CASE AUTH/2028/7/07

NOVO NORDISK v SANOFI-AVENTIS

Promotion of Lantus

Novo Nordisk complained about claims for 24-hour glycaemic control in the promotion of Lantus (insulin glargine) by Sanofi-Aventis. Novo Nordisk alleged that claiming 24-hour control without stating that duration of glycaemic control (duration of action) was dose dependent was not accurate information based on and reflecting an up-to-date evaluation of all available evidence and it misled health professionals.

Novo Nordisk noted that the only reference cited by Sanofi-Aventis was from an isoglycaemic 24-hour clamp study (Lepore *et al*, 2000), in which the average duration of action was substantially shorter than 24 hours (20.5±3.7), at a Lantus dose of 0.35units/kg. Sanofi-Aventis had emphasised that in 16 out of the 20 patients, the average duration of action would have been longer, but the clamp investigation was stopped at 24 hours according to the trial protocol. Had the study lasted longer the average duration of action would have been close to or over 24 hours. However Novo Nordisk was concerned about the 4 patients (20%) in which the average duration of action was much shorter than 24 hours.

Klein *et al* (2007) compared the duration of action of Lantus in type 2 diabetes, using a euglycaemic clamp technique and concluded that the duration of action was dose-dependent.

Novo Nordisk alleged that the findings of these studies highlighted the need to modify the 24-hour claim of Lantus to provide accurate information to health professionals.

Novo Nordisk further noted that the Lantus summary of product characteristics (SPC) did not state that it conferred 24-hour glycaemic control and only stated that 'Lantus contains insulin glargine, an insulin analogue, with prolonged duration of action'. Furthermore the SPC correctly noted that 'The time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual.' Therefore Novo Nordisk alleged that to claim a 24-hour duration of action for Lantus, without stating that the action was dose-dependent, contradicted the SPC.

Finally, since the launch of Lantus, accumulating clinical experience had shown that a significant proportion of type 1 diabetics required twice daily dosing (Garg *et al*, 2004, Albright *et al*, 2004).

On the basis of the above Novo Nordisk alleged that the claim of 24-hour control was exaggerated, misleading and not capable of substantiation.

The Panel noted that on a poster and a leavepiece the claim '24 hour glycaemic control' appeared as a strapline beneath the Lantus product logo. 'Once daily 24-hour glycaemic control' appeared in a similar position on another poster. On a leaflet and leavepiece 'Once Daily 24-Hour' appeared as part of the product logo. In a patient booklet there were a number of references to Lantus working for 24 hours.

The Panel noted that Sanofi-Aventis had submitted three papers in support of the claim – Lepore *et al*, Porcellati *et al* (2007a) and Porcellati *et al* (2007b). Lepore *et al* had studied the pharmacokinetic and pharmacodynamic effects of Lantus in 20 patients using an isoglycaemic 24-hour clamp technique. The authors reported that Lantus had a peakless, nearly 24-hour duration of action. The mean duration of action was 20.5±3.7 hours. However, the authors observed that the duration of action noted for Lantus was probably an underestimate and it was likely that in 16/20 patients it would have been longer than 24 hours. In order to determine this with accuracy, the study would have had to have been conducted over a longer period of time but this would have been unacceptable to patients. The authors further noted that the dose of Lantus was well within the range used in type 1 diabetics. It was also noted that as patients were only studied once with Lantus, there was no opportunity to examine intrasubject variability.

Porcellati *et al* (2007a) presented results on 24 patients with type 1 diabetes treated with Lantus once daily for two weeks. After 14 days of treatment all subjects underwent an euglycaemic clamp for 24 hours. The results showed that Lantus maintained glycaemic control in all patients for at least 24 hours.

Porcellati *et al* (2007b) compared the pharmacokinetics and pharmacodynamics of Lantus after a first injection and then again after one week of once daily use. The results showed that after one week of use Lantus had an earlier onset and longer duration of action compared with the first day of its use. The authors commented that the duration of action was underestimated because in some subjects end of action was beyond the 32 hour time limit of the study. The authors further noted that intrasubject variability of Lantus was lower after one week of use.

The SPC stated that Lantus was an insulin analogue with a prolonged duration of action. It should be administered once daily at any time but at the same time each day. The dosage and timing should be individually adjusted. Section 5.1 included a graph comparing the activity profile in patients with type 1

diabetes of insulin glargine and NPH insulin. The graph showed that the activity profile of insulin glargine was similar between 15 and 24 hours (which was when the observation period ended).

The European Public Assessment Report (EPAR) stated that the median time-action profile in type 1 diabetes indicated that Lantus displayed a moderate sustained glucose lowering activity over 24 hours compared to a distinct peak in activity with NPH insulin.

It appeared that the data in the SPC and EPAR was the Lepore data.

