL-6 because that was where its interest and expertise lay. Sanofi Genzyme submitted that, however, sharing its knowledge about IL-6 and its role in rheumatoid arthritis and educating health professionals about the importance of IL-6 was not the same as promoting a specific product, either directly or indirectly.

Sanofi Genzyme noted Janssen's reference to Case AUTH/2651/11/13 which highlighted the promotion

of receptor activity for a specific indication or treatment but submitted that it did not promote any receptor activity. IL-6 was not a receptor, it was a cytokine, which was a component part of a complex signalling pathway; it interacted with receptors to cause various physiological and pathological effects. Sanofi Genzyme submitted that those effects were highlighted and explained in the materials on its stand but it did not present anything about the potential for blocking or inhibiting receptors, nor did it present any other mechanistic concepts, such as inhibiting the production of IL-6, nor increasing the metabolism or clearance of IL-6, nor any other potential mode of action for a potential medicine. Sanofi Genzyme submitted that it meticulously avoided mentioning any potential mode of action of a medicine. It also noted that in Case AUTH/2651/11/13, Merck Sharp & Dohme listed its pipeline products by name and ran a satellite symposium at the same conference, yet the Panel ruled no breach of the Code.

Sanofi Genzyme submitted that there were numerous potential methods that might inhibit or reduce the activity of IL-6 and there were several companies, including Janssen, which had medicines in development that targeted IL-6 in various different ways; Roche already marketed tocilizumab that inhibited IL-6. Sarilumab was not unique or exceptional in its mode of action and there were numerous other potential modes of action that could impact IL-6 activity. Sanofi Genzyme submitted therefore, that presenting information about IL-6 in the way that it did, did not solicit questions specifically about sarilumab but was more likely to lead to a discussion about the complexity of the signalling pathways and the multitude of associated pathological effects, as confirmed by the staff who manned the stand.

Sanofi Genzyme noted that Janssen used the term 'promoting' when describing the presentations and materials on its exhibition stand. Sanofi Genzyme submitted that it was difficult to see how it could 'promote' IL-6. IL-6 was not a medicine. Sanofi Genzyme submitted that with high quality and certified materials it had appropriately, and in a considered way, highlighted the importance of IL-6 and the extensive pathophysiological effects it could have. The purpose of the materials and presentations was to educate interested health professionals about the role of IL-6 in rheumatoid arthritis.

Sanofi Genzyme noted that Janssen had not complained about the posters or the symposium but about the overall conference activity and that it was especially concerned about the exhibition stand but even then the complaint was only in the context of the scientific conference and with the background of the scientific presentations on sarilumab. Sanofi Genzyme submitted that Janssen failed to demonstrate any statement or claim made at the stand or in any materials available at the stand that referenced the posters or the sponsored symposium or that could be construed as promotional, for the simple reason that there were no such statements or materials in use.

The scientific posters and symposium were part of the independently organised scientific conference programme, selected independently of Sanofi Genzyme and included data on sarilumab. Sanofi Genzyme noted that the title, theme and branding of the symposium were different and distinct from that of the exhibition stand and the educational and disease awareness materials and were not linked in any way. Janssen did not complain about those activities and they were not raised as a concern nor even mentioned by Janssen during inter-company dialogue. It would thus seem inappropriate to now link them to this complaint. Sanofi Genzyme submitted that if Janssen accepted that the posters and symposium were acceptable in the context of the scientific conference then it should not have to justify them or defend them as part of this response to the complaint. Sanofi Genzyme submitted that a reasonable concern might be if it had shared data on sarilumab at the stand or if it had referenced that data in some way at the stand, but it had not.

