CASE AUTH/2809/12/15

SANOFI GENZYME v AMICUS

Promotion of a medicine to a patient organisation

Genzyme (now Sanofi Genzyme) complained about a 30 minute presentation given by Amicus Therapeutics at a meeting of a patient organisation international network held in the UK in November 2015. Genzyme was concerned about references to Amicus's product migalastat which did not have a marketing authorization.

Genzyme explained that Amicus had claimed that its presentation was for the purpose of disease awareness and which was made to an audience of patient association representatives, patients and health professionals.

Genzyme recalled that most of the presentation was a review of the clinical development of migalastat including the phase I, II and III study designs, continuation protocols detailing the indications, investigational uses and dosing regimens. Genzyme alleged that this was 'product awareness', not disease awareness, which promoted migalastat before the grant of its marketing authorization.

Genzyme further alleged that promotion of a medicine and particularly an unlicensed one at a patient organisation meeting was in breach of the Code.

Genzyme submitted that lack of a reference number on the presentation raised concerns over a robust review and approval process from appropriately qualified and registered personnel in accordance with the Code. During inter-company dialogue, Amicus stated that all of its material was thoroughly reviewed and the presentation had been reviewed and approved by appropriate medical, legal and regulatory practitioners along with a large international law firm. Genzyme alleged that the process described did not comply with the Code.

Genzyme alleged that the breaches were gross and broad in scope, constituted a failure to maintain high standards and undermined the standing of the pharmaceutical industry in breach of Clause 2.

The detailed response from Amicus is given below.

With regard to Genzyme's concern that the presentation at issue promoted migalastat before the grant of a marketing authorization. The Panel noted five slides (21-25) referred to migalastat studies, including phase III studies, and provided details of study designs including dosage and/or endpoints. No clinical results from the studies were given. Slide 26 was headed 'Next Steps for Migalastat' and stated that the European Medicines Agency's (EMA) review of the marketing authorization application for migalastat remained on track under accelerated assessment and that the Committee for Medicinal Products for Human Use (CHMP) opinion was anticipated by early 2016. In the Panel's view, this slide at the very least implied that the results from the clinical trials were positive. In that regard the Panel considered that claims had been made for migalastat contrary to Amicus's submission that it had provided no information about the product.

The Panel considered that it was immaterial that the presentation did not refer to any specific clinical results; merely raising awareness of studies would draw attention to, and encourage interest in them. This was especially so given that the audience primarily comprised leaders of national patients' organisations. In the Panel's view, reference to the encouraging regulatory status of migalastat would prepare the delegates for a new product entry in 2016. Although the legitimate exchange of medical and scientific information was permitted during the development of a medicine, the presentation at issue was, in the Panel's view, the straightforward provision of information; there was apparently no information exchange between the presenter and the delegates. In that regard the presentation could not take the benefit of the exemption to the Code. Overall, the Panel considered that the presentation had promoted migalastat prior to the grant of its marketing authorization and a breach of the Code was ruled.

The Panel noted the alleged breach of the Code in that the meeting at issue had included patients and patient representatives. The Code prohibited the promotion of prescription only medicines to the public. The Panel noted that although not everyone at the meeting was a health professional, those that were not were senior executives of the international network organisation or of relevant national patient organisations. The Panel noted from the meeting programme that the primary aim of the international network was to facilitate collaboration between patient organisations around the world to support those affected by Fabry Disease. The Panel considered that, in the context of a patient organisation expert meeting, the executives that had been invited to attend were not members of the general public *per se*. In that regard, notwithstanding its ruling of a breach of the Code above, the Panel ruled no breaches of the Code.

The Panel noted that Amicus acknowledged that the presentation aimed at an audience of patient organisations although reviewed by senior company employees, had not been formally certified and breaches of the Code were 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 a ruling of a breach of Clause 2 was a sign of particular censure. In that regard the Panel noted that migalastat had been promoted prior to the grant of its marketing authorization; the patient organisation international network had been given information such as to expect a possible new product entry in 2016. Further, the presentation at issue had not been formally certified before use. On balance, a breach of Clause 2 was ruled.

Upon appeal by Amicus the Appeal Board considered that the pharmaceutical industry should be able to inform patient groups about medicines and/or general research interests. Companies, however, had to ensure that the provision of such information complied with the Code including the differences between proactive provision and reactive provision. The audience at the patient organisation expert meeting were all senior officials of various patient groups worldwide. The Appeal Board noted that the Panel had considered that, in the context of the meeting in question, the patient organisation executives were not members of the public *per se*. The Appeal Board noted, however, that this matter was not before it for consideration and thus made no comment on this decision. In the Appeal Board's view attendees at the meeting were likely to take messages back to their respective organisations.

The Appeal Board noted that slides 21-25 of the presentation gave an overview of clinical trial protocols for migalastat studies. Slide 23 referred to monotherapy for patients with amenable mutations. The Appeal Board noted that mutation analysis and the possibility of targeting therapy to patients with particular gene mutations was an emerging concept in the treatment of Fabry Disease. It noted Sanofi Genzyme's submission that patient suitability characteristics for migalastat such as amenable and non-amenable mutations were discussed. The Appeal Board noted that the slides presented at the meeting referred to the need for patients to know their mutation as this could impact on symptoms and their treatment. According to the presentation the registration studies were carried out on patients with amenable mutations. Amicus's representatives at the appeal confirmed that amenable mutations were mentioned at the meeting including which ones might be relevant to migalastat. The representatives at the appeal stated that it was a matter for the regulators to decide which would be included in the marketing authorisation/SPC. Slide 26 was headed 'Next Steps for Migalastat' and gave an overview of the regulatory status of the medicine. It was stated that the EMA review of the marketing authorization application for migalastat remained on track under accelerated assessment and that the CHMP opinion was anticipated by early 2016. In the Appeal Board's view, these statements together implied a positive outcome.

