CASE AUTH/2310/4/10

NOVO NORDISK v LILLY

Promotion of Byetta

Novo Nordisk complained about Lilly's activities associated with the Diabetes UK Annual Professional Conference which took place 3 – 5 March 2010. At issue were presentations given at a Lilly-sponsored symposium held on the eve of the conference which were alleged to have covered, *inter alia*, the unlicensed use of Byetta (exenatide) with insulin and the development of the once-weekly formulation of exenatide. Novo Nordisk also complained about exhibition panels used by Lilly.

The detailed response from Lilly is given below.

Novo Nordisk noted that the first presentation entitled 'The Association of British Clinical Diabetologists (ABCD) Nationwide Exenatide Audit Update', detailed, *inter alia*, results from patients using Byetta in combination with insulin. This was an off-licence use of Byetta which should have been emphasized by the external speaker and made clear on the related slides. The implication that Byetta could be used in combination with insulin was misleading since this was inconsistent with its summary of product characteristics (SPC).

In inter-company dialogue Lilly described its symposium as a non-promotional forum for the legitimate exchange of medical and scientific information. Novo Nordisk submitted that it was difficult to consider a Lilly-sponsored symposium, which almost entirely focused on the company's marketed and future GLP-1 agonist products, as non-promotional. Nevertheless the fact that during the symposium, whether promotional or not, neither the speaker nor the slides presented declared that the use of Byetta in combination with insulin was not licensed, constituted a breach of the Code.

The Panel noted Lilly's submission that its symposium was to facilitate the legitimate exchange of medical and scientific information. Supplementary information to the Code stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion. The Panel noted that the symposium was alleged to have covered, *inter alia*, the unlicensed use of Byetta with insulin and the development of a once-weekly formulation of exenatide. That the meeting would perhaps elicit interest in these two topics might not necessarily be unacceptable if the arrangements for the meeting and its content satisfied the supplementary information to the Code.

The Panel noted that the Lilly symposium had taken place on the eve of the Diabetes UK Annual Professional Conference. The symposium had been part of the official conference programme although Lilly had chosen not to have it advertised in the official conference programme. The arrangements for the symposium were supplied to, and agreed by, the conference organising committee in advance. The official application form for sponsorship, exhibition stands etc referred to evening symposia and listed Tuesday, 2 March (6-11pm) as an option. Potential attendees had been invited and offered return travel for the meeting and overnight accommodation. The timing of the return journey was flexible depending on the number of days the invitee planned to attend the main conference. There was nothing on the invitation which indicated that recipients had already arranged to attend the main conference. The invitation was headed 'Lilly Annual Diabetes Medical Satellite Symposium at the Diabetes UK 2010 Annual Professional Conference'. Lilly acknowledged that, although unlikely, some of the attendees might not have subsequently attended the main conference. Lilly's meeting began at 5.45pm with drinks and canapés. The scientific session started at 6.15pm and ended at 8.15pm with pre-dinner drinks followed by dinner at 8.30pm. The briefing material for those members of the sales force that would attend the main conference stated 'No Sales Force to attend the symposium'. It was not clear whether this meant that the sales force could nonetheless attend the pre-symposium drinks and the dinner afterwards.

The symposium had taken place in the context of a major UK scientific/clinical conference. In that regard the Panel considered that such conferences might be an appropriate setting for the legitimate exchange of medical and scientific information. Nonetheless, the Panel considered that just because a symposium took place in association with a major conference did not automatically mean that it would be regarded as the legitimate exchange of medical and scientific information.

The Panel noted that Lilly's meeting was by invitation only; the attendee list and invitation process was controlled by Lilly. The Panel considered that the overall impression was that Lilly had organised its own stand-alone meeting, albeit on the eve of a national conference. The invitation included prescribing information for Byetta; it thus appeared that Lilly considered the invitation to the symposium to be promotional. The impression given to invitees might be that Lilly considered the symposium to be promotional. The invitation stated that ABCD

would present further analysis of their exenatide audit. The meeting would also discuss the benefits of glucose and weight control with both current and future GLP-1 receptor agonists and new data comparing GLP-1 receptor antagonists DPP-4 inhibitors. The emphasis would be on how this new information might enhance attendees' current and future clinical practice. In the Panel's view it was extremely difficult to argue that the symposium could take the benefit of the supplementary information to the Code if Lilly considered any part of it to be promotional, requiring prescribing information. Context was important. In stating that it could take the benefit of the supplementary information Lilly had not explained how the material satisfied the requirement of being 'during the development of a medicine'. Exenatide had a marketing authorization. The long acting version did not. In the opinion of the Panel disseminating data to prescribers which potentially expanded a licensed product's market share might be different to the legitimate exchange of medical and scientific information during the development of a medicine which implied debate which enhanced the current state of scientific knowledge. The status of the audience was relevant: delegates should be able to participate in debate for it to be an exchange of medical and scientific information. The Panel queried whether the invited audience, GPs with an interest in diabetes and diabetes specialist nurses would participate at the requisite level. In the Panel's view, taking all of the circumstances into account, overall the meeting was a promotional meeting for Byetta; on balance it went beyond being the legitimate exchange of medical and scientific information during the development of a medicine.

The Panel noted that the speaker briefing stated that the objective of the presentation was to present the ABCD audit results on exenatide use in the UK and give a fair and balanced interpretation and analysis of the data. Key points to communicate were to clarify and emphasise the Byetta licence and indications for use and to highlight any off-licence use of Byetta. The Panel noted that in a promotional meeting for a medicine there should be no reference to off-licence use of that medicine. The speaker's attention was drawn to the requirements of the Code. Throughout the presentation exenatide was only referred to by its non-proprietary name and no product or company logos were used. Some slides referred to the 'restricted licence for use of exenatide with insulin and glitazones. Also fear of hypoglycaemia in using exenatide with insulin and sulphonylureas'. In the Panel's view this statement did not promote or encourage the use of exenatide with insulin. The Panel noted, however, that some slides at the end of the presentation referred to the use of exenatide plus insulin and detailed some of the clinical results observed. In a statement from the presenter provided by Lilly, it was noted that these were reserve slides with some limited data on the use of exenatide with insulin, they were not used at the meeting but were available on the ABCD password-protected website for viewing by contributors to the audit.

The Panel considered that Novo Nordisk had to establish on the balance of probabilities that the reserve slides had been used and that the slides used were in breach of the Code. Lilly denied that the reserve slides at issue had been used. Overall, the Panel did not consider that the presentation used at the symposium had been misleading about the licensed use of exenatide nor did it promote Byetta for use in combination with insulin. No breaches of the Code were ruled.

The second presentation, entitled 'Comparison of the Incretin-based Therapies; DDP-4 inhibitors and GLP-1 receptor agonists. An update of recent trial data', referred to exenatide long-acting release (LAR) for once weekly dosing. Exenatide once-weekly was not currently licensed. The new drug application was submitted to the FDA in the US in May 2009. In March 2010 an application was submitted to the European Medicines Evaluation Agency (EMEA). A European licence was not expected for another 12-18 months.

Novo Nordisk noted that this presentation did not clarify (either verbally by the external speaker or on the slides) that exenatide LAR did not have a UK marketing authorization. This misled the health professionals about the regulatory status of the compound. Novo Nordisk suspected that the speaker's had been inadequate and as such Lilly was responsible for the pre-licence promotion of exenatide LAR in breach of the Code.

The Panel noted its comments above regarding the arrangements for and nature of the symposium.

The Panel noted that the speaker briefing stated that the objective of the presentation was to give a fair and balanced presentation of data comparing GLP mimetics vs DPP4 class of therapy. Key points to be communicated were the differentiation of the classes; the presentation of data should be consistent with each medicine's SPC. The speaker was asked to highlight data not considered within the licence and to remind the audience of the licence status if discussing exenatide LAR. The Panel noted Lilly's submission that this was done. The speaker's attention was drawn to the requirements of the Code. Throughout the presentation exenatide was only referred to by its non-proprietary name and no product or company logos were used.

The Panel noted that several of the slides detailed information about exenatide once weekly. The presentation included the results of a study whereby exenatide once weekly demonstrated superior glycaemic control and weight reduction compared with sitagliptin or pioglitazone after 26 weeks' treatment (Bergenstal *et al*). The Panel considered that, in the context of a promotional meeting, the presentation promoted exenatide

LAR prior to the grant of its marketing authorization. A breach of the Code was ruled. None of the slides noted that exenatide LAR was not licensed although Lilly submitted that this information was given verbally by the speaker. On balance the Panel considered that the presentation was misleading with regard to the regulatory status of exenatide LAR. A breach of the Code was ruled. These rulings were appealed. The Appeal Board noted that the title of the symposium organised by Lilly was 'The benefits of GLP-1 Receptor Agonists; current and future therapies'. Invitees were told that the emphasis of the discussions throughout the symposium would be on how the information presented might enhance their present and future clinical practice. In that regard the Appeal Board considered that Lilly appeared to expect the information presented to influence, *inter alia*, current prescribing practice. The Appeal Board further considered that, given the inclusion of prescribing information on the invitation, most attendees would accept the invitation on the basis that the symposium was promotional. In that regard, the Appeal Board noted that the sales force brief referred to the meeting as the 'Byetta Symposium 2010'.