The Panel was concerned about the strength of the evidence prior to the Porcellati *et al* data, when the materials were approved and issued. However it considered that taking into account all the data supplied by Sanofi Aventis there was data to support the claim for 24 hour glycaemic control. The Panel considered that the SPC did not appear to allow twice daily dosing. The Panel did not consider that the failure to state that glycaemic control was dose dependent meant that the claim for 24 hour control was inaccurate, misleading or inconsistent with the SPC as alleged. In the Panel's view health professionals would be well aware that dose was an important consideration.

The Panel considered that the claim for 24 hour glycaemic control was capable of substantiation and was not exaggerated or misleading as alleged. It was not inconsistent with the SPC. No breach of the Code was ruled in relation to each of the items at issue. The Panel did not consider that Sanofi-Aventis had failed to maintain high standards. All of these rulings were appealed by Novo Nordisk.

The Appeal Board noted that on one poster and the leavepiece the claim '24 hour glycaemic control' appeared as a strapline beneath the Lantus product logo. 'Once daily 24-hour glycaemic control' appeared in a similar position on the other poster. On the leaflet 'Once Daily 24-Hour' appeared as part of the product logo. The patient booklet had a number of references to Lantus working for 24 hours.

The Appeal Board noted that of the data provided in substantiation of the claims at issue, the only data available when the complaint was made was Lepore *et al* which examined duration of action of Levemir, not its efficacy in terms of glycaemic control.

In the Appeal Board's view, in the context of diabetes, 'control' referred to glycaemic control ie the maintenance of blood glucose between set parameters. The Appeal Board noted that Lantus was a basal insulin designed to provide a background, constant suppression of blood glucose. Section 5.1 of the SPC included a graph comparing the activity profile in patients with type 1 diabetes of insulin glargine and NPH insulin. The graph showed that the activity profile of insulin glargine was smooth, peakless and almost constant between 9 and 24 hours (which was when the observation period ended).

The Appeal Board noted that no type 1 diabetic would be controlled solely on Lantus and only about half of type 2 diabetics would be controlled on a combination of Lantus and oral agents. Most diabetics would thus require short-acting insulin, in addition to Lantus, to cope with daily glucose peaks resulting from meals. The Appeal Board thus considered that a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control.

The Appeal Board considered that claims for 24-hour control or 24-hour glycaemic control were not capable of substantiation and were exaggerated and misleading in that regard. The Appeal Board ruled breaches of the Code. The Appeal Board did not consider that Sanofi-Aventis had failed to maintain high standards.

Novo Nordisk also complained about a book authored by Joseph JM Fraser, published by Wiley, 'Joe's Rough Guide to Diabetes' book. Although Sanofi-Aventis' logo was on the back of the book there was no statement regarding the extent of the company's involvement and a breach of the Code was alleged.

Novo Nordisk also alleged that a chart in the book contained information regarding the onset of action, the peak of action and duration of action of some insulin preparations which was not consistent with the relevant SPCs.

Sanofi-Aventis stated in one of its replies during the inter-company discussion, that its only involvement has been to purchase copies to provide health professionals (as an educational service, not as a promotional item) and considered it as a valuable resource with considerable educational value for this audience. In this case, it would further increase the need for providing accurate, fair and balanced information. This book clearly failed to provide such basic information.

Novo Nordisk was very concerned that Sanofi-Aventis considered the content was fair and accurate and of significant educational merit when the book clearly tried to highlight differences between Lantus and Levemir that were direct market competitors. Novo Nordisk thus alleged that the book was clearly in breach of the Code and requested that Sanofi-Aventis withdrew it from distribution. Indeed, Novo Nordisk queried whether the dissemination of such misleading information under the guise of an educational aide warranted the issue of a corrective statement to the recipients of this book relating to the claims/'facts' contained therein.

The Panel noted that the back cover of the book included the Sanofi-Aventis logo and a statement 'Because health matters'. Sanofi-Aventis had no role in the initiation, creation or production of the book. The copies that it purchased cost less than the maximum £6 plus VAT permitted for promotional aids. The book was aimed at teenagers with diabetes; the foreword suggested that the book ought to be

available to every young diabetic and to anybody involved in helping young people to grow up with diabetes.

The Panel considered that the purpose of the book was not entirely clear. Sanofi-Aventis' written submission stated that it was provided to health professionals to increase their understanding of teenage life with regard to diabetes care ie as an educational resource for the health professional. The representatives' briefing material stated that it was a mixture of practical advice and personal experience; a great read for anyone but was particularly relevant to adolescents and young adults. The book was part of the support the company wanted to offer to adolescent patients. It was to be used in centres dealing with high numbers of adolescents and young people. The Panel thus considered that representatives had been instructed to use the book as a gift intended for use by patients.

The Panel noted that Clause 9.10 required that material relating to the medicines sponsored by a company must clearly indicate that it had been sponsored by that company. Sanofi-Aventis had purchased copies (at £1.25 per copy) to supply to health professionals.