The Appeal Board noted the statements and discussion about amenable mutations and the implied positive regulatory status of migalastat. Although much of the information was in the public domain, on balance, the Appeal Board considered that the presentation had raised the prospect of a new treatment for Fabry patients with amenable mutations and in that regard, had promoted migalastat prior to the grant of a marketing authorization. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted its ruling above and considered that as the promotional presentation was not formally certified it upheld the Panel's ruling of a breach of the Code. The appeal on that point was unsuccessful. The Appeal Board considered that as the presentation was aimed at a patient organisation and had not been formally certified it upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

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

Although noting its comments above, the Appeal Board did not consider that in the particular circumstances of this case a ruling of a breach of Clause 2 was warranted and so the Appeal Board ruled no breach of that clause. The appeal on this point was successful.

Genzyme (now Sanofi Genzyme) complained about a presentation given by Amicus Therapeutics at a meeting of the patient organisation international network, held in the UK in November 2015. Genzyme was concerned about references to migalastat which did not have a marketing authorization.

COMPLAINT

Genzyme explained that Amicus had claimed that its 30-minute presentation was for the purpose of disease awareness. Amicus would not give Genzyme a copy of its presentation and so Genzyme stated that its complaint was based on its recollection of the meeting itself, but without documentation. The presentation was made to an audience of patient association representatives, patients, and health professionals.

Genzyme stated that over 20 minutes of the presentation was devoted to a comprehensive review of the clinical development activities for migalastat. The presentation included details of the phase I, II and III study designs including continuation protocols with details of the indications, investigational uses and dosing regimens. Genzyme alleged that this was 'product awareness', not disease awareness, and thus promoted migalastat prior to the grant of its marketing authorization in breach of Clause 3.1.

Genzyme further alleged a breach of Clause 26.1 given that the meeting included patients and patient representatives and the presentation was promotional.

Genzyme noted that Clause 27.2 described '… the prohibition on advertising prescription only medicines to the public (Clause 26.1)' in the context of working with patient organisations. Genzyme

alleged that promotion of an unlicensed medicine at a patient organisation meeting was in breach of Clause 27.2.

Genzyme submitted that the presentation did not appear to have a UK reference number which raised concerns over a robust review and approval process from appropriately qualified and registered personnel in accordance with the Code. This point had been raised previously in inter-company dialogue in order to encourage Amicus to develop proper processes. On this occasion Amicus stated in inter-company dialogue: 'Additionally, as we have described to your company in the past, all Amicus material is thoroughly reviewed in accordance with a clear process by a review board known internally as the 'Copy Review Board' and the presentation made at [the patient organisation meeting] is no exception having been reviewed and approved by appropriate medical, legal and regulatory practitioners along with a large international law firm'. Genzyme did not consider that the process so described complied with the Code and alleged breaches of Clauses 14.1, and 14.3.

Genzyme considered that the breaches were gross and broad in scope and had been wilfully and serially perpetrated despite its numerous attempts at constructive inter-company dialogue. This constituted a failure to maintain high standards in breach of Clause 9.1.

In their entirety and in view of the repeated breaches in the face of failed inter-company dialogue, Genzyme alleged that Amicus had undermined the standing of the pharmaceutical industry in the eyes of both patient associations and health professionals in breach of Clause 2.

RESPONSE

Amicus submitted that contrary to Genzyme's assertion that it had claimed that the presentation at issue was for the purposes of disease awareness, Amicus was well aware that its slides did not consist *exclusively* of disease awareness. In inter-company dialogue, Amicus characterised the presentation as including *both* disease awareness *and* corporate communications. Almost all of the slides presented consisted of corporate information and disease awareness information. For example, 16 of 27 slides consisted of title and sub-heading slides, an agenda slide, a corporate mission slide, a corporate development pipeline slide, a headquarters and offices slide, slides regarding the company's patient advocacy department and its corporate mission, a cost of drug development slide, and a slide on publicly known regulatory timelines. Additionally, 6 of 27 were legitimate disease awareness slides presenting facts about the disease.

Amicus stated that Genzyme's complaint was arguably about slides 21-25 which provided a high-level general overview of the company's AT-1001 study design and endpoints. While these slides might not fit squarely within the categories of disease awareness or corporate information, they were not promotional. Genzyme had tried to characterise the information in these slides as 'product awareness' so as to provide the necessary bridge to promotion. But product awareness implied knowledge about the benefits and risks of a product. If an individual had no knowledge about the benefits or risks of a product, no knowledge about that product's efficacy or safety profile, then he/she could not have any awareness about it. Amicus stated that since it provided no information about the characteristics, features, benefits or risks of its investigational product, it could not have engaged in product awareness. Indeed, in the 5 slides at issue, and in the rest of the presentation, no results were disclosed regarding product efficacy or safety and no other product characterisations were made which might encourage, or be perceived to encourage, the use of product.