The Appeal Board noted that the speaker briefings given to the Chairman and to the speaker only referred in detail to certain clauses of the Code. The speaker was asked to highlight data not considered within licence and to remind the audience of the licence status if discussing exenatide LAR. The Chairman was asked to ensure any pre-licence therapies were highlighted in the presentations. In the Appeal Board's view these instructions were ambiguous particularly given that the requirements of Clause 3 had not been referred to in detail.

The Appeal Board noted that a high percentage of the slides in the presentation at issue referred to unlicensed medicines/indications. Further, three members of the marketing team had attended the symposium as well as the drinks and dinner.

The Appeal Board rejected Lilly's submission that the symposium constituted the legitimate exchange of medical and scientific information during the development of a medicine and could thus take the benefit of the exemption described in the supplementary information to the Code. In the Appeal Board's view, the symposium, as arranged, was promotional and in that regard the presentation in question promoted exenatide LAR prior to the grant of the marketing authorization. The presentation was misleading with regard to the regulatory status of exenatide LAR. The Appeal Board upheld the Panel's rulings of breaches of the Code.

Novo Nordisk stated that the third presentation, entitled 'The benefits of GLP-1 Receptor Agonists: An overview of future therapies and their data', was delivered by a Lilly employee who did not state that exenatide LAR did not have a marketing authorization. Thus the presentation was misleading in breach of the Code including Clause 2. Novo Nordisk drew parallels with Case AUTH/2234/5/09.

The Panel noted its comments above regarding the arrangements for and nature of the symposium.

The Panel noted that the speaker briefing stated that the objective of the presentation was to provide an overview of current and future data showing the development of GLP-1 receptor agonists and to ensure that the audience knew that exenatide once weekly was currently not licensed. Key points to be communicated were a fair and balanced representation of data around the development of the class and to emphasise that Byetta and Victoza were currently the only licensed GLP analogues available. The speaker's attention was drawn to the requirements of certain clauses of the Code. Throughout the presentation exenatide was only referred to by its non-proprietary name and no company or product logos were used. The presentation gave a positive overview of the development of exenatide once weekly; two slides clearly stated that exenatide once weekly was not currently licensed.

The Panel considered that the presentation promoted exenatide once weekly before the relevant marketing authorization had been granted. The inclusion of statements that the product was not currently licensed were irrelevant in that regard. A breach of the Code was ruled. This ruling was appealed. The Panel considered, however, that the presentation had not been misleading with regard to the regulatory status of exenatide once weekly and in that regard ruled no breach of the Code.

The Panel noted its rulings above that exenatide once weekly had been promoted before the grant of the relevant marketing authorization. The Panel considered that high standards had not been maintained and ruled a breach of the Code. This ruling was appealed. The Panel noted from the supplementary information to Clause 2 that promoting a medicine before the grant of a marketing authorization was an activity likely to be in breach of Clause 2. That clause was reserved as a sign of particular censure. The Panel ruled a breach of Clause 2. This ruling was appealed.

The Appeal Board noted its comments above and that, in its view, the meeting as arranged, was promotional.

The Appeal Board noted the details of the speaker briefing as described above and in particular that there was no mention of the requirements of Clause 3 of the Code.

The Appeal Board considered that the presentation promoted exenatide once weekly before the relevant marketing authorization had been granted. The inclusion of statements that the product was not currently licensed was irrelevant in that regard. The Appeal Board upheld the

Panel's ruling of a breach of the Code.

The Appeal Board noted that the symposium included discussions about the future availability of exenatide LAR and mention was made of the unlicensed use of exenatide with insulin. The Appeal Board further noted that the invitation to the symposium stated that the emphasis of the discussions would be on how the data presented might enhance an attendee's current and future clinical practice. The licence application for exenatide LAR was submitted two days after the symposium. The Appeal Board considered that the attendance of three members of the marketing team added to the impression that the meeting was promotional.

Overall, given the arrangements for and the content of the symposium, the Appeal Board considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of the Code.

The Appeal Board noted from the supplementary information to Clause 2 that promoting a medicine before the grant of a marketing authorization was an activity likely to be in breach of Clause 2. That clause was reserved as a sign of particular censure. The Appeal Board noted its comments above and upheld the Panel's ruling of a breach of Clause 2.

Novo Nordisk noted that Lilly's exhibition panels featured two graphs from Klonoff *et al* (2008). The first graph showed the HbA_{1c} improvement from the core phase of three randomized, controlled trials and their 3-year long, uncontrolled, observational extension period. The graph contained a suppressed zero y-axis to exaggerate the 1% HbA_{1c} decrease revealed by the study. Regardless of no comparator on the graph, this was misleading, and did not maintain high standards.

Novo Nordisk noted that shortening the y-axis exaggerated the observed glycaemic improvement. Lilly's view that health professionals would be able to interpret such results suggested that this type of presentation was acceptable in every case when there was no comparator on the graph. This was clearly not so as this presentation did not give a clear, fair, balanced view of the matter. Further, it had not been stated on the exhibition panel that the analysis was post-hoc. This was an important piece of information to interpret the results correctly and its omission was misleading.

Novo Nordisk noted that more importantly Lilly had not stated that this post-hoc analyzed patient subgroup (n=217) represented only 22.5% of the total patient population exposed to exenatide during the core randomized, controlled phases of the study (n=963). Klonoff *et al* reported that the intention to treat (ITT) population that entered the extension phase was 527, but even in this case the reported graphs represented only 41% of the study population. Knowing this piece of information, one could easily conclude that the paper reported the results from the responders and in fact most patients needed to be switched to other therapies due to the inadequate response to exenatide during the study period. Conversely, without knowing this information, one could conclude that the 1% HbA_{1c} improvement could be sustained with exenatide for 3 years in the general type 2 diabetes population. Clearly the missing pieces of information were highly important and the graphs on the exhibition panels (HbA_{1c} improvement and weight change) misled and failed to maintain high standards.

Novo Nordisk alleged that the graphs were a deliberate attempt to mislead the participants at the largest diabetes scientific event of the UK in breach of Clause 2.

The Panel noted that Lilly's exhibition panel included a graph of the 'Change in HbA_{1c} from baseline in 3 year completer population'. The heading to that section of the exhibition panel was 'Choose BYETTA to provide sustained HbA_{1c} improvement over 3 years'. The x axis plotted weeks of treatment and the y axis was labelled HbA_{1c} (%). The y axis was shortened between 0 to 5% and then showed 5 to 9%. The Panel noted Lilly's submission that the y axis represented a physiological range of HbA_{1c}. The results obtained for Byetta showed that from a baseline of 8.2%, HbA_{1c} fell sharply within the first 26 weeks, and that an initial 1% fall was maintained at week 156. A claim to the right of the graph stated 'Almost half (46%) of patients achieved $HbA_{1c} \leq 7\%$. The graph and the claim were derived from Klonoff et al. Only data for Byetta was shown; there was no comparison with any other medicine.

The Panel noted that clinicians would be familiar with the physiological range of HbA_{1c} and that they would treat patients to a target HbA_{1c} of around 7%. It considered that to shorten the y axis between 0 to 5% did not mean that a suppressed zero was used in a misleading way. The decrease in HbA_{1c} was clearly stated and not exaggerated. The Panel did not consider that the graph was misleading or exaggerated as alleged. In that regard the Panel did not consider that high standards had not been maintained. No breaches of the Code were ruled.

The Panel noted that Klonoff *et al* had taken patients from three placebo controlled trials and their open-label extensions and enrolled them into one open-ended, open-label clinical trial. There had been 527 patients in the ITT population from the three studies; only 217 completed 3 years of exenatide therapy ie only 41% of the original patients. The Panel noted the claim that 'Almost half (46%) of patients achieved $HbA_{1c} \leq 7\%$' referred only to the 3 year completers and so in that regard it was 46% of 41% ie approximately 19%. The Panel considered that the claim implied that almost half of all diabetic patients would achieve $HbA_{1c} \leq 7\%$ with exenatide therapy whereas with

the population studied it was only about 19%. Similarly, claims were made regarding the percentage of patients who would lose weight whilst on exenatide therapy. The Panel considered that with regard to the data from Klonoff *et al*, important information had been omitted from the exhibition panel; the material was not sufficiently complete such as to allow clinicians to form their own opinion of the therapeutic value of exenatide. The Panel considered that the exhibition panel was misleading as alleged. High standards had not been maintained. Breaches of the Code were ruled.