Sanofi Genzyme noted Janssen's statement that by consistently highlighting the importance of IL-6 in rheumatoid arthritis and the negative consequences of a persistently elevated IL-6 in rheumatoid arthritis, there was an inference on the benefit that inhibiting IL-6 in rheumatoid arthritis would provide. Sanofi Genzyme presumed that Janssen intended to state that there was an implication rather than an inference, however, either way, the inference that there might be benefit in inhibiting IL-6 could be correct, but there were other inferences that could be taken, such as that reducing the amount of IL-6 could be beneficial or that blocking an IL-6 receptor could be beneficial or that there might be some other effective way of reducing or ameliorating the consequences of elevated levels of IL-6 that might have a therapeutic benefit in rheumatoid arthritis. All of those inferences could be correct but none of them promoted the use a specific product, licensed or unlicensed, and so there was logical *non sequitur* in Janssen's argument. Sanofi Genzyme submitted that by highlighting the importance of IL-6 it did not follow that it had promoted a specific product nor solicited questions about a specific product.

Neither the exhibition stand itself nor the educational monographs or other material available on it, referred directly or indirectly to any unlicensed product. The stand was manned exclusively by members of the medical departments of Sanofi Genzyme and Regeneron.

Sanofi Genzyme noted that Clause 9.1 stated that high standards must be maintained at all times. Review of the copies of the materials, supplied as part of this response, would testify to their high scientific quality. There was nothing trivial, distasteful, irreverent or inappropriate to the intended audience nor to the intended purpose of the materials. Furthermore, each item was reviewed and approved globally and locally by appropriately qualified signatories on behalf of both companies. The approval codes supplied reflected that dual process. Sanofi Genzyme and Regeneron strongly considered that high standards were maintained throughout all activities and materials used at the

2016 EULAR Congress and so complied with Clause 9.1 in both their content and their execution.

Sanofi Genzyme submitted that Janssen's alleged breach of Clause 9.1 showed that it misunderstood the meaning and purpose of that clause which was to ensure high standards of materials and activities, in that they should recognise the special nature of medicines and the professional standing of the audience. Even if its activities and materials were considered to be promotional (which Sanofi Genzyme did not believe they were) they were nonetheless still of a high standard, and so Clause 9.1 was irrelevant to this complaint.

Sanofi Genzyme concluded that it could understand that Janssen did not want health professionals to think of Sanofi Genzyme as a leader in the field of rheumatoid arthritis with expertise in the science of IL-6, as that might impact Janssen's own profile with those health professionals. However, that was not a justifiable reason to try to stop the legitimate exchange of medical and scientific information. Sanofi Genzyme accepted the part of Janssen's conclusions that its stand was designed to highlight the importance of IL-6 in rheumatoid arthritis and to initiate discussion on IL-6 in rheumatoid arthritis using different mediums and tools which was accurate. Sanofi Genzyme disagreed that it followed that it would solicit enquiries on sarilumab. Sanofi Genzyme submitted that the materials on its stand solicited many wide ranging discussions on the role of IL-6 and the pathophysiology of rheumatoid arthritis and the many and varied inflammatory effects of IL-6.

Sanofi Genzyme submitted that Janssen had not given one concrete example of any statement that could be construed as promotional. Janssen had complained about the content of Sanofi Genzyme's material but had not pointed to anything specific that might be considered to even hint at a specific product. Sanofi Genzyme submitted that Janssen's complaint was without foundation and might even reflect a poor understanding of both the spirit and the detail of the Code. Sanofi Genzyme submitted that all of its materials were of a high standard and so it rejected the alleged breach of Clause 9.1. Sanofi Genzyme submitted that all of its material and presentations at the exhibition stand were part of the legitimate exchange of medical and scientific information and so it rejected the alleged breach of Clause 3.1 and considered that there was no real case to answer. Sanofi Genzyme submitted that it wholeheartedly embraced both the principles and the detail of the Code and genuinely believed it had upheld it fully in all its materials and activities at the EULAR 2016 Congress.

PANEL RULING

The Panel noted Sanofi Genzyme's submission that Janssen had not cited any statement that could be construed as promotional and that all of the claims on the exhibition stand were about IL-6 and not about sarilumab. The Panel noted, however, that it was an accepted principle under the Code that a product could be promoted without its name ever being mentioned. Further, the introduction to the Constitution and Procedure stated that a complainant had the burden of proving their complaint on the balance of probabilities.