Amicus submitted that the 5 slides provided high-level 'study awareness'. Like disease awareness, study awareness was not promotional. It was not designed to convince or to encourage an audience to take specific action, but was rather intended to raise general awareness regarding the existence of a study without disclosing any results. As the first Amicus UK employees were hired in 2015 and the first UK office formally opened in November 2015, the purpose of the presentation was to raise awareness of Amicus itself (corporate slides) and to explain at a high level what it was working on (study awareness slides). The audience at this patient organisation expert meeting consisted of its board of directors and the leaders of country patient organisations that were members (28), healthcare specialists (7), and representatives from industry (8). This was not a general patient meeting or patient support event, and Amicus did not present to an audience of general patients. The patient organisation leadership, like the leadership of other patient advocacy organisations, was very sophisticated regarding the disease affecting its members and its minimum expectation of the pharmaceutical industry was that it kept it aware of the existence, name, and profile of companies investigating treatments for the disease affecting its membership and that the industry kept it aware at a high level of relevant investigations.

Amicus stated that in its view, the sharing of this minimal information was a basic responsibility to the leadership of these patient advocacy communities. The company understood that it could not disclose any actual results, and it did not do so. No data was disclosed, nor any statements made, about product efficacy, benefits, safety or any other data. Nor did Amicus encourage use of an investigational product. Amicus believed this understanding was consistent with EU law and the directive against promotion of a prescription-only medicine to patients because the intent was basic awareness, not product promotion. Amicus noted that the European Court of Justice had made clear that the key basis for distinguishing non-promotional information from advertising was the purpose of the communication. In this regard, Amicus submitted that the slides spoke for themselves. Not only were they devoid of product data and characterisation, but they also had no branding (no brand name, brand designs or logos, no marketing messages). Nor were there any product comparisons or superiority claims. None of

the hallmarks indicative of promotion were present in the slides.

Amicus hoped that based on the information above, and after review of the information below, the Panel would agree that the presentation at the patient organisation's expert meeting was not advertising because its purpose was to provide non-promotional corporate, disease awareness, and limited study awareness information without seeking to promote the prescription, supply, sale, or consumption of a medicine.

With regard to Clause 3.1, Amicus noted that Genzyme had alleged that over 20 minutes was devoted to a comprehensive review of the clinical development activities for migalastat. As set out above, this was incorrect. Most of the presentation (22 of 27 slides) consisted of corporate information and disease awareness information. Genzyme then proceeded to allege that the 5 slides which provided a high-level general overview of the AT-1001 study design and endpoints constituted promotion. As described at length above, simply providing a high-level overview of a study's parameters to a sophisticated audience of patient organization leaders and healthcare specialists for the purpose of providing 'study awareness', without providing any results or encouraging use, could not constitute promotion because the intent was not to induce the prescription, consumption, administration, purchase, sale, supply or use of a product.

Moreover, pursuant to the transparency requirements in the laws and codes of many jurisdictions, these basic study parameters had to be publicly disclosed in a manner accessible to patients, healthcare providers and others and in that regard Amicus referred to Clause 9 of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Code of Practice which stated that 'it is recognized that there are important public health benefits associated with making clinical trial information more publicly available to healthcare practitioners, patients and others' and that companies 'disclose clinical trial information' as set forth in the codes of many jurisdictions. The purpose of these transparency and public health requirements was 'study awareness' so patients, health professionals and others could have basic awareness of ongoing trials. Indeed, these laws and codes implicitly recognized the important distinction between 'study awareness' (which was required) and 'product awareness'. In Amicus's case, the basic study parameters shared at the meeting were already publicly available and accessible on the clinicaltrials.gov website pursuant to the company's transparency obligations; Amicus stated that it did not go beyond study awareness by disclosing efficacy and safety data that would transform its presentation into product awareness.

With regard to Clause 26.1, Amicus noted that Genzyme alleged that the presentation advertised a prescription only medicine to the public. Such an allegation was a gross mischaracterisation of the presentation and of the limited audience. First, the patient organisation expert meeting was not a general patient meeting or patient support event. Amicus stated that it did not present to an audience of general patients. Rather, the patient organisation expert meeting was a small invitation-only meeting. The audience consisted of approximately 28 leaders of patient organisations, 7 healthcare specialists and 8 industry representatives. The supplementary information to Clause 26.2 provided examples of situations in which information could be deemed to have been disseminated to the public, including dissemination of information to journalists through press conferences, press announcements, television or radio reports, public relations activities, posters in spaces available to the public and information posted on websites. The common theme in all these examples was that information became accessible to the public. The presentation at issue was made to a small number of invited individuals at a closed-door meeting and was not otherwise made publicly available. Secondly, as set out above, the presentation was not in substance or intention promotional. Since the presentation was neither promotional advertising nor disseminated to the public, it could not constitute advertising to the public. A breach of Clause 26.1 was denied.

Amicus noted that Clause 14 required certain written materials to be reviewed and approved internally before they could be used with external audiences. Clause 14.1 applied to promotional materials and Clause 14.3 applied to non-promotional materials. Amicus submitted that as the presentation was non-promotional, Clause 14.1 was not applicable.