The Panel did not know whether the book would have existed if Sanofi-Aventis had not purchased 20,000 copies to distribute as gifts. The Panel was concerned that the logo appeared on the book without a clear explanation as to Sanofi-Aventis' involvement. The Panel considered that on the information before it as Sanofi-Aventis had not contributed to the expenses of producing the book, it had not sponsored it and no breach of the Code was ruled in that regard.

The Panel noted Novo Nordisk's concerns about the information given about a number of insulins and the advice to discuss matters with the diabetes team. There was a direct comparison of Levemir and Lantus. The Levemir SPC stated that it was a long acting insulin analogue used as a basal insulin and that when Levemir was used as part of basal-bolus insulin regimen it should be administered once or twice daily depending on patient's needs. The duration of action was up to 24 hours. The book stated that the duration of action of Levemir was '6 to 23 hours' which was not accurate. The Panel queried whether the book met the requirements of the Code. Novo Nordisk had only cited certain clauses of the Code.

The Panel did not consider that, on the information before it, the book was unacceptable either as a promotional aid for health professionals or as a gift for use by patients. The book was well within the cost limitation for promotional aids and relevant and thus no breach was ruled.

The Panel noted Sanofi Aventis' submission that the book had been approved as required by the Code and thus ruled no breach was ruled.

Novo Nordisk Limited complained about the promotion of Lantus (insulin glargine) by Sanofi-Aventis. Novo Nordisk marketed a number of insulin products including Levemir (insulin detemir). Both Lantus and Levemir were long-acting insulins.

1 Claim that insulin glargine provided 24-hour glycaemic control

This claim appeared in the following items for health professionals: a poster (LAN 05/215 superseded in March 2007 by LAN 07/1038), a leaflet (CLI 06/023) and a leavepiece (API 06/063). The claim also appeared in a Lantus patient booklet (LAN 05/023).

COMPLAINT

Novo Nordisk alleged that claiming 24-hour control without stating that duration of glycaemic control (duration of action) provided by any insulin preparation including Lantus was always dose dependent was not accurate information based on and reflecting an up-to-date evaluation of all available evidence and it misled health professionals.

Novo Nordisk noted that the only reference cited by Sanofi-Aventis to substantiate its claim was from an isoglycaemic 24-hour clamp study (Lepore *et al*, 2000), in which the average duration of action was 20.5±3.7 hours, at a Lantus dose of 0.35units/kg, which was substantially shorter than 24 hours. During inter-company dialogue, Sanofi-Aventis had emphasised that in 16 out of 20 patients who participated in the study, the average duration of action would have been longer, but the clamp investigation was stopped at 24 hours according to the trial protocol. Sanofi-Aventis argued that in the case of continuing the clamp investigation over 24 hours the average duration of action would have been close to or over 24 hours. However Novo Nordisk had major concerns regarding the 4 out of 20 patients (20%) in which the average duration of action was much shorter than 24 hours.

Klein *et al* (2007) compared the duration of action of Lantus and Levemir in type 2 diabetes, using a euglycaemic clamp technique and concluded that the duration of action was dose-dependent in both cases.

Novo Nordisk alleged that the findings of these studies highlighted the need to modify the 24-hour claim of Lantus to provide accurate information to health professionals.

Novo Nordisk further noted that the Lantus summary of product characteristics (SPC) did not state that it conferred 24-hour glycaemic control and only stated that 'Lantus contains insulin glargine, an insulin analogue, with prolonged duration of action'. Furthermore the SPC correctly pointed out that 'The time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual.' Therefore Novo Nordisk alleged that to claim a 24-hour duration of action for Lantus, without stating that the action was dose-dependent, contradicted the SPC.

Finally, since the launch of Lantus, accumulating clinical experience in type 1 diabetes had shown that a significant proportion of patients required twice daily dosing (Garg *et al*, 2004, Albright *et al*, 2004).

On the basis of the above Novo Nordisk alleged that the claim of 24-hour control was exaggerated and misled health professionals in breach of Clauses 7.2, 7.4 and 9.1 of the Code. As the claim was not capable of substantiation, Novo Nordisk had asked Sanofi-Aventis withdraw all materials containing this claim.

RESPONSE

Sanofi-Aventis submitted that the claim was based on the results of a pharmacokinetic and pharmacodynamic study performed to support the registration of Lantus (Lepore *et al*). Lepore *et al* measured the long-acting properties of a subcutaneous injection of Lantus using a euglycaemic clamp method for up to 24 hours. This was the gold-standard method for defining the pharmacodynamic properties of insulin. The dose of Lantus used was 0.3 units/kg body weight, which at 21 units for a 70kg person represented a dose lower than that used on average in clinical practice (typically 28-35 units). Lepore *et al* reported that in subjects receiving a single dose of Lantus, the mean glucose concentration at 24 hours (141±5mg/dl) remained below the threshold defined as demonstrating glycaemic control (150mg/dl), this being the most appropriate and scientifically valid measure of prolonged efficacy after a single insulin administration. In addition, the glucose infusion rate remained nearly constant between 3 and 24 hours after the injection.