The Panel noted its rulings above and considered that the exhibition panel, although misleading, was not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

Novo Nordisk complained about the promotion of Byetta (exenatide) by Eli Lilly and Company Limited at the Diabetes UK Annual Professional Conference which took place in Liverpool, 3-5 March 2010. Matters had not been resolved through inter-company dialogue.

A Lilly-sponsored symposium – The benefits of GLP-1 [glucagon-like peptide-1] Receptor Antagonists; current and future therapies

Lilly explained that the objective of the symposium was to facilitate the legitimate exchange of medical and scientific information with diabetes specialists. In this regard, the symposium was relevant to the purpose of the Diabetes UK conference. Indeed, the latter was reflected in the wide-ranging content of the symposium which included a balanced and fair discussion of other GLP-1 based therapies including liraglutide, taspoglutide, albiglutide and DPP-4 [dipeptidyl peptidase-4] inhibitors. In line with the objective of exchanging scientific data, the meeting included off-licence data, therefore members of the sales team were excluded, including the national sales manager and the Byetta marketing managers. Only health professionals attending the Diabetes UK conference with a valid scientific interest in understanding the benefits of the GLP-1 based treatments were invited to attend. Invitees were then required to register online for the symposium. There was also an onsite registration facility only for those invited guests who had not registered online prior to the symposium.

Lilly submitted that the symposium was consistent with its own standard operating procedures (SOPs) and Clause 3 of the Code which stated that 'The legitimate exchange of medical and scientific information during the development of a medicine is not prohibited provided that any such information or activity does not constitute promotion which is prohibited under this or any other clause'.

Lilly provided a copy of the brief to its sales force team attending the conference indicating that all potential Byetta once weekly discussions be directed to members of the medical team. Also provided was email correspondence from the brand manager discussing communication to the sales force reiterating the company's approach to pre-licence discussions.

In response to a request for further information Lilly submitted that the symposium was part of the Diabetes UK Annual Professional Conference. Lilly booked an official conference satellite symposium for the evening of 2 March for which it paid a fee to the conference organisers. The arrangements for the symposium were supplied to, and agreed by, the conference organising committee in advance. The symposium was not included in the official conference programme. Lilly decided not to have its symposium listed on the conference programme and website.

Lilly explained that its SOP required that attendees to any of its satellite symposia which involved off-licence information needed to be limited and controlled; therefore Lilly opted not to widely advertise its symposium. This helped restrict attendance to suitably qualified health professionals. It was therefore agreed with the conference organisers that Lilly would invite appropriate health professionals to the symposium. The attendee list and invitation process was controlled by Lilly's medical team. Lilly noted that its general sponsorship of the conference was clearly mentioned in the conference guide.

Lilly explained that health professionals who were expected to attend the conference were invited to arrive earlier to attend the symposium. Given the timing of the symposium, and that delegates were expected to attend the main conference the following morning, it was deemed appropriate to provide overnight accommodation on the night of Tuesday 2 March. Return travel to Liverpool, in conjunction with the overnight stay, was provided to allow delegates to attend the symposium and then the conference. Lilly's invitation did not include conference registration and as such attendance at the conference was outside Lilly's remit. It was therefore possible, but unlikely, that some of those who attended the symposium did not subsequently attend the conference. Lilly submitted that thirty-six attendees were reimbursed for travel costs and twenty-five were provided with overnight accommodation.

Lilly submitted that its symposium was a professional meeting held on the occasion of, and in association with, the Diabetes UK Annual Professional Conference. Only health professionals with a valid scientific interest in understanding the benefits of the GLP-1 based treatments, and who Lilly considered would have attended the conference regardless, were invited. Of the suitably qualified diabetes health professionals (consultant diabetologists, diabetes nurse specialists, specialist registrars in diabetes and GPs with a special interest in diabetes) who were expected to attend the conference, 2,170 were invited to attend the symposium. Invitations were initially sent to 240 health professionals but only a

small number were able to attend and so a second, and then third wave of invitations were sent out to health professionals, who met Lilly's criteria. Seventy-three delegates attended the symposium. An attendee list was provided.

1 Presentation – The Association of British Clinical Diabetologists (ABCD) Nationwide Exenatide Audit Update

COMPLAINT

Novo Nordisk noted that an external health professional presented the latest data from the audit as the first speaker of the symposium. Part of the presentation provided results from patients using Byetta in combination with insulin. This was an off-licence use of Byetta which should have been emphasized by the speaker and made clear on the related slides. Novo Nordisk considered that Lilly was responsible for presenting results in relation to the off-licence use of Byetta, without highlighting this important information appropriately to the audience. The implication that Byetta could be used in combination with insulin was misleading since this was inconsistent with its summary of product characteristics (SPC). Novo Nordisk alleged a breach of Clauses 3.2 and 7.2.

In inter-company dialogue Lilly described its corporate symposium as a non-promotional forum for the legitimate exchange of medical and scientific information. Novo Nordisk submitted that it was difficult to consider a Lilly-sponsored symposium, which almost entirely focused on the company's marketed and future GLP-1 agonist products, as non-promotional. Nevertheless the fact that during the symposium, whether promotional or not, neither the speaker nor the slides presented declared that the use of Byetta in combination with insulin was not licensed, constituted a breach of the Code as alleged above.

Novo Nordisk had asked for a copy of the speaker briefing document and the slides in order to assess the measures Lilly took with regard to the data presented concerning this off-licence use. However Lilly had not provided either document although in inter-company correspondence it consistently referred to them.

Novo Nordisk did not understand Lilly's reference in inter-company dialogue to the liraglutide (Victoza) audit, also conducted by the ABCD. Any audit collected data on real life use of the audited product which might cover off-licence use of the medicine. This was a scientifically valid way to collect post-marketing data on the effectiveness of marketed products. Such activities were encouraged by regulatory authorities. The fact that the nationwide exenatide audit revealed a significant proportion of type 2 diabetics using Byetta in combination with insulin was clinically important. Novo Nordisk acknowledged that physicians needed to receive information about this finding, however it was concerned about using and sharing this information with prescribers at a Lilly-sponsored symposium without sufficiently declaring that Byetta was not indicated in combination with insulin.

RESPONSE

Lilly submitted that the external speaker, a member of the ABCD steering group, presented the results of a nationwide clinical audit on the use of Byetta in clinical practice. The independent audit was designed, undertaken, implemented and published by the ABCD with administrative and IT support funded by Lilly under a partnership agreement.

In anticipation that the audit also investigated the extent to which health professionals used Byetta off-licence with insulin, Lilly's briefing required the speaker to appropriately highlight that such use of Byetta was unlicensed and remind the audience of the precise licensed indication of Byetta. Indeed, the speaker also discussed the place of Byetta in the management of type 2 diabetes with reference to the National Institute for Health and Clinical Excellence (NICE) guidelines which further clarified the licensed indication of Byetta.

Whilst Lilly selected the speaker, other than with respect to the briefing, it did not exert any editorial control or influence over the content of the presentation. As the meeting was non-promotional, it was desirable for Lilly to ensure that the speaker's presentation was, and was seen to be, an independent view and opinion informed by independent research. Lilly noted that the written speaker brief expressly directed the speaker to comply with the Code and present a fair and balanced interpretation and analysis of the audit findings. A copy was provided.

Lilly submitted that it was imperative to highlight that no off-licence use of Byetta in combination with insulin or glitazones was presented by the speaker at this symposium as alleged. Although one of the speaker's slides included the statement '… restricted licence for use of exenatide with insulin and glitazones', in view of the speaker brief given, the speaker kept this slide as a 'backup' and did not present it at the symposium. A statement to confirm this was provided from the speaker.

Lilly denied breaches of Clauses 3.2 and 7.2.

PANEL RULING

The Panel noted Lilly's submission that its annual diabetes medical satellite symposium at the Diabetes UK 2010 annual professional conference was to facilitate the legitimate exchange of medical and scientific information. The supplementary information to Clause 3, Marketing Authorization, stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under Clause 3 or any other clause. The Panel noted that the symposium was alleged to have covered, *inter alia*, the unlicensed

use of Byetta with insulin and the development of a once-weekly formulation of exenatide. That the meeting would perhaps elicit interest in these two topics might not necessarily be unacceptable if the arrangements for the meeting and its content satisfied the supplementary information to Clause 3.1.