The presentation at issue was reviewed internally a week before the meeting. Unfortunately, one of the company's UK signatories had gone on sick leave about two weeks earlier. Amicus engaged an alternative signatory from 8 December 2015. Thus, Amicus acknowledged that between 3 November and 8 December 2015 it was a signatory short. A senior manager stepped in as reviewer during this time. Amicus stated that it released no materials without them first being reviewed and approved by a competent medical reviewer to ensure their medical and scientific accuracy. In addition to the review by the manager, the slides presented at the patient organisation expert meeting were also reviewed and approved by senior company officials from the legal and regulatory departments pursuant to the company's process as well as by a large international law firm and by an additional authorised signatory. All of these reviewers agreed that the slides were factual, objective, non-misleading and non-promotional under the Code and EU law for the reasons described above. The reviewers approved the presentation for a single use consistent with the venue, date and audience specified on the introductory slide.

Amicus submitted that although it did not have a UK approval certificate for the presentation given a signatory's sick leave, it thoroughly reviewed the substance of the presentation to ensure that it complied with the Code in all other respects. Additionally, as described above, although the company was short of one signatory during November, this role was carried out by a contractor until the return of the permanent employee from

sick leave. Amicus stated that it now had a detailed UK standard operating procedure to ensure that all UK materials were reviewed and approved before being used externally to ensure compliance with the Code (a copy was provided). Amicus hoped that it had been able to convey that it was fully aware of its responsibilities under the Code, that it took those responsibilities very seriously and that it had made every effort to comply with the Code to date despite the unexpected sick leave of a UK signatory, its very limited UK resources and the very recent opening of its UK office in November 2015.

Amicus noted Genzyme's allegation that 'the breaches were gross and broad in scope and had been wilfully and serially perpetrated'. In that regard, Amicus noted that Genzyme had misleadingly invoked clauses that did not apply in the context of an investigational product without a label that was not on the market, a small closed-door meeting of patient organisation leaders and healthcare specialists and slides that consisted of corporate and disease awareness information and 5 high-level study awareness slides.

Genzyme had also misleadingly mischaracterised the nature and content of the slides. For example, Genzyme alleged that most of the presentation was devoted to a comprehensive review of clinical development activities. This was not so. There were only 5, high-level study awareness slides which did not disclose any actual data.

Thirdly, Genzyme had also tried to make it seem as though there had been repeated breaches associated with several materials when the only material at issue in this case was the presentation. For example, Genzyme alleged that breaches had been 'serially perpetrated' and even that 'in view of repeated breaches' Clause 2 had also been breached. Given that no materials had previously been found in breach of any code or law in any jurisdiction, Amicus submitted that Genzyme's language was intentionally calculated to create the impression of a pattern of inappropriate behaviour.

Amicus stated that the essence of this case was whether 5 slides which provided a high-level general overview of the AT-1001 study design and endpoints, presented to a small audience of patient organisation leaders and healthcare specialists without any general patients in the audience, and without disclosing any actual efficacy or other data, constituted pre-approval promotion. For all of the reasons provided above, Amicus stated that the slides were not promotional. The company aimed to raise general awareness about the organisation (corporate slides) and to explain at a high level what it was working on by sharing limited, publicly available information from clinicaltrials.gov (study awareness slides).

Amicus submitted that the Panel had ruled in other cases that if materials did not fit squarely within one of the exemptions to the definition of promotion, those materials would still be deemed non-promotional when the totality of the facts and circumstances made clear on balance that the material was not promotional. For example, in Case AUTH/2651/11/13, although the information displayed at a scientific conference did not 'satisfy the requirements for the legitimate exchange of medical and scientific information during the development of a medicine', the Panel nevertheless concluded that the information presented did not amount to the promotion of an unlicensed medicine and no breach of Clause 3.1 was ruled. Although the context of the current case was different from Case AUTH/2651/11/13 in that the presentation was to a limited audience of patient advocacy leaders at a patient advocacy leadership meeting, and not to health professionals at a scientific conference, the cases were very similar in that multiple facts in each case pointed to the non-promotional substance and intent of the presentations at issue and on balance both were non-promotional.

Amicus reiterated that its slides were devoid not only of product data and characterisations, but also of product comparisons, superiority claims and any elements of branding (no brand name, designs or logos, no marketing messages), thus the slides were neither promotional in substance nor in appearance. Additionally, the person who presented the slides was from Amicus's patient advocacy function not from sales or marketing nor was the presenter subject to any form of bonus incentive plan based on sales or product use. In fact, because the product was investigational as it had not been approved by any regulatory agency, Amicus had not developed or implemented a bonus incentive plan for any of its employees anywhere in the world. It was very clear to the audience at the meeting that the presenter was from patient advocacy and not from sales and marketing and that there was no actual promotion.

Amicus stated that contrary to Genzyme's portrayal of it, it was not a careless company. In fact, Amicus had made every effort to comply with the Code to date despite the unexpected sick leave of its UK signatory, its very limited UK resources and the very recent opening of its UK office in November 2015. The company took its responsibilities under the Code very seriously and understood the special nature of medicines and was committed to maintaining high standards at all times. Nothing in the presentation at issue could have caused offence or reduced the high standards expected of the pharmaceutical industry, so there was no breach of Clause 9.1. But most importantly, the presentation of high-level slides at the patient organisation expert meeting did not bring discredit to, or reduce confidence in, the pharmaceutical industry. The Panel had consistently held that a breach of Clause 2 was reserved to indicate particular censure; Amicus stated that considering all of the facts and circumstances in this case, a finding of a breach of Clause 2, on balance, was not warranted.

PANEL RULING

The Panel noted Genzyme's concern that the presentation at issue promoted migalastat before the grant of a marketing authorization. The company drew particular attention to a comprehensive review of the clinical development activities for migalastat.