Sanofi-Aventis submitted that Lepore *et al* provided evidence that Lantus maintained 24 hour glycaemic control when used at a normal, or even lower than normal, clinical dose, and as this was the most appropriate methodology, it was difficult to argue that results obtained by other methods rendered these results invalid. The authors discussed the fact that the mean duration of the study period was terminated at 24 hours, this was to be expected. More relevant was the fact that 16 of the 20 patients still demonstrated maintenance of glycaemic control at the final 24 hour time point.

Sanofi-Aventis submitted that two more recent papers supported the findings of Lepore *et al*. Porcellati *et al* (2007a) reported on 24 diabetic patients in a randomised, single-dose, double-blind, two-way, cross-over study, using the euglycaemic glucose clamp technique. Using a dose of 0.35units/kg body weight, which equated to approximately 24.5 units per day in a 70kg adult and therefore lower than average daily practice, all 24 Lantus patients had a satisfactory maintenance of glycaemic control at the end of the 24 hour clamp study. Porcellati *et al* (2007b) assessed Lantus using a dose of 0.3units/kg body weight in 20 diabetic patients, by clamp technique for 32 hours, and concluded that after one week of once daily dosing the median duration of action was 24 hours. This paper also noted that 24 hours was an underestimate, as in some patients the duration of end of action was beyond the 32-hour end-point of the study.
The evidence was further supported by the European Medicines Evaluation Agency (EMEA) scientific discussion (2005) which reflected the initial scientific discussion for the approval of Lantus and stated 'The median time-action profile after subcutaneous injection of insulin glargine in subjects with type 1 diabetes mellitus also indicated that insulin glargine displays a moderate sustained glucose lowering activity over 24 hours, compared to a distinct peak in activity with NPH insulin'.

In summary Sanofi-Aventis submitted that the above provided robust evidence to substantiate the claim that Lantus provided '24-hour glycaemic control'.

Sanofi-Aventis noted that Novo Nordisk suggested that the duration of action of Lantus was dose-dependent (as suggested by Klein *et al*) but failed to show that this duration was shorter than 24 hours. Sanofi-Aventis submitted that this reference described an increasing duration of action for Lantus, which was used at higher doses than in the study above. However, this paper was limited by its methodology, in which the only measure of duration was the maintenance of glucose infusion rate in the clamp methodology, not the preservation of normal blood glucose levels referred to by Lepore *et al* and Porcellati *et al*. As discussed in Klein *et al*, glucose infusion rate was not an effective measure of duration of action – it was better suited to assessing the short-term response to a meal than the ability to maintain blood glucose levels for up to 24 hours.

This deficiency in the methodology therefore limited the ability to define the actual duration of action of the insulins studied in Klein *et al*, and this was recognized by the authors. However, they acknowledged that Lantus was suited to once daily administration supporting the fact that 24-hour efficacy was likely to have been demonstrated.

Sanofi-Aventis concluded that although the duration of action of Lantus in Klein *et al* was dose-dependent, the methodology used was not appropriate to measure this, and this did not support the complainant's arguments. Although the duration of action of Lantus was dose-dependent, this would not be inconsistent with the 24-hour duration of action as an increase in the dose might simply reflect efficacy beyond this time point (as evidenced by 100% of patients having normal blood glucose levels at 24 hours with the highest dose of Lantus).

Sanofi-Aventis submitted that the evidence outlined above showed that:

- Lantus had demonstrated 24-hour efficacy through preservation of normal blood glucose levels up to 24 hours;
- an increase in dose might result in an increased effect above this, although the methodology presented was inadequate to make this assessment accurately;
- the current claim of 24-hour efficacy was consistent with the current Lantus SPC and this was not inconsistent with the duration being dose-

dependent (24-hour control had been demonstrated with a low-normal clinical dose, a higher dose would be more likely to result in an extension beyond this time-point).

PANEL RULING

The Panel noted that on the poster (LAN 07/1038) and the leavepiece the claim '24 hour glycaemic control' appeared as a strapline beneath the Lantus product logo. 'Once daily 24-hour glycaemic control' appeared in a similar position on poster LAN05/215. On the leaflet and leavepiece 'Once Daily 24-Hour' appeared as part of the product logo. In the patient booklet there were a number of references to Lantus working for 24 hours.