The Panel considered that when determining whether a meeting was promotion before the grant of a marketing authorization, or the legitimate exchange of medical and scientific information, the content and context in which it had taken place were important as were the general arrangements.

The Panel noted that the Lilly symposium had taken place on the eve of the Diabetes UK Annual Professional Conference. The symposium had been part of the official conference programme although Lilly had chosen not to have it advertised in the official conference programme. The arrangements for the symposium were supplied to, and agreed by, the conference organising committee in advance. The official application form for sponsorship, exhibition stands etc referred to evening symposia and listed Tuesday, 2 March (6-11pm) as an option. Potential attendees had been invited and offered return travel to Liverpool for the meeting and accommodation for the night of Tuesday, 2 March. The timing of the return journey was flexible depending on the number of days the invitee planned to attend the main conference. There was nothing on the invitation which indicated that recipients had already arranged to attend the main conference. The invitation was headed 'Lilly Annual Diabetes Medical Satellite Symposium at the Diabetes UK 2010 Annual Professional Conference'. Lilly acknowledged that, although unlikely, some of the attendees might not have subsequently attended the main conference. Lilly's meeting began at 5.45pm with drinks and canapés. The scientific session started at 6.15pm and ended at 8.15pm with pre-dinner drinks followed by dinner at 8.30pm. The briefing material for those members of the sales force that would attend the Diabetes UK conference stated 'No Sales Force to attend the symposium'. It was not clear whether this meant that the sales force could nonetheless attend the pre-symposium drinks and the dinner afterwards.

The Panel noted that the symposium had taken place in the context of a major UK scientific/clinical conference. In that regard the Panel considered that such conferences might be an appropriate setting for the legitimate exchange of medical and scientific information. Nonetheless, the Panel considered that just because a symposium took place in association with a major conference did not automatically mean that it would be regarded as the legitimate exchange of medical and scientific information.

The Panel noted that one of the slides from the presentation on the audit stated that the headlines from the data analysis would be presented at a trilogy of events. These were listed as; DUK [Diabetes UK] satellite symposium 2 March, DUK main meeting 3 March and ABCD Spring meeting 7 May.

The Panel noted that Lilly's meeting was by invitation only; over 2,000 health professionals were invited, seventy-three attended. The attendee list and invitation process was controlled by Lilly. The Panel considered that the overall impression was that Lilly had organised its own stand-alone meeting, albeit on the eve of a national conference. The invitation to the symposium had included prescribing information for Byetta; it thus appeared that Lilly considered the invitation to the symposium to be promotional. The impression given to invitees might be that Lilly considered the symposium to be promotional. The invitation stated that ABCD would present further analysis of their exenatide audit. The meeting would also discuss the benefits of glucose and weight control with both current and future GLP-1 receptor agonists and new data comparing GLP-1 receptor antagonists DPP-4 inhibitors. The emphasis would be on how this new information might enhance attendees' current and future clinical practice. In the Panel's view it was extremely difficult to argue that the symposium could take the benefit of the supplementary information to Clause 3.1 if Lilly considered any part of it to be promotional, requiring prescribing information. Context was important. In stating that it could take the benefit of the supplementary information to Clause 3.1 Lilly had not explained how the material satisfied the requirement of being 'during the development of a medicine'. Exenatide had a marketing authorization. The long acting version did not. In the opinion of the Panel disseminating data to prescribers which potentially expanded a licensed product's market share might be different to the legitimate exchange of medical and scientific information during the development of a medicine which implied debate which enhanced the current state of scientific knowledge. The status of the audience was relevant: delegates should be able to participate in debate for it to be an exchange of medical and scientific information. The Panel queried whether the invited audience, GPs with an interest in diabetes and diabetes specialist nurses would participate at the requisite level. The Panel also noted the apparent difficulty of encouraging attendance to the meeting. In the Panel's view, taking all of the circumstances into account, overall the meeting was a promotional meeting for Byetta; on balance it went beyond being the legitimate exchange of medical and scientific information during the development of a medicine.

The Panel noted that the speaker briefing stated that the objective of the presentation was to present the ABCD audit results on exenatide use in the UK and give a fair and balanced interpretation and analysis of the data. Key points to communicate were to clarify and emphasise the Byetta licence and indications for use and to highlight any off-licence use of Byetta. The Panel noted that in a promotional meeting for a medicine there should be no reference to off-licence use of that medicine. The speaker's attention was drawn to the requirements of Clauses 7.2 and 7.4. Throughout the presentation

exenatide was only referred to by its non-proprietary name and no product or company logos were used. Some slides referred to the 'restricted licence for use of exenatide with insulin and glitazones. Also fear of hypoglycaemia in using exenatide with insulin and sulphonylureas'. In the Panel's view this statement did not promote or encourage the use of exenatide with insulin. The Panel noted, however, that some slides at the end of the presentation referred to the use of exenatide plus insulin and detailed some of the clinical results observed. In a statement from the presenter provided by Lilly, it was noted that these were reserve slides with some limited data on the use of exenatide with insulin, they were not used at the meeting but were available on the ABCD password-protected website for viewing by contributors to the audit.

The Panel considered that the parties' accounts differed. The Panel considered that Novo Nordisk had to establish on the balance of probabilities that the reserve slides had been used and that the slides used were in breach of the Code. Lilly denied that the reserve slides at issue had been used. Overall, the Panel did not consider that the presentation used at the symposium had been misleading about the licensed use of exenatide nor did it promote Byetta for use in combination with insulin. No breach of Clauses 3.2 and 7.2 was ruled.

2 Presentation – Comparison of the Incretin-based Therapies; DDP-4 inhibitors and GLP-1 receptor agonists. An update of recent trial data

This presentation referred to exenatide long-acting release (LAR) for once weekly dosing. Lilly explained that exenatide once-weekly was an extended-release medicine for type 2 diabetes designed to deliver continuous therapeutic levels of exenatide in a single weekly dose. Exenatide once-weekly was not currently licensed for use. The new drug application was submitted to the FDA in the US in May 2009 and accepted in July 2009. It was based on data from the DURATION (Diabetes therapy Utilisation: Researching changes in A1C, weight, and other factors Through Intervention with exenatide Once weekly) clinical trial program. In March 2010 a licence application was submitted to the European Medicines Evaluation Agency (EMEA). A European licence was not expected for another 12-18 months.

COMPLAINT

Novo Nordisk noted that this presentation, by another external health professional, detailed results from DURATION-2 without clarifying (either verbally by the speaker or on the slides) that exenatide LAR did not have a UK marketing authorization. This misled the health professionals about the regulatory status of the compound. Although Novo Nordisk had not seen the speaker's brief, despite requesting a copy of it, it seemed that it might have been inadequate and as such Lilly was responsible for the pre-licence promotion of exenatide LAR by the speaker. Novo Nordisk alleged breaches of Clauses 3.1 and 7.2.

Novo Nordisk noted that Lilly had not provided it with copies of the speaker's brief or the slides as requested during inter-company dialogue. It was only these documents which could clarify whether Lilly made appropriate efforts to ensure compliance with the Code in terms of this presentation.

Novo Nordisk stated that it was irrelevant that an external, independent diabetes professor presented the otherwise publically available results to the audience. On a company-sponsored symposium the slides about exenatide LAR should have included a clear statement as to its regulatory status.

Novo Nordisk again noted its concern about Lilly's corporate symposium as a non-promotional, educational event. Novo Nordisk alleged that the detailed discussion about Lilly's future compound constituted pre-licence promotional activity.

RESPONSE

Lilly stated that it provided the speaker, a renowned professor of diabetes, with a written brief to present on the topic of 'Comparison of Incretin-based therapies; DPP-4 inhibitors and GLP-1 receptor agonists. An update of recent trial data'. Given the premise for the Lilly symposium, as discussed above, the inclusion of this presentation was deemed relevant and proportional given that diabetes specialists attending this major specialist/academic meeting would have a legitimate interest in medical and scientific information about products in development including exenatide once-weekly.

Lilly noted that the brief expressly directed the speaker to comply with the Code and present a fair and balanced discussion of the information presented. Indeed, in anticipation that the presentation would discuss, in part, exenatide once-weekly, which was not currently licensed for use, Lilly's briefing required the speaker to appropriately highlight the latter; which was done. A copy of the brief was provided.

Whilst Lilly had selected and briefed the speaker, it had no editorial control or influence over the content of the presentation. Given this meeting was non-promotional it was desirable for Lilly to ensure that the presentation was, and was seen to be, the speaker's own independent view and opinion. Lilly noted that the speaker's presentation included information about the DURATION-2 study which had previously been presented at other conferences of high academic standing such as the American Diabetes Association. Indeed, the results of this particular study were also presented as part of the proceedings of the Diabetes UK conference itself. A copy was provided.