Five slides (21-25) referred to migalastat studies, including phase III studies, and provided details of study designs including dosage and/or endpoints. No clinical results from the studies were given. Slide 26 (to which Amicus had not referred) was headed 'Next Steps for Migalastat' and stated that the European Medicines Agency's (EMA) review of the marketing authorization application (MAA) for migalastat remained on track under accelerated assessment and that the Committee for Medicinal Products for Human Use (CHMP) opinion was anticipated by early 2016. In the Panel's view, this slide at the very least implied that the results from the clinical trials were positive. In that regard the Panel considered that claims had been made for migalastat contrary to Amicus's submission that it had provided no information about the product.

The Panel considered that it was immaterial that the presentation did not refer to any specific clinical results; merely raising awareness of studies would draw attention to, and encourage interest in them. This was especially so given that the audience primarily comprised leaders of national patients' organisations. In the Panel's view, reference to the encouraging regulatory status of migalastat would prepare the delegates for a new product entry in 2016. Although the Panel noted that the legitimate exchange of medical and scientific information was permitted during the development of a medicine, the presentation at issue was, in the Panel's view, the straightforward provision of information; there was apparently no information exchange between the presenter and the delegates. In that regard the presentation could not take the benefit of the exemption to Clause 3.1. Overall, the Panel considered that the presentation had promoted migalastat prior to the grant of its marketing authorization and a breach of Clause 3.1 was ruled.

The Panel noted the alleged breach of Clause 26.1 in that the meeting at issue had included patients and patient representatives. Clause 26.1 prohibited the promotion of prescription only medicines to the public. The Panel noted that although not everyone at the meeting was a health professional, those that were not were senior executives of the patient organisation or of relevant national patient organisations. The Panel noted from the meeting programme provided that the primary aim of the international network was to facilitate collaboration between patient organisations around the world to support those affected by Fabry Disease. The Panel considered that, in the context of a patient organisation expert meeting, the patient organisation executives that had been invited to attend were not members of the general public *per se*. In that regard, notwithstanding its ruling of a breach of Clause 3.1 above, the Panel ruled no breach of Clause 26.1 and thus no breach of Clause 27.2.

The Panel noted that Amicus had acknowledged that the presentation, although reviewed by senior company employees from medical, legal and regulatory, had not been formally certified. A breach of Clause 14.1 was ruled. The Panel noted that Genzyme had also alleged a breach of Clause 14.3 which required certain materials, other than promotional materials but including, *inter alia*, material related to working with patient organisations, to be certified. The Panel considered that as the presentation was aimed at a patient organisation, it required certification under Clause 14.3. As noted above, the presentation had been reviewed but not formally certified. A breach of Clause 14.3 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 a ruling of a breach of Clause 2 was seen as a sign of particular censure. In that regard the Panel noted that migalastat had been promoted prior to the grant of its marketing authorization; the patient organisation international network had been given information such as to expect a possible new product entry in 2016. Further, the presentation at issue had not been formally certified before use. On balance, a breach of Clause 2 was ruled.

APPEAL BY AMICUS

Amicus appealed all of the Panel's ruling of breaches of the Code.

Clause 3.1

Amicus submitted that this was a very important case because no pharmaceutical association in any country had ever addressed whether simply sharing the design and endpoints of a study during an international, closed-door meeting of patient organisation leaders, could be seen as pre-approval promotion. This had important implications for the pharmaceutical industry and for the leaders of patient organisations.

The appeal against this ruling was based in five key areas:

1 A factual update regarding regulatory status was non-promotional

This appeal related to 6 slides out of 27 (slides 21-26) which provided a high-level overview of study design and endpoints, as well as a factual update regarding the regulatory status of migalastat. Regarding slide 26, the regulatory update, Amicus submitted that it appeared the Panel might have misinterpreted the statement 'remains on track under accelerated assessment' to mean there was positive news about the application and/or that it was likely to be approved because the Panel stated that 'reference to the encouraging regulatory status of migalastat would prepare the delegates for a new product entry in 2016'.

The European update (slide 26) stated:

- European Medicines Agency's (EMA) review of the marketing authorization application (MAA) for migalastat remains on track under accelerated assessment
- Committee for Medicinal Products for Human Use (CHMP) opinion is anticipated by early 2016.'

Amicus submitted that these were factual statements which were neither encouraging nor implied a positive outcome to the regulatory submission. 'Remains on track' demonstrated that Amicus was currently working with the EMA as part of the review process. 'Accelerated assessment' was a regulatory term well known to an audience of experts in rare and orphan disease, which simply described the type of process selected by the EMA to appraise migalastat. This was first announced by the EMA in a press release on 22 May 2015 (copy provided) which was publicly available via the EMA's website. Neither statement meant that there was positive or encouraging news about an application. The end result for an application reviewed under accelerated assessment might be positive or negative, just like any other regulatory pathway.

Amicus submitted that it was reasonable to conclude that if it had inferred an encouraging regulatory status it might imply a positive clinical outcome from the studies. However, Amicus had simply reiterated the regulatory process it was being assessed under and when it was anticipated to conclude. These facts, already in the public domain, did not imply anything and as such were non-promotional.

2 Sharing study design and endpoints was non-promotional

Amicus submitted that the key question was whether five slides, which provided a high-level general overview of study design and endpoints, when presented to a small audience of invited, international, patient organisation leaders, and without disclosing any actual efficacy or other data, constituted pre-approval promotion. For all of the reasons stated above, the presentation of this limited and high-level information was not promotional.