The Panel noted that Janssen's complaint was about information about IL-6 presented on the Sanofi Genzyme exhibition stand at the EULAR Congress in June 2016. Although there was no complaint about other activities at the conference, the Panel agreed with Janssen's submission that the materials etc on the exhibition stand had to be viewed in the context of Sanofi Genzyme's other activities about IL-6 at the conference. Sanofi Genzyme's medicine, sarilumab, blocked IL-6 and was being developed as a possible treatment for rheumatoid arthritis. When the EULAR Congress was held, sarilumab did not have a marketing authorization although a licence had been applied for in the US and an EU licence application was about to be made; the EU licence application was accepted for review by the EMA on 14 July ie shortly after the EULAR Congress closed.

The Panel noted that although Clause 3 prohibited the promotion of a medicine prior to the grant of its marketing authorization, the Code permitted companies to undertake certain activities with regard to unlicensed medicines. The supplementary information to Clause 3 provided additional details, including a clear statement that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that this did not constitute promotion which was prohibited by Clause 3 or any other clause. The PMCPA Guidance about Clause 3 further stated that companies must ensure that such activities constituted a genuine exchange of information and were not promotional. Documents must not have the appearance of promotional material. It should be borne in mind that it would be a breach of the Code if non-promotional information on products or indications that were not licensed was used for a promotional purpose.

Clause 1.2 defined promotion as any activity undertaken by a pharmaceutical company or with its authority which promoted the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines.

The Panel noted that in addition to having the exhibition stand at the EULAR Congress, Sanofi Genzyme had sponsored a scientific symposium entitled 'IL-6 as a driver of joint destruction in rheumatoid arthritis: translating complex science into patient benefits'. It was stated on the invitation that one of the speakers would give an overview of the management of joint damage in rheumatoid arthritis, including the effectiveness of IL-6 inhibition. The graphics used on the invitation, although different to those used on the exhibition stand, were not wholly dissimilar in that joints of the hand were highlighted in red.

The exhibition stand appeared to be, from the photographs supplied by Janssen and the plans provided by Sanofi Genzyme, typical of those used by pharmaceutical companies at large conferences.

One corner of the stand was designated as the medical corner. The statement 'As IL-6 elevates, the effects go beyond the joints' could be seen on what appeared to be the front and the back of the stand. Material on the stand was exclusively about IL-6 and its role in rheumatoid arthritis. One video for use on the stand was entitled 'IL-6 and articular manifestations of rheumatoid arthritis' and concluded that persistently elevated IL-6 might play a central role in the articular manifestations of rheumatoid arthritis, resulting in pain and disability in patients. A second module was entitled 'The role of IL-6 signalling in rheumatoid arthritis' and concluded that elevated IL-6 signalling in rheumatoid arthritis might lead to the disruption of homeostasis in many cell types and physiologic processes. Two key opinion leader videos on IL-6 in rheumatoid arthritis concluded with invitations for the viewer to review the relevant monographs which were available on the stand. Interactive touch screen panels detailed the role of elevated IL-6 levels in the articular and systemic manifestations of rheumatoid arthritis.