Lilly denied breaches of Clauses 3.1 and 7.2.

PANEL RULING

The Panel noted its comments at point A1 above regarding the arrangements for and nature of the symposium.

The Panel noted that the speaker briefing stated that the objective of the presentation was to give a fair and balanced presentation of data comparing GLP mimetics vs DPP4 class of therapy. Key points to be communicated were the differentiation of the classes; the presentation of data should be consistent with each medicine's SPC. The speaker was asked to highlight data not considered within the licence and to remind the audience of the licence status if discussing exenatide LAR. The Panel noted Lilly's submission that this was done. The speaker's attention was drawn to the requirements of Clauses 7.2 and 7.4. Throughout the presentation exenatide was only referred to by its non-proprietary name and no product or company logos were used.

The Panel noted that several of the slides detailed information about exenatide once weekly. The presentation included the results of a study whereby exenatide once weekly demonstrated superior glycaemic control and weight reduction compared with sitagliptin or pioglitazone after 26 weeks' treatment (Bergenstal *et al*). The Panel considered that, in the context of a promotional meeting, the presentation promoted exenatide LAR prior to the grant of its marketing authorization. A breach of Clause 3.1 was ruled. None of the slides noted that exenatide LAR was not licensed although Lilly submitted that this information was given verbally by the speaker. On balance the Panel considered that the presentation was misleading with regard to the regulatory status of exenatide LAR. A breach of Clause 7.2 was ruled.

APPEAL BY LILLY

Lilly did not believe that the content, context and general arrangements supporting its meeting at the Diabetes UK conference constituted the promotion of Byetta, or the pre-licence promotion of the once-weekly formulation of exenatide such that it could not take the benefit of the supplementary information to Clause 3.1.

Lilly agreed that to determine whether a meeting was promotional or not, the content and context in which it had taken place were important but its intent and purpose should also be considered. The meeting was solely to facilitate the legitimate exchange of medical and scientific information relating to Byetta as well as the once-weekly formulation of exenatide, a new medicine currently in development.

Lilly submitted that as evidenced by the documents previously provided, it had ensured that its medical department owned and controlled the symposium which demonstrated from the outset that the meeting was intended to be non-promotional. The invitation and delegate selection process was carefully controlled by the medical department, the speaker briefings were explicit about the objectives of the meeting and the express requirements of the Code regarding off-licence promotion, the presentations did not use company or product logos and only referred to exenatide by its non-proprietary name. Importantly, sales staff involvement was strictly prohibited. These arrangements clearly demonstrated Lilly's intent to comply with both the letter and spirit of the Code and the non-promotional purpose of the meeting.

Lilly submitted that if it had intended the symposium to be promotional, it would have been controlled by the marketing department and advertised widely; the company would have permitted product branding on the invitations and speaker presentations and allowed the sales force to attend and engage with delegates both at the drinks beforehand and the dinner afterwards.

Lilly submitted that its position that its symposium was non-promotional was supported by the Panel's ruling of no breach of Clauses 3.2 and 7.2 in relation to the alleged promotion of Byetta for use in combination with insulin, outside of its licence at point A1 above. The Panel commented in its ruling that some slides in the presentation 'The Association of British Clinical Diabetologists (ABCD) Nationwide Exenatide Audit Update' referred to the 'restricted licence for use with exenatide with insulins …' but that '[I]n the Panel's view this statement did not promote or encourage the use of …' exenatide outside of its licence. The Panel further commented that '[it] did not consider that [this] presentation … had been misleading about the licensed use of Byetta nor did it promote Byetta for use in combination with insulin'.

Lilly disagreed with the following assertions made by the Panel about the arrangements for and nature of the symposium:

Assertion: Inclusion of Byetta prescribing information on the invitation to the symposium indicated that Lilly considered the invitation to be promotional and created the impression that Lilly considered the meeting to be promotional.

Comment: Lilly noted that the invitation referred to 'The benefits of GLP-1 Receptor Agonists; current and future therapies' and made claims in respect of these. Lilly submitted that Byetta was the first in this class of medicines and data in support of this was to be discussed at the meeting. As such, the Byetta prescribing information was included in the invitation to satisfy Clause 4.1; omission of the prescribing information would have invited a breach of that clause. Lilly therefore disagreed with the Panel's assertion that the inclusion of the Byetta prescribing information indicated that it considered the invitation to be promotional and that, by implication, this might have implied to invitees that Lilly considered the symposium to be promotional.

Notwithstanding the latter, Lilly also referred to established precedents where inclusion of

prescribing information did not automatically render materials promotional; this would be dependent upon their purpose eg invitations to advisory boards. Advisory boards were deemed to be non-promotional by the Code. However, the Code also recognised that prescribing information must form part of the invitation to an advisory board if it mentioned product(s) or a class of medicine to which a product could be easily ascribed and also referred to a claim or indication with respect of these. Similarly the intent and purpose of dissemination of product information to patients via health professionals was also deemed to be non-promotional. In this situation, the dissemination of this data to the health professionals, in the first instance, also necessitated incorporation of the relevant prescribing information. These examples clearly demonstrated that inclusion of prescribing information did not necessarily render a meeting or activity promotional and that the purpose, alongside content and context, was an important consideration.

As stated above, the invitation did not carry the Byetta logo and it only referred to exenatide, its non-proprietary name. If Lilly intended the symposium be to promotional, the invitation would have carried the company and product logos and referred to Byetta, the brand name.

Assertion: The Lilly meeting was deemed to be a standalone symposium because the invitation did not indicate whether recipients had already arranged to attend the main conference and the company's acknowledgement that, although unlikely, some of the symposium attendees might not have subsequently attended the main conference.

Comment: Lilly submitted that its symposium was part of the official conference programme as referred to in the invitation. Whilst the reply to the invitation did not ask recipients to indicate whether they were to attend the main conference, the invitation process clearly anticipated that those who accepted the invitation to the symposium would subsequently attend the main conference. In this regard Lilly noted that of the seventy-three attendees, sixty were officially registered to attend the main conference as evidenced by the pre-published conference delegate list. Of the other thirteen delegates who had not registered to attend the main conference in advance, and whose name would therefore [not] have appeared on the pre-published delegate list, there was a likely possibility that they registered for the conference on the day.

Thus Lilly did not accept that the invitation implied that the company had organised its own standalone symposium, albeit on the eve of a national conference.

Assertion: The Lilly briefing materials which clearly excluded members of the sales force attending the conference from the meeting did not clarify whether this included attendance to the pre-symposium drinks and dinner.

Comment: Lilly submitted that consistent with the purpose of the meeting, all of its representatives attending the conference were specifically excluded from the symposium as well as the pre-symposium drinks and dinner afterwards.

Assertion: Lilly had not explained how the material supporting the discussion of the once-weekly formulation of exenatide could take benefit of the supplementary information to Clause 3.1 particularly in relation to the wording 'during the development of a medicine'.

Comment: The Panel's view was that '… disseminating data to prescribers which potentially expanded a licensed product's market share might be different to the legitimate exchange of medical and scientific information during the development of a medicine …'. Thus the discussion of exenatide, which had a marketing authorization, alongside the once-weekly formulation of exenatide, which did not, entailed promotion of Byetta and, by implication, the once-weekly formulation of exenatide.

Lilly submitted that the Panel ruling implied that the once-weekly formulation of exenatide could not be considered to be a medicine in development and that therefore the discussion of the once-weekly formulation of extenatide was inconsistent with the legitimate exchange of medical and scientific information which was permissible during the development of a medicine when undertaken in the context of a major UK clinical/scientific conference such as the conference in question.

Lilly submitted that the once-weekly formulation of exenatide was currently under development and a European licence had been applied for. The once-weekly formulation of exenatide was a new medicine and was being evaluated as such by the regulatory authorities; it was not a line extension. Therefore, in the context of the conference and the symposium, discussion of data from the ongoing DURATION clinical trial program was legitimate and could not be said to have promoted or expanded the market share of Byetta or the once-weekly formulation of exenatide prior to the grant of its marketing authorization.

Assertion: The invited audience, GPs with a specialist interest in diabetes and diabetes specialist nurses, could not participate in '… debate which enhanced the current state of scientific knowledge' and it was questionable whether they '… would participate at the requisite level'.

Comment: Lilly submitted that the meeting was a closed professional meeting and only those health professionals either known to be attending or expected to attend the conference with a valid scientific interest in gaining an understanding of the benefits of the GLP-1 based treatments were invited. In this regard, the audience appropriately reflected the important role that both primary and secondary care health professionals played in the management of type 2 diabetes. The Panel ruling

asserted that only delegates attending the main conference were likely to participate at the requisite level. This was somewhat inconsistent with the fact that the majority of delegates attending the meeting also attended the main conference. It was therefore reasonable to assume that these particular delegates would have participated at the requisite level required by both meetings.