Amicus submitted that an important consideration in deciding if a communication was promotional was if it encouraged administration, consumption, prescription, purchase, recommendation, sale, supply or use of a medicine. The presentation did not use any language that encouraged use of a product; it was silent about the characteristics, features, benefits and claims relating to any product, and there were no elements of branding that were typically seen in promotional communications (no brand name, no brand designs or logos, no marketing messages). The fact that there was no promotional language or content in the slides provided strong evidence that the presentation was non-promotional.

Amicus submitted that it was tempting to quote the multiple regulations regarding clinical trial transparency (European Clinical Trial Regulation EMA/36398/2015: 'The information that will be made public for all clinical trials will include amongst other: the major characteristics of the trial; treatment population characteristics and number of subjects; inclusion and exclusion criteria, main objectives and endpoints'. Clause 9 of the International Federation of Pharmaceutical Manufacturers & Associations Code; European Federation of Pharmaceutical Industries and Associations/Pharmaceutical Research and Manufacturers of America – Joint Principles for Responsible Clinical Trial Data Sharing to Benefit Patients (2014); ABPI – Clinical Trial Disclosure Toolkit; Section 801 of the US Food and Drug Administration Amendments Act) and to note that it was required by law and encouraged by the codes of many jurisdictions to transparently disclose study design and endpoint information. Amicus asked the Appeal Board to consider the intent of these regulations. The regulations were designed to ensure that patients had appropriate high-level understanding of the research undertaken by industry and by inference such study awareness was the responsibility of industry.

As further context, Amicus submitted that the PMCPA's Guidance about Clause 3 made clear that the role of the employee carrying out the activity had a contextual bearing on whether it was promotional. It was clear to the international audience that the Amicus executive who presented at the patient organisation expert meeting was a senior executive who sat on the company's corporate executive committee, with a global remit to ensure the company worked transparently and collaboratively with patient organisations across the world to benefit patients. The purpose of this presentation was to raise awareness of Amicus and to explain at a high level what the company was working on rather than promoting a product.

3 The reasoning in Case AUTH/2651/11/13 was applicable

Amicus submitted that whilst most non-promotional information provided during the pre-approval timeframe could be categorised as corporate information, disease awareness or scientific exchange, other information was not automatically promotional simply because it did not fit into one of those categories. As discussed above, to be promotional there must be language or evidence, such as features, benefits or claims, to demonstrate the promotional intent or purpose of the communication.

Amicus submitted that in Case AUTH/2651/11/13 the Panel recognised this important principle and ruled that the information disclosed in the posters did not 'satisfy the requirements for the legitimate exchange of medical and scientific information during the development of a medicine' and did not fit within any other exemption to the definition of promotion (eg was not corporate information or disease awareness information), the Panel nevertheless concluded that there had been no promotion. The posters did not amount to the promotion of an unlicensed medicine and no breach of Clause 3.1 was ruled.

Amicus urged the Appeal Board to recognize that the very limited category of information at issue in this case (study design and endpoints) was a clear example of information which, on its own, could not be considered promotional despite the fact that it did not fit within a pre-existing category of non-promotional information.

4 Public policy reasons for sharing study design and endpoints with patient organisation leaders

Amicus submitted that, not only was limited study design and endpoint information not promotional, there were strong public policy reasons why a pharmaceutical company should provide such information to patient organisation leaders who were key stakeholders in the healthcare system and yet often treated as being less entitled to basic healthcare information than other key stakeholders such as healthcare providers, regulators and even investors. By ruling against the presentation of limited, high-level information about study design and endpoints to patient organisation leaders while allowing (and even mandating) the disclosure of such information in other forums (for example, in the press, through public clinical trial registers, and to investors), the credibility and responsibility of patient organisation leaders to participate in appropriate engagement with the medicine development community became severely undermined. In contrast, having the right to basic study awareness allowed patient leaders to have a broad perspective on what companies were working on, which was essential to their mandate of developing initiatives, programmes, and awareness campaigns that were in the best interests of patients.

Amicus submitted that basic study design and endpoints were already publicly available via clinicaltrials.gov, press releases, physician conferences and also through industry media and published financial analysts' reports which were readily accessed through Google alerts and other means. Patient leaders often used such notifications to remain informed about key developments, and also used this information to raise issues and questions with industry. To state that patient organisation leaders must search through all of these sources to obtain basic study awareness information rather than obtain the same information directly from the pharmaceutical industry devalued the integral role played by patient leaders and harmed the industry's relationship with them.

Amicus submitted that, importantly, this case would set the tone for the industry's future relationship with patient organisation leaders. Companies could either recognise that patient organisation leaders were key stakeholders, entitled to basic awareness of studies and so foster a relationship of partnership between them and the industry or deny them even the most basic information about studies and industry or deny and limit the valuable role they could and should play in the system.

Amicus submitted that if the provision of even basic study design and endpoint information to patient organisation leaders was held to be promotional, even in the absence of any actual clinical data being presented, it would stop patient organisation leaders being able to receive such basic information from industry which was contrary to the intent of the transparency directives and could result in a loss of trust and respect for industry by one of its important stakeholders. This would fundamentally be at odds with the ABPI Guidance 'Working together, delivering for patients', which identified clarity of purpose, integrity, independence and transparency as the core tenants of working together.