The Panel noted that Sanofi-Aventis had submitted three papers in support of the claim – Lepore *et al*, Porcellati *et al* (2007a) and Porcellati *et al* (2007b). Lepore *et al* had studied the pharmacokinetic and pharmacodynamic effects of Lantus in 20 patients using an isoglycaemic 24-hour clamp technique. The authors reported that Lantus had a peakless, nearly 24-hour duration of action. The mean duration of action was 20.5±3.7 hours. In their discussion, however, the authors observed that given the way in which end of action was defined, the duration of action noted for Lantus was probably an underestimate and it was likely that in 16/20 patients it would have been longer than 24 hours. In order to determine this with accuracy, the study would have had to have been conducted over a longer period of time but this would have been unacceptable to patients. The authors further noted that the dose of Lantus was well within the range used in type 1 diabetics. It was also noted that as patients were only studied once with Lantus, there was no opportunity to examine intrasubject variability.

Porcellati *et al* (2007a) presented results on 24 patients with type 1 diabetes treated with Lantus once daily for two weeks. After 14 days of treatment all subjects underwent an euglycaemic clamp for 24 hours. The results showed that Lantus maintained glycaemic control in all patients for at least 24 hours.

Porcellati *et al* (2007b) compared the pharmacokinetics and pharmacodynamics of Lantus after a first injection and then again after one week of once daily use. The results showed that after one week of use Lantus had an earlier onset and longer duration of action compared with the first day of its use. On day one the mean duration of action was 20.2 hours (17-25) vs 24 hours (22-28.5) on day seven. The authors commented that the duration of action was underestimated because in some subjects end of action was beyond the 32 hour time limit of the study. The authors further noted that intrasubject variability of Lantus was lower after one week of use.

The Lantus SPC (2006) stated that Lantus was an insulin analogue with a prolonged duration of action. It should be administered once daily at any time but at the same time each day. The dosage and timing should be individually adjusted. Section 5.1 included a graph comparing the activity profile in patients with type 1 diabetes of insulin glargine and NPH insulin. The graph showed that the activity profile of insulin glargine was similar between 15 and 24 hours (which was when the observation period ended).

The European Public Assessment Report (EPAR) stated that the median time-action profile in type 1 diabetes indicated that Lantus displayed a moderate sustained glucose lowering activity over 24 hours compared to a distinct peak in activity with NPH insulin.

It appeared that the data in the SPC and EPAR was the Lepore data.

The Panel had some concerns about the strength of the evidence prior to the Porcellati *et al* data, when the materials were approved and issued. However it considered that taking into account all the data supplied by Sanofi Aventis there was data to support the claim for 24 hour glycaemic control. The Panel considered that the SPC did not appear to allow twice daily dosing. The Panel did not consider that the failure to state that glycaemic control was dose dependent meant that the claim for 24 hour control was inaccurate, misleading or inconsistent with the SPC as alleged. In the Panel's view health professionals would be well aware that dose was an important consideration.

The Panel considered that the claim for 24 hour glycaemic control was capable of substantiation and was not exaggerated or misleading as alleged. It was not inconsistent with the SPC. No breach of Clauses 7.2 and 7.4 was ruled in relation to each of the items at issue. The Panel did not consider that Sanofi-Aventis had failed to maintain high standards and no breach of Clause 9.1 was ruled. All of these rulings were appealed by Novo Nordisk.

APPEAL BY NOVO NORDISK

Novo Nordisk stated that the major problem with Sanofi-Aventis' argument was that the evidence was based on the average duration of action of the given dose of Lantus from pharmacokinetic/dynamic clamp studies. However in real clinical practice health professionals had also to deal with patients whose basal requirement was not infrequently less than average. On the basis of Lepore *et al* the proportion of these patients with type 1 diabetes was significant at 20%. Of course, in these patients Lantus could theoretically cover a 24-hour period, but this would require a higher basal insulin dose than they really needed which could result in more hypoglycaemic events. Novo Nordisk also disagreed with Sanofi-Aventis' submission that the typical type 1 specific basal insulin dose used in clinical practice was between 28-34 units/day. Novo Nordisk produced a table of data which it submitted were exclusively from Sanofi-Aventis' trials in type 1 diabetes.

Novo Nordisk observed that in nine out of twelve trials the average dose of Lantus was below 25.5 units/day. Therefore Sanofi-Aventis' claim that the given dose in the Lepore *et al* was lower than the clinical dose typically used with Lantus was not valid.

The 0.3 units/kg/day dose for the basal insulin in type 1 diabetes was rather more typical. This meant that, if the Lepore *et al* results were extrapolated to real life, Lantus might not be suitable for once-daily dosing in 20% of patients with type 1 diabetes.

Novo Nordisk agreed that health professionals would be well aware that the dose was an important consideration, but only in case of specialists who were experienced in insulin treatment. However, this assumption was not valid. GPs were increasingly providing diabetes care for insulin-treated patients, in line with government strategy. Indeed NHS strategy in the UK envisaged diabetes being managed, for the most part, in primary care, (including more complicated insulin treatment regimens). Therefore, in this particular context, there was significant potential for 'all embracing' claims to result in patient harm. There needed to be no scope for ambiguity in claims relating to insulin products.