Lilly submitted that the symposium was to facilitate the legitimate exchange of medical scientific information, and this was evident by the many questions from the audience to the three speakers and meeting chair. This interaction was consistent with the level of debate and discussion expected of such a meeting and which enhanced the scientific knowledge amongst the delegates. Thus the symposium clearly offered the facility for the legitimate exchange of medical and scientific information.

Indeed, if the symposium had been open to all conference delegates, the potentially larger number of attendees might have diluted the focus and substance of the debate and discussion that took place at the meeting. This was clearly not Lilly's intent or the purpose of the symposium.

Assertion: That over 2,000 health professionals were invited and only seventy-three attended implied an apparent difficulty of encouraging attendance to the symposium.

Comment: Lilly reiterated that the invitation process was phased and controlled by the medical department; it was not a single mailing as would have been the case for a promotional symposium. The process allowed the medical department to control the number and specialism of the health professionals invited as well as to carefully monitor the replies and subsequent delegate numbers.

Lilly submitted that a large number of invitations were sent because Lilly needed to ensure that only suitably qualified diabetes health professionals, who expected to attend the conference, were invited. The final number of delegates did not reflect the difficulty of encouraging attendance to the symposium but further demonstrated that the symposium was not intended to be promotional; it was to ensure that the meeting could take the benefit of the supplementary information to Clause 3.1, facilitating debate and the legitimate exchange of medical and scientific information at the requisite level.

With regard to the Panel's rulings, Lilly submitted that the meeting was always intended and set up to be non-promotional and, as such, the legitimate exchange of scientific and medical information, ie the presentation of Bergenstal *et al* was permitted. As Lilly did not agree that the symposium was promotional, it appealed the Panel's ruling that the presentation promoted the once-weekly formulation of exenatide in breach of Clause 3.1.

Lilly submitted that the speaker referred to the regulatory status of the once-weekly formulation of exenatide as expressly required by the speaker briefing. The presentation must be considered as a whole, the speaker's slides as well as what was said, thus Lilly disagreed with the Panel's ruling that, on balance, the presentation was misleading. Lilly maintained that the speaker clearly stated that the once-weekly formulation of extenatide was not licensed.

Lilly also noted that the importance attached by the Panel in its ruling regarding the requirement to include a statement about the regulatory status of the once-weekly formulation of exenatide in the presentation slides themselves appeared to be negated by its ruling of a breach of Clause 3.1 at point A3. In that ruling the Panel stated that 'The inclusion of statements that the product exenatide LAR was not currently licensed were irrelevant …'. This was inconsistent with the Panel's comment at point A2 that 'None of the slides noted that exenatide LAR was not licensed …'. Lilly therefore appealed the Panel's ruling of a breach of Clause 7.2.

COMMENTS FROM NOVO NORDISK

Novo Nordisk had no comments upon Lilly's reasons for appeal.

FURTHER RESPONSE FROM LILLY

During the submission of presentation slides for its appeal Lilly noted that in error, in its response, it had stated that, in line with the objective of exchanging scientific data the meeting included off-licence data, therefore members of the sales team were excluded, including the national sales manager and the Byetta marketing managers. Lilly stated that this clearly suggested that, *inter alia* no exenatide marketing managers were present at the satellite symposium. That was not so: whilst no representative or sales managers were present three members of the marketing department were at the satellite symposium (and the drinks beforehand, as well as the drinks and dinner afterwards). Lilly understood that those concerned took no part in the proceedings and were solely there for the purpose of relationship building.

FURTHER COMMENTS FROM NOVO NORDISK

Novo Nordisk submitted that the presence of the members from the marketing department further confirmed the promotional nature of the symposium. 'Relationship building' by marketeers was a promotional activity based on the ultimate aim of the marketing department to sell the company's products. In addition, Novo Nordisk queried whether they had any responsibility for the management of the sales force. If they had, then effectively a sales function of the business was present at the symposium.

Novo Nordisk submitted that slide 5 of the briefing material about the meeting clearly stated that members of the sales force could not attend the symposium itself. The symposium – according to

the heading of the slide - was defined as the activities between 5.45 – 7.30pm (interestingly the bullet points defined it differently). However the symposium ended with dinner and the document did not cover whether members of the sales force were able to attend this social activity which was clearly an integral part of the event. The wording of this slide suggested that the sales force had the chance to attend the dinner with their customers to build further relationships and potentially to discuss exenatide LAR data. In fact the overview of the week (slide 3) distinguished between the symposium and the dinner which further confirmed that the specific instruction for the sales force to not attend the symposium strictly related to the symposium itself and they were allowed to meet the customers during dinner.

Novo Nordisk further submitted that the internal document did not specify the involvement of the marketing department in the social activity parts of the symposium.

Novo Nordisk submitted that according to the activity briefing document the purpose of the meeting was 'To discuss the benefits of current/future GLP-1 receptor agonists together with the audit data & GLP-1R agonists v DPPIV's with an audience of experts'. That the meeting consisted not only of the symposium but the pre-symposium drinks and moreover the pre-dinner drinks and the dinner itself, suggested that Lilly aimed to specifically discuss exenatide LAR during the social part of the event. On the basis of the evidence provided by Lilly, it was impossible to exclude the presence of members of the sales force and marketing department during the dinner which raised further serious concerns as to whether the company actually organised the event in a non-promotional manner.

Novo Nordisk noted that with regards to the briefing document given to the chairman of the symposium, Lilly emphasised Clauses 7.2 and 7.4 as the relevant clauses of the Code but failed to highlight the importance of Clause 3.1 (from an exenatide LAR perspective) and Clause 3.2 (from the perspective of the combination of exenatide and insulin).

On the basis of the above, Novo Nordisk submitted that the new evidence produced by Lilly further confirmed that the symposium was promotional.

APPEAL BOARD RULING

The Appeal Board noted that the title of the symposium organised by Lilly was 'The benefits of GLP-1 Receptor Agonists; current and future therapies'. Invitees were told that the emphasis of the discussions throughout the symposium would be on how the information presented might enhance their present and future clinical practice. In that regard the Appeal Board considered that Lilly appeared to expect the information presented to influence, *inter alia*, current prescribing practice. The Appeal Board further considered that, given the inclusion of prescribing information on the invitation, most attendees would accept the invitation on the basis that the symposium was promotional. In that regard, the Appeal Board noted that the sales force brief referred to the meeting as the 'Byetta Symposium 2010'.

The Appeal Board noted that the speaker briefings given to the Chairman and to the speaker only referred in detail to Clauses 7.2 and 7.4. The speaker was asked to highlight data not considered within licence and to remind the audience of the licence status if discussing exenatide LAR. The Chairman was asked to ensure any pre-licence therapies were highlighted in the presentations. In the Appeal Board's view these instructions were ambiguous particularly given that the requirements of Clause 3 had not been referred to in detail.

The Appeal Board noted that a high percentage of the slides in the presentation at issue referred to unlicensed medicines/indications. Further, three members of the marketing team had attended the symposium as well as the pre-symposium drinks and the post-symposium dinner.

The Appeal Board rejected Lilly's submission that the symposium constituted the legitimate exchange of medical and scientific information during the development of a medicine and could thus take the benefit of the exemption described in the supplementary information to Clause 3. In the Appeal Board's view, the symposium, as arranged, was promotional and in that regard the presentation in question promoted exenatide LAR prior to the grant of the marketing authorization. The presentation was misleading with regard to the regulatory status of exenatide LAR. The Appeal Board upheld the Panel's rulings of breaches of Clauses 3.1 and 7.2 of the Code. The appeal on this point was thus unsuccessful.

3 Presentation – The benefits of GLP-1 Receptor Agonists: An overview of future therapies and their data

COMPLAINT

Novo Nordisk noted that in this session a Lilly employee detailed the results from DURATION-1 without stating that exenatide LAR did not have a marketing authorization. Thus the presentation was misleading, in breach of Clauses 3.1 and 7.2.

In inter-company dialogue Lilly claimed that appropriate briefing was provided to the speaker to comply with the Code, however Lilly had not sent the briefing material or the slides to Novo Nordisk to substantiate its claims.

Novo Nordisk referred to Case AUTH/2234/5/09 in which Lilly had complained about Novo Nordisk's promotion of liraglutide. As issue in that case had been a symposium, organised by Novo Nordisk at the University of Nottingham, to cover clinically relevant topics for a diabetes specialist nurse

audience. A topic of the agenda was covered by a world-wide known scientific expert on GLP-1, a Novo Nordisk employee who presented data on liraglutide in March 2009 before liraglutide was granted its marketing authorization by the EMEA. Lilly alleged that the presentation promoted the product, and misleadingly implied that liraglutide was a licensed and relevant treatment option for the management of diabetes. The Panel considered the meeting was promotional because it was sponsored by Novo Nordisk and as a result ruled to be in breach of Clauses 2, 3.1, 7.2 and 7.3.