5 This case could be used to provide an appropriate boundary for the pharmaceutical industry

Amicus submitted that although this was a precedent-setting case, the question at issue was very narrow, namely whether a presentation of the following should be ruled as pre-approval promotion:

- Simple design and endpoints of a study
- No sharing of any data collected in the studies
- A factual account of full, current regulatory status
- No features, benefits, or claims in regard of a product
- To a closed audience of international, expert, patient organisation leaders.

Amicus submitted that the great advantage of being able to narrowly frame the question was that a clear decision could be reached with identifiable boundaries and no confusion. If it was decided that providing such limited study design and endpoint information did not constitute pre-approval promotion, then the pharmaceutical industry would have a clear ruling that the provision of such information was permissible. The industry would also know that the provision of information that went beyond that of this case was not protected by the Appeal Board's ruling.

Clause 14.1

Amicus submitted that because Clause 14.1 applied exclusively to promotional materials, and because of the reason already submitted in its original response and appeal, Clause 14.1 did not apply and thus had not been breached.

Clause 14.3

Amicus submitted that in its response to the complaint it had attempted to show that it had followed appropriate processes and that all materials were carefully reviewed by qualified staff in the unfortunate absence of one of its signatories. Amicus appealed this clause to gain clarification. The content did not fall comfortably under any of the bulleted examples provided in Clause 14.3. Amicus referred to the supplementary information regarding other materials issued by companies which related to medicines but was not intended as promotional material for those medicines *per se* which required 'examination only'. Amicus accepted that if the Appeal Board decided that its presentation was defined by one of the bullets of Clause 14.3, then indeed it had breached that clause.

Clauses 9.1 and 2

Amicus reiterated, for reasons of context, that it hired its first UK employees in mid 2015 and formally opened its UK office in November 2015. As such, the purpose of the presentation was to raise awareness of the company with a corporate overview and to explain at a high level what it was working on regarding research and development. Indeed, Amicus submitted that it had acted with the highest ethical and medical standards (and always sought to

do so) and that its presentation was consistent with the Code and was in the best interests of patients.

Amicus submitted that its actions could not in totality be considered as not having maintained high standards, or indeed brought discredit on the industry. The intent of the presentation was company, disease, study and regulatory awareness. There were no reasons why this would be viewed as promotional. As such Amicus submitted that it was not in breach of Clauses 3.1, 14.1 and thus Clauses 9.1 and 2. With respect to Clause 14.3, Amicus asked for guidance regarding the applicability of these materials to this clause.

Consistent with the ABPI guide to collaboration between charities and pharmaceutical companies in the UK, 'Working together, delivering for patients', collaboration needed to be based on mutual understanding and Amicus submitted that a ruling of a breach of Clause 2 would send a conflicting message to patient organisations and was disproportionate.

COMMENTS FROM SANOFI GENZYME

Sanofi Genzyme noted Amicus submitted that its appeal related to 6 slides out of 27 – the complaint did not mention specific slides (these had never been made available to Sanofi Genzyme, despite a request to Amicus), but rather that Amicus's presentation and discussion about the clinical development of migalastat, comprised the majority of overall presentation. Sanofi Genzyme alleged that approximately 20 minutes of the total agenda was devoted to the presentation of the clinical development plan, and clinical aspects of migalastat use (such as patients with amenable or non-amenable genetic mutations). The number of actual slides was immaterial and did not reflect the likelihood of a breach of the Code having occurred.

Sanofi Genzyme noted that Amicus also stated that 'no pharmaceutical association in any country has ever addressed whether simply sharing the design and endpoint of a study, during an international, closed-door meeting of patient organisation leaders, can be seen as pre-approval promotion'. Sanofi Genzyme alleged that this was disingenuous as not only was a significant amount of time devoted to the clinical development programme for a medicine that had not received its marketing authorization, but there was also significant discussion of the meaning of amenable mutations, and from whom patients could seek advice on whether they had an amenable mutation. One of the physicians in the audience observed that Amicus was informing patients about the medicine and advising them to speak to their physician to see if they would be suitable for treatment, all in a pre-approval environment, and that Amicus should not be informing patients about the medicine, because it put the physician in an awkward position when patients asked whether they had an amenable mutation (as the physician in question had been asked by Amicus to sign a non-disclosure agreement on this subject). This highlighted that at least one of the non-industry physician members of the audience at this meeting was troubled by the pre-approval activity of Amicus, driving potential patients to their physicians to enquire about an unlicensed product which the physician was unable to respond to due to being bound by confidentiality to Amicus.

Sanofi Genzyme noted that Amicus considered that the Panel might have misinterpreted the statement 'remains on track under accelerated assessment' to mean there was positive news about the application and/or that the application was likely to be approved. Amicus stated during the presentation 'At the moment, because we are in the process of regulatory approval, we've got to be careful', and 'when we market the [medicine], it will be on the SmPC' (emphasis added). So in addition to the content of the slides (and referred to by the Panel), this was reinforced by a spoken clear expectation for a positive outcome of the regulatory submission, and the subsequent marketing of the medicine was considered a certainty.

Sanofi Genzyme noted that Amicus also stated that the purpose of this presentation was to raise awareness of the company and to explain at a high level what the company was working on rather than promoting a product. Sanofi Genzyme alleged that as already stated, as approximately 20 minutes of a 30 minute presentation was devoted to discussing the entire clinical development plan for migalastat, the regulatory submission, and patient suitability characteristics such as amendable and non-amenable mutations (with respect to treatment), pre-approval promotion must be considered to be the primary focus of the presentation rather than general company awareness.