Briefing material reminded all Sanofi Genzyme and Regeneron staff (members of the medical departments of both companies) attending the EULAR Congress that sarilumab was an investigational, unlicensed product in Europe and must not be pro-actively discussed with congress attendees. Although the term 'investigational' was not defined, the Panel queried whether a product for which a marketing authorization had been applied for in the US and would, within 5 weeks, be applied for in Europe, could be considered to be an 'investigational molecule' as stated in the briefing material or as being 'in development' as stated by Sanofi Genzyme in its response. In the Panel's view, health professionals were likely to view sarilumab as a pre-licence product. The briefing material continued by stating that if attendees wanted more information about sarilumab or IL-6 inhibitors then they should be referred to scientific advisers (medical scientific liaison (MSLs)) or medical personnel in the medical area of the stand. In the Panel's view, it was reasonable to assume that, on the balance of probabilities, many of the stand visitors would ask about IL-6 inhibition in general and/or Sanofi Genzyme's interest in the area in particular; a virtual reality presentation on the stand invited questions about IL-6 and rheumatoid arthritis. The briefing material had prepared staff for such questions and a discreet area on the stand in which to answer questions about sarilumab had been provided. A press release to accompany the US licence application might have generated interest in the medical press in the early part of the year and so some visitors to the stand might have already known about Sanofi Genzyme's forthcoming product. The briefing material stated that delegates from every continent would be at the EULAR Congress. The symposium had discussed the effectiveness of IL-6 inhibition in the management of rheumatoid arthritis. In the Panel's view, given the content of the stand and the messages about the role of elevated IL-6 in rheumatoid arthritis, such questions could not take the benefit of personal, unsolicited requests for information referred to at Clause 1.2 of the Code. In the Panel's view the exhibition stand, within the context of Sanofi Genzyme's other activities about IL-6 at the conference, would prepare the market for the introduction of a new medicine for rheumatoid arthritis which would decrease IL-6 levels and solicit questions about the same; Sanofi Genzyme had a commercial interest in one such medicine. Given that that medicine was unlicensed, a breach of Clause 3.1 was ruled. In that regard the Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. Both rulings were appealed.

APPEAL BY SANOFI GENZYME

Sanofi Genzyme submitted that both Janssen's complaint, which it received on 5 July 2016, and the subsequent inter-company dialogue, were entirely focused on the activities and materials at its exhibition stand at the EULAR Congress. There was no mention of any concern about Sanofi Genzyme's sponsored symposium at the congress or that its exhibition stand needed to be considered in the context of that symposium. The first indication that the sponsored symposium was part of the complaint was Janssen's complaint to the PMCPA on 11 August 2016. Sanofi Genzyme was therefore not given any opportunity to respond to this aspect of the complaint, or discuss it in inter-company dialogue before it was escalated to the PMCPA.

Sanofi Genzyme submitted that the complaint did not meet the requirements of Paragraph 5.3 of the Constitution and Procedure and that the Panel should not have included that aspect of the complaint in its ruling. Clause 1 stated that the scope of the Code did not include information relating to human health or diseases provided there was no reference, either direct or indirect, to specific medicines. There was no direct or indirect reference to sarilumab in any of the materials or activities at the exhibition stand. In order to infer such a reference to a specific product, a health professional would have had to link the materials at the stand with a poster or a presentation at the symposium or a press release or some other information source, all of which were removed, in varying degrees, in time, location and visual appearance and were distinct and separate from the exhibition stand. The Panel ruling had ignored this clear and overt separation and suggested that any scientific exchange activity might need to be considered as if it were juxtaposed to all other information available, no matter where or when such other information could have been acquired.

Sanofi Genzyme submitted that it appeared from the Authority's letter notifying it of the outcome of the Panel's consideration that insufficient consideration and attention might have been given to the company's arguments in defence of its activities and materials displayed on the exhibition stand. At the outset the Panel noted that Sanofi Genzyme had submitted that Janssen had not cited any statement that could be construed as promotional and that all of the claims on the stand were about IL-6 and not sarilumab. This defence was dismissed in the next sentence. No other points from Sanofi Genzyme's submission were mentioned anywhere

in the letter. In addition, throughout its ruling, the Panel used the terms 'claims' and 'promotion' to describe Sanofi Genzyme's presentation of material on IL-6. These were rather prejudicial terms normally used in relation to promotional activities rather than educational activities or scientific exchange and so it appeared to be some conflation of IL-6 and sarilumab, such that presenting the role of IL-6 was seen as tantamount to promotion of sarilumab.