Novo Nordisk considered that Lilly's presentation now at issue, by a Lilly employee who did not clarify the licence status of exenatide LAR should be judged similarly as Case AUTH/2234/5/09 and as such Novo Nordisk alleged a breach of Clauses 9.1 and 2.

Novo Nordisk noted that in inter-company dialogue it gave Lilly the opportunity to address the above mentioned matters and requested copies of the three presentations and the related speaker briefings. Although Lilly referred to the requested materials in its response it did not provide the documents to Novo Nordisk. This blatant lack of response to a clear request in inter-company dialogue was very concerning, and suggested that Lilly deliberately withheld information from Novo Nordisk.

RESPONSE

Lilly explained that its US employee, an eminent diabetologist and expert in GLP-1 based therapies, was provided with a written speaker brief by Lilly in the UK to present on the topic of 'The benefits of GLP-1 Receptor Agonists: An overview of future therapies and their data'. As per Lilly policy the speaker was aware of the requirements of the Code and that the presentation should be accurate and objective, consistent with SPC (where applicable), balanced and capable of substantiation. Indeed, the speaker brief also clearly addressed this requirement. In anticipation that the presentation would discuss, in part, exenatide once-weekly, which was not currently licensed, Lilly's briefing required the speaker to appropriately highlight the latter; which was done. Indeed, contrary to Novo Nordisk's allegation, the presentation included statements to clarify this; initially at the onset of the exenatide once weekly data presentation (slide entitled Development of Exenatide Once Weekly, bullet point 2) and also in the final summary slide of the whole presentation (entitled Conclusions, bullet point 4). Lilly therefore refuted the allegation that this presentation was in breach of Clauses 3.1 and 7.2.

Lilly noted that the speaker's presentation was based on information from the DURATION-1 study that had been previously published in a peer reviewed publication (Drucker *et al* 2008). Lilly provided a copy of the presentation and of the speaker's brief.

Lilly denied a breach of Clauses 9.1 and 2.

PANEL RULING

The Panel noted its comments at point A1 above regarding the arrangements for and nature of the symposium.

The Panel noted that the speaker briefing stated that the objective of the presentation was to provide an overview of current and future data showing the development of GLP-1 receptor agonists and to ensure that the audience was aware that exenatide once weekly was currently not licensed. Key points to be communicated were a fair and balanced representation of data around the development of the class and to emphasise that Byetta and Victoza were currently the only licensed GLP analogues available. The speaker's attention was drawn to the requirements of Clauses 7.2 and 7.4. Throughout the presentation exenatide was only referred to by its non-proprietary name and no company or product logos were used. The presentation gave a positive overview of the development of exenatide once weekly and the clinical results observed; two slides clearly stated that exenatide once weekly was not currently licensed.

The Panel considered that the presentation promoted exenatide once weekly before the relevant marketing authorization had been granted. The inclusion of statements that the product was not currently licensed were irrelevant in that regard. A breach of Clause 3.1 was ruled. The Panel considered, however, that the presentation had not been misleading with regard to the regulatory status of exenatide once weekly and in that regard the Panel ruled no breach of Clause 7.2.

The Panel noted its rulings above, and at point A2, that exenatide once weekly had been promoted before the grant of the relevant marketing authorization. The Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1. The Panel noted from the supplementary information to Clause 2 that promoting a medicine before the grant of a marketing authorization was an activity likely to be in breach of Clause 2. That clause was reserved as a sign of particular censure. The Panel ruled a breach of Clause 2.

APPEAL BY LILLY

Lilly repeated its general comments in its appeal at point A2 above about the arrangements for and nature of the symposium.

Lilly noted that the Panel had ruled a breach of Clause 3.1 in that the presentation at issue promoted the once-weekly formulation of exenatide before the relevant marketing authorization had been granted. The Panel acknowledged in its ruling that the presentation contained two slides which clearly stated that the once-weekly formulation of exenatide was not currently licensed.

Further, Lilly submitted that in the context of a non-promotional meeting, the presentation of an

overview of the development of the once-weekly formulation of exenatide, a new medicine, and the clinical results observed during its development amounted to the legitimate exchange of scientific and medical information such that it could take the benefit of the supplementary information to Clause 3.1 of the Code. For these reasons, Lilly appealed the Panel's ruling of a breach of Clause 3.1.

Lilly noted that the Panel ruled that high standards had not been maintained in that the once-weekly formulation of exenatide had been promoted before the grant of the relevant marketing authorization in breach of Clause 9.1 and that this also amounted to a breach of Clause 2.

For all the reasons set out above, Lilly disagreed with the Panel's assessment that the meeting was promotional and that, as a result, the content of the two presentations referred to in the Panel's ruling above amounted to the pre-licence promotion of the once-weekly formulation of exenatide.

Lilly submitted that at all times the intent and the purpose of the symposium was not to circumvent the requirements of the Code, including Clause 3; organised by its medical department, it was a genuine and serious attempt to engage health professionals in the legitimate exchange of medical and scientific information of value thereby further enhancing their knowledge and understanding of the management of type 2 diabetes. Lilly therefore appealed the Panel's rulings of breaches of Clauses 2 and 9.1.

COMMENTS FROM NOVO NORDISK

Novo Nordisk had no comments upon Lilly's reasons for appeal.

APPEAL BOARD RULING

The Appeal Board noted its comments at point A2 and that, in its view, the meeting as arranged, was promotional.

The Appeal Board noted that the speaker briefing stated that the objective of the presentation was to provide an overview of current and future data showing the development of GLP-1 receptor agonists and to ensure that the audience was aware that exenatide once weekly was currently not licensed. Key points to be communicated were a fair and balanced representation of data around the development of the class and to emphasise that Byetta and Victoza were currently the only licensed GLP analogues available. The speaker's attention was drawn to the requirements of Clauses 7.2 and 7.4 but again, as in point A2 above, there was no mention of the requirements of Clause 3. The presentation gave a positive overview of the development of exenatide once weekly and the clinical results observed; two slides clearly stated that exenatide once weekly was not currently licensed.

The Appeal Board considered that the presentation promoted exenatide once weekly before the relevant marketing authorization had been granted. The inclusion of statements that the product was not currently licensed was irrelevant in that regard. 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 that the symposium included discussions about the future availability of exenatide LAR and mention was made of the unlicensed use of exenatide with insulin. The Appeal Board further noted that the invitation to the symposium stated that the emphasis of the discussions would be on how the data presented might enhance an attendee's current and future clinical practice. The Appeal Board noted that the licence application for exenatide LAR was submitted two days after the symposium. The Appeal Board considered that the attendance of three members of the marketing team added to the impression that the meeting was promotional.

Overall, given the arrangements for and the content of the symposium, the Appeal Board considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

The Appeal Board noted from the supplementary information to Clause 2 that promoting a medicine before the grant of a marketing authorization was an activity likely to be in breach of Clause 2. That clause was reserved as a sign of particular censure. The Appeal Board noted its comments above and upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

B Exhibition panels

COMPLAINT

Novo Nordisk noted that Lilly's exhibition panels featured two graphs from Klonoff *et al* (2008). The first graph showed the HbA_{1c} improvement from the core phase of three randomized, controlled trials and their 3-year long, uncontrolled, observational extension period. The graph contained a suppressed zero y-axis to exaggerate the 1% HbA_{1c} decrease revealed by the study. Regardless of no comparator on the graph, this was misleading, and did not maintain high standards in breach of Clauses 7.2, 7.8 and 9.1.

In inter-company dialogue, Lilly claimed it was acceptable to use a suppressed zero on the graph since the data were not comparative and health professionals could interpret the 1% HbA_{1c} reduction from clinical perspective. Novo Nordisk disagreed and noted that shortening the y-axis gave a misleading impression and exaggerated the observed glycaemic improvement. The argument that health professionals would be able to interpret such results despite the use of a suppressed zero suggested that this type of presentation was acceptable in every case when there was no comparator on the graph. This was clearly not the

case since this presentation did not give a clear, fair, balanced view of the matter.

Furthermore the lack of detailed information about the study setting was also misleading. In the paper it was clearly emphasized that the analysis was post-hoc which was an important piece of information to interpret the results correctly. This was missing from the exhibition panel.