Novo Nordisk noted that one might argue that in case of type 1 diabetes, the majority of patients still received and probably would receive diabetes care from specialists. However the problem of the dose-dependent duration of action was equally important in type 2 diabetes as well. Considering the results from the clinical trials Sanofi-Aventis conducted in type 2 diabetes where Lantus was initiated in combination with oral hypoglycaemic agents, they reported 8-point mean blood glucose profile in 4 out of 11 trials. Novo Nordisk reproduced six graphs from Janka *et al*, (2005), Fritsche *et al*, (2003), Yki-Yärvinen *et al*, (2000) and Yki-Yärvinen *et al*, (2006) showing the difference in blood glucose profiles as measured eight times through the day ie before and after each meal, at bedtime and in the early hours of the morning, according to different insulin regimens.

Novo Nordisk alleged that the results showed that Lantus failed to maintain an adequate level of glycaemic control as measured before dinner, whilst maintaining control of pre-breakfast glucose levels. This meant a peak effect around morning hours and a significantly shorter duration of action than 24 hours at the given dose. Undoubtedly this finding might not only be exclusively indicative of the pharmacodynamic properties of the insulin preparation. However from a clinical perspective it was at least as important as the results of a complicated clamp trial. Since the promotional materials provided by Sanofi-Aventis to help GPs with insulin initiation in type 2 diabetes focussed solely on a titration based on the pre-breakfast blood glucose levels, the overall 24-hour claim indicated that there was no need to check pre-dinner blood glucose values. The misinterpretation of this claim might result in failing to attain blood glucose levels before dinner, which clearly detracted from achieving HbA1c targets in these patients.

Novo Nordisk was disappointed that the Panel only considered the results from clamp trials and omitted relevant clinical findings accumulated in both types of diabetes since the launch of Lantus. Health professionals needed to individualise insulin treatment according to blood glucose levels measured in real life, as shown by the titration and intensification of insulin therapy to target measured blood glucose levels, in the recently published '4-T' trial (Treating To Target in Type 2 diabetes) (Holman *et al*, 2007). Therefore the conflicting clinical findings should be considered when this promotional claim was evaluated.

Novo Nordisk submitted that making a valid and more precise claim of 'up to 24-hour duration' instead of '24-hour duration', would more accurately reflect the properties of Lantus.

Novo Nordisk also noted guidelines provided by the Medicines and Healthcare products Regulatory Agency (MHRA) on 24 hour claims – 'data must show clinical effect over the 24 hour period. The product should be for once daily dosing but a once daily dosing interval alone is insufficient to support a 24 hour claim' (emphasis added) (MHRA Blue Guide section 5.6). From the evidence presented above, data to demonstrate a 24 hour clinical effect was lacking, particularly from the 8 point daily glucose profiles. The MHRA update in relation to this issue stated 'Claims for fast or 24 hour relief may only be included on labelling where the claim is supported by the SPC' (MHRA Mail No. 141 Jan/Feb 2004). The Lantus SPC stated that it was suitable for once daily doing, and stated nothing to support a 24 hour claim.

On the basis of the evidence presented above, Novo Nordisk alleged that the '24 hour' claim for Lantus was in breach of Clauses 7.2, 7.4 and 9.1.

COMMENTS FROM SANOFI-AVENTIS

Sanofi-Aventis submitted that Novo Nordisk's appeal appeared to comprise several components, each of which would be addressed individually:

- That the 24 hour duration that had been demonstrated was based on an average value and that as some patients might have a less than average response, it was wrong to make this claim.
- An assumption that primary care physicians were not as knowledgeable as secondary care diabetologists.
- A collection of data from patients with type 2 diabetes demonstrating that there could be a statistically significant increase in blood glucose concentration between pre-breakfast and pre-dinner readings in patients receiving Lantus.

The 24 hour duration was an 'average' value

Novo Nordisk argued that although a 24 hour duration had been demonstrated, this was based on an average value and suggested that in a normal clinical setting some patients would have a response below average. Sanofi-Aventis submitted that in general terms, this would be expected of any medicine in any therapy area and it was unrealistic to accept such an argument as justification that a claim be invalid (else almost all efficacy claims for any product would be negated).

Sanofi-Aventis submitted that more specifically, the argument proposed with reference to the table of data

submitted by Novo Nordisk was that the range of Lantus doses in the trials included in the table was in some instances less than the typical 28-35 units for a 70kg man. The reader was asked to consider that this range of doses reflected real life practice and to assume that as some of these studies demonstrated an average dose lower than 28 units, and conclude that the duration of action would be less than the 24 hours already demonstrated. Sanofi-Aventis submitted that, as with the complaint, no evidence was proposed that demonstrated that, at the Lantus dose used in these studies, a duration of action less than 24 hours had been demonstrated.