Sanofi Genzyme submitted that activity at an exhibition stand was not limited to product promotion. The exhibition stand was used for many other purposes including scientific exchange, disease awareness and education activities. Sanofi Genzyme submitted that none of the stand materials mentioned sarilumab or its development and none of them mentioned any potential mode of action of any therapy or potential therapy. The materials were all entirely focused on the effects of the IL-6 cytokine, not the mechanism of blockade of IL-6 or the merits of such blockade.

Sanofi Genzyme submitted that that the Panel assumed that its activities and materials would solicit questions about sarilumab and implied that that was its intention. Actively soliciting enquiries on sarilumab was definitely not Sanofi Genzyme's intention, nor did it happen. Sanofi Genzyme recognised *a priori* that some conference delegates might be aware of sarilumab, and that some might want to enquire about it or other unlicensed therapies which was why a dedicated 'medical corner' was allocated to answer unsolicited questions.

Sanofi Genzyme submitted that the emerging role of IL-6 in the pathophysiology of rheumatoid arthritis was a legitimate topic about which to engage in the exchange of scientific and medical information. IL-6 was one of the major cytokines in the pathophysiology of rheumatoid arthritis and new research findings showed the increasing importance of IL-6 compared with the role of other cytokines.

Sanofi Genzyme noted that the Panel stated that its activities would 'prepare the market for the introduction of a new medicine for rheumatoid arthritis which would decrease IL-6 levels and solicit questions about the same'. Sanofi Genzyme submitted that it was not unreasonable to prepare the market for the introduction of a new product by educating and informing health professionals about scientific advances and new emerging knowledge, as long as it did not promote a specific product or solicit questions about a specific product. If a specific product was subsequently licensed, then a health professional could make a more informed decision about its appropriate use if the underlying science was understood. Educating health professionals about the underlying science could stop well short of suggesting or recommending therapeutic targets or modes of action and was not the same as promoting a product.

Sanofi Genzyme submitted that at the time of the EULAR Congress, no application for a marketing authorization in Europe had been made.

Sanofi Genzyme noted that the Panel had questioned its use of the terms 'investigational' and 'in development' and suggested that sarilumab should be considered 'pre-licence'. Sanofi Genzyme submitted that a reasonable and consistent cut-off point needed to be applied when considering whether legitimate scientific exchange might be construed as promotion simply because a product licence application was being compiled. In previous PMCPA cases periods significantly shorter than a year prior to licence had been deemed sufficient distance to judge an activity not to be pre-licence promotion (Cases AUTH/2651/11/13, AUTH/2479/2/12 and AUTH/2480/2/12). Although the FDA had accepted a sarilumab licence submission for review on 8 January 2016, the product development programme continued and work was ongoing to compile a marketing authorization submission for the EMA. The EULAR Congress was a European event and so it should be the European and UK product licence status that was applicable. As this event took place before a marketing authorization application had been submitted in Europe and more than a year before the potential grant of a European marketing authorization and even longer before potential commercial availability of the product, then it seemed premature and presumptuous to describe the product as 'pre-licence'.

Sanofi Genzyme submitted that the exhibition stand materials and the sponsored symposium materials were completely different from each other.

Sanofi Genzyme noted that the Panel had accepted that the graphics used on the invitation to the sponsored symposium were different to those used on the exhibition stand, yet it went on to state that they were not dissimilar because joints of the hand were highlighted in red. Sanofi Genzyme submitted that they were entirely dissimilar. They were conceived, designed and produced by different teams and while the symposium invitation depicted the redness of inflammation limited to the joints, the stand graphics conveyed the impression of spreading flames using shades of orange and yellow extending beyond the joints to affect other parts of the body. The visual impressions were distinct and there was no suggestion of a link, nor any intent to link the symposium and the stand.

Sanofi Genzyme submitted that sarilumab was only one of several similar IL-6 inhibitors in development at the time of the EULAR Congress and there was one already marketed, so without mentioning any by name, it would not be possible to promote a specific product, even indirectly.