Novo Nordisk noted that more importantly Lilly had not stated that this post-hoc analyzed patient subgroup (n=217) represented only 22.5% of the total patient population exposed to exenatide during the core randomized, controlled phases of the study (n=963). Klonoff *et al* reported that the intention to treat (ITT) population that entered the extension phase was 527, but even in this case the reported graphs represented only 41% of the study population. Knowing this piece of information, one could easily conclude that the paper reported the results from the responders and in fact most patients needed to be switched to other therapies due to the inadequate response to exenatide during the study period. Conversely, without knowing this information, one could conclude that the 1% HbA_{1c} improvement could be sustained with exenatide for 3 years in the general type 2 diabetes population. Clearly the missing pieces of information were highly important and the graphs on the exhibition panels (HbA_{1c} improvement and weight change) misled and failed to maintain high standards, in breach of Clauses 7.2 and 9.1.

Novo Nordisk considered that the layout of the graphs represented a deliberate attempt to mislead the participants at the largest diabetes scientific event of the UK therefore constituted a breach of Clause 2.

RESPONSE

Lilly stated that the exhibition panel at issue was associated with the Lilly diabetes promotional stand at the Diabetes UK conference. The aspects of the panel which concerned Novo Nordisk referred to and were substantiated by Klonoff *et al*. Klonoff *et al* evaluated the effects of at least 3 years' exenatide therapy on glycaemic control, body weight, cardiometabolic markers and safety. Patients from the three initial 30-week, placebo-controlled studies and their open-label extensions were enrolled into one open-label clinical trial. Patients were randomised to twice daily placebo, 5mcg exenatide, or 10mcg exenatide for 30 weeks, followed by 5mcg exenatide twice daily for 4 weeks, then 10mcg exenatide twice daily for at least 3 years of exenatide exposure. Patients continued metformin and/or sulphonylureas.

The inclusion criteria for the three 30-week, placebo-controlled trials were that patients were between 19 and 70 years of age with type 2 diabetes, treated for at least 3 months prior to screening with at least 1500mg/day metformin, or at least the maximally-effective dose of a sulphonylurea, or a combination of metformin and sulphonylurea. Additional inclusion criteria were an $A_{1c} \leq 11.0\%$ and body mass index of 22-45kg/m. To enrol in the open-label, uncontrolled extensions of the 30-week studies, patients were required to complete the antecedent 30-week placebo controlled trial. Patients completing the extension studies were invited to enrol into the single open-ended, open-label trial analysed in this paper. All patients in this report had been treated with exenatide for at least 3 years, irrespective of their treatment group in the 30-week, placebo-controlled trials.

The 3-year and 3.5-year completer cohorts were defined as all patients who had the opportunity to achieve 3 years or 3.5 years of exenatide exposure, respectively, regardless of their treatment arm in the 30-week placebo-controlled trails. Patient disposition from the beginning of the open-ended, open-label extension trial was as follows: 3-year eligible ITT population (n=527), 3-year completers (n=217) and withdrew (n=310).

Lilly rejected the allegation regarding the suppressed zero on the y-axis of the graph on the basis that the actual published graph also did not employ a zero value for the percentage of HbA_{1c} on the ordinate axis; this axis was labelled as starting from an HbA_{1c} of 4%. The chart shown on the exhibition panel was marked as being 'Adapted from Klonoff DC *et al*' and as such did not include the starting value for HbA_{1c} of 4%. At no stage had Lilly claimed it was acceptable to use a suppressed zero on the graph as alleged by Novo Nordisk.

Notwithstanding the latter, the data represented were not comparative and as such Lilly was confident that diabetologists attending the conference were not misled and would have been able to surmise both the numerical and clinical implication and relevance of a 1% reduction of HbA_{1c} depicted on the exhibition panel irrespective of the labelling on the ordinate axis. To add to this clarity, a blue box highlighting the 1% HbA_{1c} drop was clearly depicted within the graph on the aforementioned panel. Furthermore, the ordinate axis represented a physiological range of HbA_{1c} and as such diabetologists would not be misled if a data point with respect to an HbA_{1c} of 0% was not shown. Indeed, the critical aspect of this chart was the abscissa which depicted the duration over which the reported reduction in HbA_{1c} occurred.

With regard to not stating that the analysis presented was post-hoc, Lilly noted that whilst specific post-hoc analyses were performed at weeks 156 and 182 for the within-group comparisons at endpoint, with sub-analyses by weight change quartiles at weeks 156 and 182, the exhibition panel at issue referred only to results in relation to a priori analyses investigating changes from baseline in HbA_{1c} and body weight in the 3-year completer population and not with reference to the post-hoc analyses involving within-group comparisons at endpoint.

Lilly noted that Novo Nordisk asserted that the non-completer population discussed in this study were

non-responders or patients who had an inadequate response to exenatide therapy and consequently had to be switched to other medicine. This was not so; whilst 310 patients withdrew (ITT vs completers), this was for a variety of reasons and only 18 patients (3%) withdrew due to loss of glucose control whilst on exenatide.

The exhibition panel contained graphs which were clearly titled as 'completer population' to aid clarity. The exhibition panel provided the relevant information pertaining to the 3-year completer population (ie n=217, baseline mean HbA_{1c}: 8.2±0.1%, week 156: -1% (95% CI; -1.1 to -0.8%) and p<0.0001) and these were labelled as being parameters specific only to this particular population. The exhibition panel did not extrapolate the applicability of the results depicted to type 2 diabetic patients in general. Notwithstanding the latter, Lilly noted that the demographics, baseline metabolic parameters reported were typical of type 2 diabetics and not outliers as asserted by Novo Nordisk. This was also evidenced by the authors who in the conclusion stated, without qualification, that '… exenatide represents an option for adjunctive therapy for patients with type 2 diabetes not achieving adequate glycaemic control'.

On all counts, Lilly denied that the exhibition panel was in breach of Clauses 2, 7.2, 7.8 and 9.1. The company also refuted the allegations that the layout of the graph represented a deliberate attempt to mislead health professional and constituted a breach of Clause 2.

In conclusion, Lilly was cognisant of its responsibilities with respect to the Code and had ensured that all aspects of its attendance at the Diabetes UK conference were consistent with this (including, without limitation, Clauses 2, 3.1, 7.2, 7.8 and 9.1) and of the highest standard and quality.

PANEL RULING

The Panel noted that Lilly's exhibition panel included a graph of the 'Change in HbA_{1c} from baseline in 3 year completer population'. The heading to that section of the exhibition panel was 'Choose BYETTA to provide sustained HbA_{1c} improvement over 3 years'. The x axis plotted weeks of treatment and the y axis was labelled HbA_{1c} (%). The y axis was shortened between 0 to 5% and then showed 5 to 9%. The Panel noted Lilly's submission that the y axis represented a physiological range of HbA_{1c}. The results obtained for Byetta showed that from a baseline of 8.2%, HbA_{1c} fell sharply within the first 26 weeks, and that an initial 1% fall was maintained at week 156. A claim to the right of the graph stated 'Almost half (46%) of patients achieved $HbA_{1c} \leq 7\%$. The graph and the claim were derived from Klonoff *et al*. Only data for Byetta was shown; there was no comparison with any other medicine.

The Panel noted that clinicians would be familiar with the physiological range of HbA_{1c} and that they would treat patients to a target HbA_{1c} of around 7%. It considered that to shorten the y axis between 0 to 5% did not mean that a suppressed zero was used in a misleading way. The decrease in HbA_{1c} was clearly stated and not exaggerated. The Panel did not consider that the graph was misleading or exaggerated as alleged. No breach of Clauses 7.2 and 7.8 was ruled. In that regard the Panel did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled.

The Panel noted that Klonoff *et al* had taken patients from three placebo controlled trials and their open-label extensions and enrolled them into one open-ended, open-label clinical trial. There had been 527 patients in the ITT population from the three studies; only 217 completed 3 years of exenatide therapy ie only 41% of the original patients. The Panel noted the claim that 'Almost half (46%) of patients achieved $HbA_{1c} \leq 7\%$' referred only to the 3 year completers and so in that regard it was 46% of 41% ie approximately 19%. The Panel considered that the claim implied that almost half of all diabetic patients would achieve $HbA_{1c} \leq 7\%$ with exenatide therapy whereas with the population studied it was only about 19%. Similarly, claims were made regarding the percentage of patients who would lose weight whilst on exenatide therapy. The Panel considered that with regard to the data from Klonoff *et al*, important information had been omitted from the exhibition panel; the material was not sufficiently complete such as to allow clinicians to form their own opinion of the therapeutic value of exenatide. The Panel considered that the exhibition panel was misleading as alleged and ruled a breach of Clause 7.2. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted its rulings above and considered that the exhibition panel, although misleading, was not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. A ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

Complaint received **7 April 2010**

Case completed **2 November 2010**