Sanofi Genzyme noted Amicus's submission that it could choose to either recognise that patient organisation leaders were key stakeholders, entitled to basic awareness of studies and so foster a relationship of partnership between them and the industry, or deny and limit the valuable role they could and should play in the system. Sanofi Genzyme alleged that this was a fallacious argument, and not what it had contended with its complaint. Sanofi Genzyme alleged that, on balance, the material presented by Amicus with the emphasis and focus (and majority of time) spent on presenting the clinical development programme and population of patients amenable for treatment in a specific indication of an unlicensed product amounted to pre-approval promotion, and that was what the focus of consideration should be. Sanofi Genzyme did not dispute the value of legitimate, appropriately timed and conducted engagement with patient organisations but it did not support the pre-approval promotion of uncertified material.

Sanofi Genzyme noted that Amicus had submitted that because Clause 14.1 applied exclusively to promotional materials, and because of the reasons submitted in its response and appeal, Clause 14.1 did not apply and this had not been breached. Sanofi Genzyme alleged that this was promotional material and promotional activity, given the nature and extent of the information presented and discussed relating to a product that had not received UK marketing authorization. Therefore Clause 14.1 had been

breached. Furthermore, in previous correspondence, Amicus had alleged that one of its signatories had gone on sick leave prior to this event, so therefore had no appropriately qualified medical signatory at the time of this event. Sanofi Genzyme was rather surprised, therefore, that having already supplied this explanation, in its appeal, Amicus now submitted that the reason for no medical signatory was because it believed one was not required. These two lines of argument were inconsistent, and raised questions over not only Amicus's understanding of the Code, but also its internal review, approval and certification processes.

Sanofi Genzyme asked the Appeal Board to uphold the Panel's rulings of breaches of Clauses 2, 3.1, 14.1, 14.3 and 9.1. Promotion of a product before it received its marketing authorization was a serious breach of the Code and was cited as an example of activity which was likely to be in breach of Clause 2.

* * * * *

It became apparent that Sanofi Genzyme had not received the copy of the letter providing the slides at issue. In response to being provided with a copy of the slides Sanofi Genzyme made the following additional response.

Sanofi Genzyme stated that the proportion of slides devoted to product in the presentation was very much less than the proportion of time devoted to discussion of product; Sanofi Genzyme made the latter point clearly in its previous submissions but could not compare it to the number of slides. Sanofi Genzyme also observed that the lengthy and detailed discussion, which it clearly recalled, on amenable mutations and recommendations by the company for patients to consult their doctor about these were not referenced in the slides.

APPEAL BOARD RULING

The Appeal Board considered that the pharmaceutical industry should be able to inform patient groups about medicines and/or general research interests. Companies, however, had to ensure that the provision of such information complied with the Code including the differences between proactive provision and reactive provision. The audience were all senior officials of various relevant patient organisation groups worldwide. The Appeal Board noted that the Panel had considered that, in the context of the meeting in question, the patient organisation executives were not members of the public *per se*. The Appeal Board noted, however, that this matter was not before it for consideration and thus made no comment on this decision. In the Appeal Board's view attendees at the meeting were likely to take messages back to their respective organisations.

The Appeal Board noted that slides 21-25 of Amicus's presentation at the meeting in question gave an overview of clinical trial protocols for migalastat studies. Slide 23 referred to monotherapy for Fabry patients with amenable mutations. The Appeal Board noted that mutation analysis and the possibility of targeting therapy to patients with particular gene mutations was an emerging concept in the treatment of Fabry Disease. It noted Sanofi Genzyme's submission that patient suitability characteristics for migalastat such as amenable and non-amenable mutations were discussed. The Appeal Board noted that the slides presented at the meeting referred to the need for patients to know their mutation as this could impact on symptoms and their treatment. According to the presentation the registration studies were carried out on patients with amenable mutations. Amicus's representatives at the appeal confirmed that amenable mutations were mentioned at the meeting including which ones might be relevant to migalastat. The representatives at the appeal stated that it was a matter for the regulators to decide which would be included in the marketing authorisation/SPC. Slide 26 was headed 'Next Steps for Migalastat' and gave an overview of the regulatory status of the medicine. It was stated that the EMA review of the marketing authorization application for migalastat remained on track under accelerated assessment and that the Committee for Medicinal Products for Human Use (CHMP) opinion was anticipated by early 2016. In the Appeal Board's view, these statements together implied a positive outcome.

The Appeal Board noted the statements and discussion about amenable mutations and the implied positive regulatory status of migalastat. Although much of the information was in the public domain, on balance, the Appeal Board considered that the presentation had raised the prospect of a new treatment for Fabry patients with amenable mutations and in that regard, had promoted migalastat prior to the grant of a marketing authorization. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.1. The appeal on this point was unsuccessful.

The Appeal Board noted its ruling above and considered that as the promotional presentation was not formally certified it upheld the Panel's ruling of a breach of Clause 14.1. The appeal on that point was unsuccessful. The Appeal Board considered that as the presentation was aimed at a patient organisation and had not been formally certified it upheld the Panel's ruling of a breach of Clause 14.3. The appeal on this point was unsuccessful.

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

Although noting its comments above, the Appeal Board did not consider that in the particular circumstances of this case a ruling of a breach of Clause 2 was warranted and so the Appeal Board ruled no breach of that Clause. The appeal on this point was successful.

Complaint received **10 December 2015**

Case completed **11 April 2016**