Sanofi Genzyme submitted that the Panel's ruling went beyond previous interpretations of the Code and further restricted what could be considered to be legitimate exchange of scientific and medical information; it moved the UK out of alignment with the European Federation of Pharmaceutical Industries and Associations (EFPIA) Code and its interpretation in most other European countries. This ruling might therefore impact the ability and willingness of organisations to host international medical conferences in the UK and suggested that

it might not be acceptable for a pharmaceutical company to engage with health professionals in the context of a medical conference in the UK in scientific discussion of any pathological process where the company had a research interest.

Sanofi Genzyme noted that the ruling of a breach of Clause 9.1 followed directly from the ruling of a breach of Clause 3.1 and introduced no new material or activities deemed to be in breach and so was simply an additional sanction for the same alleged offence as that ruled on under Clause 3.1.

Sanofi Genzyme recognised that the Panel would rule a breach of Clause 2 in cases deemed to have brought discredit upon, or reduced confidence in, the pharmaceutical industry. A ruling of a breach of Clause 2 was reserved as a sign of particular censure and was applied in addition to rulings of breaches of other clauses. It seemed that, in this case, Janssen and the Panel might have interpreted Clause 9.1 in a similar way, and used it as a milder form of Clause 2, adding an additional penalty for the same alleged breach. Sanofi Genzyme was not aware that this was the purpose of Clause 9.1.

Sanofi Genzyme submitted that as noted in its response and not contested by the complainant, nor in the Panel's ruling, the activities and materials used at its exhibition stand were produced and carried out to a high standard, with quality materials presenting accurate scientific content, reviewed through a rigorous approval process, presented and discussed by highly trained medical staff, fully recognising the professional standing of the audience. Therefore, Sanofi Genzyme submitted it should not be found in breach of Clause 9.1, unless it was intended that Clause 9.1 be used as a form of supplementary penalty to add to another breach.

RESPONSE FROM JANSSEN

Janssen alleged that Sanofi Genzyme's exhibition activities at the EULAR Congress could not benefit from the exemption of the definition of promotion in Clause 1.2. By exclusively highlighting the importance of IL-6 in rheumatoid arthritis and including claims on the stand, interactive videos and handouts, the implications and benefits of IL-6 inhibition in rheumatoid arthritis were clear. Therefore, Sanofi Genzyme had in effect, indirectly promoted sarilumab before its marketing authorization had been granted.

Janssen noted that rheumatoid arthritis was a chronic, multisystem, multifactorial autoimmune disease. Although the aetiology was still not clear, it seemed that rheumatoid arthritis was strongly correlated with environmental and genetic factors. In addition to IL-6, examples of other cytokines involved in the pathogenesis of rheumatoid arthritis were TNF-alpha, IL-1, IL-4, IL-7, IL-10, IL-12, IL-13, IL-17, IL-18, IL-21, IL-23, IL-27, IL-32, IL-33, and IL-35. There were already treatment options to inhibit some of those cytokines and there were others under development. Thus, although there were many pathogenic elements responsible for rheumatoid arthritis, Janssen was concerned that Sanofi Genzyme's activities at the EULAR Congress focused only on IL-6. Janssen reproduced an illustrative example on Cytokines in the pathogenesis of rheumatoid arthritis (McInnes and Schett, 2007).

Furthermore, Janssen noted that the exhibition stand and associated materials were all Sanofi Genzyme and Regeneron branded, and these two companies had a specific partnership to develop sarilumab. Janssen therefore alleged that Sanofi Genzyme was in breach of Clause 3.1 for promoting prior to the grant of a licence and Clause 9.1 for failure to maintain high standards.