Although Novo Nordisk argued that in clinical practice patients might receive less than 28 units of Lantus, this did not imply that the duration of action would fall below 24 hours. The data provided in response to the complaint demonstrated that Lantus had a 24 hour duration of action even at the lowest dose used, 0.30 units/kg, equating to 21 units for a 70kg person and 15 units for a person of 50kg (Porcellati, *et al*). In the table of studies provided by Novo Nordisk, the average dose of Lantus (weighted by study size) was just over 28 units, more than 33% above the 21 unit dose at which 24 hour action had been confirmed. In total, 11 out of 13 studies reported doses in excess of 21 units. (Of the two that fell below, one was a short phase II study with only three weeks allowed for dose titration, a situation not reflective of clinical practice where periods of up to three months to reach an optimal dose were not unusual). Finally, this observation was made before any account was taken of the fact that over 52% of patients in these trials were female, and assuming that each weighed approximately 50kg, a lower dose of insulin would be expected to have been required (28-35 units in a 70kg person equated to 20-25 units in a person of 50kg).

In summary, Sanofi-Aventis submitted that although Novo Nordisk had suggested that real life practice might result in daily doses of Lantus below the 28-35 dose range typical for a 70kg man, it had not provided any evidence that, at such a lower dose, the duration of action of the product would be below the 24 hours claimed in the materials. On the contrary, a 24 hour period of action had been demonstrated at doses of as low as 0.3 units per kg – 21 units for a 70kg man, 15 units for a 50kg woman.

Assumption on primary care physicians' level of knowledge

Sanofi-Aventis agreed with the Panel's view that health professionals would be aware of considerations relating to dose and would not be misled by this claim of 24 hour efficacy (which was in itself robust). A suggestion that there was a lack of knowledge amongst the primary care sector was discourteous to clinical colleagues, especially given that diabetes was an increasingly common disease and comprised a significant component of general practice workload (eg comprising over 15% of the General Medical Services clinical contract points).

Experience in type 2 diabetes

Sanofi-Aventis noted that Novo Nordisk had submitted eight-point blood glucose profiles for four studies in type 2 diabetes. How these graphs were meant to be interpreted was unclear, although the text indicated that it was to expect a low blood glucose in the morning and an increase in the evening, indicating that the latter was as a result of decreased efficacy as the end of a 24 hour dosing period of Lantus was reached, suggesting a duration of action of less than this. This interpretation of the results might be credible if the studies were performed with a dose of Lantus given only in the evening – an increase in blood glucose before the following evening's dose would indeed reflect worsening control as the 24 hour time period was reached. However, the studies presented were mixed with respect to the time of day that Lantus was given – both morning and evening dosing was represented:

- In Janka *et al* (2005), all patients received Lantus in the morning. This study demonstrated very effectively that when Lantus was given first thing in the morning 24 hour control was apparent, with the 3am blood glucose level (longest interval after dosing) remaining as low as that measured at the start of the day.

- In Fritzche *et al* (2003), there were two groups, one received Lantus in the morning and one received Lantus in the evening. This study demonstrated that over a 24 hour time period, the blood glucose profiles for patients receiving Lantus in the morning or in the evening were almost superimposable, suggesting that any variation was not related to the duration of effect of Lantus but due to the effect of eating during the daytime, which resulted in a peak in blood sugar levels with each meal (which then declined post-meal due in part to the action of Lantus).

- In Yki-Yärvinen *et al* (2000) and Yki-Yärvinen *et al* (2006), patients received Lantus in the evening. Although not acknowledged in the appeal, these studies demonstrated that Lantus was effective in improving the entire 8 point blood glucose profile across 24 hours compared to baseline levels, and the authors concluded that Lantus demonstrated a peak-less and prolonged duration of action and that its use was justified in the treatment of type 2 diabetes.

Sanofi-Aventis submitted that despite the fact that patients in these studies received Lantus in either the morning or the evening, exactly the same pattern emerged in each instance. The lowest blood glucose level was apparent overnight/early in the morning as a result of the prolonged overnight fast, and as daytime passed and meals were taken, blood glucose levels rose to a peak immediately after eating and then declined subsequent to each meal. This was the normal physiological pattern (Riddle *et al*, 2006) and, as would be expected, this pattern was constant and not related to the time of day at which Lantus was given, indicating that this effect was not linked to the duration of the product. In summary, these studies did not support the notion that Lantus had a duration of action of less than 24 hours. Janka *et al* clearly

demonstrated excellent 24 hour control. Finally, these observations were consistent with Heise and Pieber (2007) that summarised that, in type 2 diabetes, the duration of action of Lantus was in excess of 24 hours.