Janssen noted that Sanofi Genzyme's activities at the congress included a large exhibition stand which addressed the cytokine IL-6, a sponsored symposium which further discussed the benefits of treating IL-6 and included information about sarilumab and posters which presented the results of sarilumab studies. Janssen recognised the right of companies to engage in legitimate scientific exchange and specifically had not complained about, and did not wish to complain about, the sponsored symposium at the EULAR Congress, nor the posters, hence this was not discussed during inter-company dialogue. Janssen submitted that the point it raised in its complaint was that the nature of the stand activities at the EULAR Congress effectively promoted sarilumab and, in the context of the broader conference activities, would have encouraged health professionals to ask about the product and each activity would have propagated interest in the other. For this reason, Janssen disagreed that the complaint did not meet the requirements of Paragraph 5.3 of the Constitution and Procedure Code and submitted that inter-company dialogue was concluded appropriately.

APPEAL BOARD RULING

The Appeal Board noted that Clause 1.2 defined promotion as any activity undertaken by a pharmaceutical company or with its authority which promoted the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines. The supplementary information to Clause 3 stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that this did not constitute promotion which was prohibited by Clause 3 or any other clause.

The Appeal Board considered that although Sanofi Genzyme's activities at the EULAR Congress were geographically separate within the conference venue, ie the poster presentations, the sponsored symposium and the exhibition stand, there was an overarching theme such that they were linked. In the Appeal Board's view, each in their own way would inform health professionals about the importance of IL-6 in the pathophysiology of rheumatoid arthritis. The Appeal Board noted Sanofi Genzyme's submission that it would be more than a year after the conference before sarilumab was commercially available but considered that as there was already one IL-6 blocker on the market, Sanofi Genzyme

would be anxious to ensure that once sarilumab was licensed, it had a rapid uptake.

The Appeal Board considered that the large Sanofi Genzyme/Regeneron exhibition stand appeared to be of the type generally associated with promotion. The Sanofi Genzyme/Regeneron partnership existed specifically for the development of, *inter alia*, sarilumab. The exhibition stand was prominently branded with the two company names, which were illuminated around the top of the stand, and was centrally placed in the exhibition hall. The more-than-life-size depiction of a woman featured on the stand graphics gave the stand a promotional appearance. The open medical corner used to answer unsolicited enquiries faced outwards on a corner of the stand and in that regard it would be possible for passers-by either to hear or join in with conversations taking place there.

The material available on the stand had been certified as non-promotional material but each certificate stated that the product was sarilumab. Sanofi Genzyme's representatives at the appeal stated that whilst the originator of the material was a commercial employee the material was generated by its parent company. The originator had been the contact point who had received the material and entered it into the approval system. He/she had not generated the material. The stand and its material were exclusively focussed on IL-6. The monographs available referred to the clinical consequences of persistently elevated IL-6 levels. The stand was manned by staff from the medical departments of Sanofi Genzyme and Regeneron and included medical science liaison staff. The Sanofi Genzyme representatives at the appeal stated that no questions were asked about sarilumab and the only mention of sarilumab was by a Janssen visitor to the stand.

The Appeal Board disagreed with Sanofi Genzyme's submission that all of its material and presentations at the exhibition stand were part of the legitimate exchange of medical and scientific information. In the Appeal Board's view Sanofi Genzyme's activities at the EULAR Congress were directed at providing information and educating health professionals. The Appeal Board considered, however, that it was difficult for Sanofi Genzyme to provide such specific education about IL-6 and rheumatoid arthritis without promoting the relevant, unlicensed medicine in which it had an interest. The Appeal Board considered that by using a large, promotional-looking stand to raise awareness of only, and very specifically, IL-6 in rheumatoid arthritis, Sanofi Genzyme had indirectly promoted, or prepared the market for sarilumab; the link between IL-6 and sarilumab was too close for this not to be so. The Appeal Board upheld the ruling of a breach of Clause 3.1. In that regard the Appeal Board considered that high standards had not been maintained. A breach of Clause 9.1 was upheld. The appeal on both points was unsuccessful.

Complaint received **11 August 2016**

Case completed **3 February 2017**