Conclusion

In summary, Sanofi-Aventis submitted that the evidence presented with the complaint firmly demonstrated that Lantus maintained glycaemic control for up to 24 hours at doses as low as 0.30 units/kg (21 units for a 70kg subject, 15 units for a 50kg subject). Novo Nordisk had not presented any data that led to a different conclusion and had in fact confirmed that in normal clinical practice the vast majority of patients with type 1 diabetes would require treatment with at least this dose and on average 33% more. In type 2 diabetes, Novo Nordisk had demonstrated that there was a normal fluctuation in daytime glucose levels as a result of peaks related to eating, and that rather than this reflecting a decrease in the efficacy of Lantus as a 24 hour period was reached, this pattern was constant regardless of treatment with Lantus being given at the start or end of the day.

Sanofi-Aventis submitted that the claim for 24 hour efficacy for Lantus was substantiable, not misleading and not inconsistent with the SPC and that complied with both the letter and the spirit of the Code and all applicable regulations.

COMMENTS FROM NOVO NORDISK

Novo Nordisk highlighted some of the difficulties surrounding the definition of 'duration of action' in clamp trials. Duration of action of the investigated insulin preparation was usually defined in two ways:

- the time from trial medicine administration until a smooth glucose infusion rate profile was consistently below 0.5mg/kg/min (Klein *et al*, 2006) and/or
- the period between onset of action (detailed definition could be found in Lepore *et al*) and end of action (defined as a time at which plasma glucose consistently increased to >150mg/dl).

Novo Nordisk alleged that both definitions used arbitrary cut-off points which were predefined by the investigators. There was no official guide or consensus with regard to the definition of pharmacokinetic parameters in clamp studies. More importantly there was no guidance on how to interpret the results from these studies for clinical practice. In clamp studies any deterioration from the pre-defined clamped blood glucose level (5.5mmol/l or 7.2mmol/l in case of euglycaemic or isoglycaemic clamp trials respectively) was a clear sign of the waning pharmacodynamic effect of the investigated insulin preparation. Assuming the argument was accepted that the first definition (rather than the methodology as pointed out by Sanofi-Aventis) had some limitations, mainly due to the difficulty in interpretating the results for clinical practice, Novo Nordisk focused on the second definition which was accepted as standard by Sanofi-Aventis.
In terms of duration of action, Novo Nordisk summarized the results from the clamp trials quoted by Sanofi-Aventis:

- Lepore *et al*: the average duration of action of Lantus was 20.5±3.7 hours with one single injection of 0.3 units/kg. The authors noted that 16 out of 20 patients who participated in the trial had an average blood glucose level under 150mg/dl at 24 hours. This meant that in 4 out of 20 patients (ie 20% of all patients) the duration of action of Lantus was above 150mg/dl, ie definitely less than 24 hours. There was no data reported in the paper about the final average blood glucose level for the other 16 patients. Novo Nordisk therefore did not know whether the glucose level had deteriorated from the predefined clamped level, which would be a clear indication of the waning effect of Lantus. However, a graph depicting plasma glucose profile in Lepore *et al* clearly indicated that there was some deterioration towards 150 mg/dl for the whole cohort.

- Porcellati *et al* (2007a): the average duration of action of Lantus was 20.2 (17.0-25.0) hours with one single injection of 0.35 units/kg and 24 (22.0-28.5) hours with an injection after achieving 'steady-state' (ie having used Lantus for 7 days). The authors did not publish the average blood glucose levels at the end of the 24-hour period (which may have indicated a waning effect), only the average blood glucose value during the 24-hour period. Nor did they report the number of patients with blood glucose levels less than or more than 150 mg/dl at the end of a 24-hour period. The investigators had only reported on the average pharmacokinetic and pharmacodynamic parameters. Thus any conclusion about the proportion of patients in whom Lantus sufficiently maintained the predefined clamped level of 7.2mmol/l (130mg/dl) could not be made.

- Porcellati *et al* (2007b): the average duration of action for Lantus at 'steady-state' (ie having used Lantus for 14 days) was 24 (23-24) hours. The investigators noted that 8% of patients, Lantus failed to maintain its metabolic effect for 24 hours.

Novo Nordisk re-emphasised that the figures above reflected the average duration of action of Lantus. Bearing in mind that insulin sensitivity was enhanced at the end of a clamp period (DeVries, 2006); the above figures might overestimate the average duration of action.

In type 1 diabetes, health professionals had to deal with an absolute lack of endogenous insulin secretion. Therefore, an overall claim of 24-hour control should reflect a duration of action covering the 24-hour period in all patients. Assuming that the duration of action of insulin glargine was dose-dependent, one could argue that with an increase in dose the 24-hour period could be covered in these patients. However, in clinical practice health professionals had to find an acceptable balance between proper metabolic control and the incidence of hypoglycaemic episodes. In those patients with type 1 diabetes who had a basal insulin

requirement less than the average, increasing the dose would result in more hypoglycaemic episodes. This could be why clinicians used Lantus twice daily in between 24.2% and 35.6% of patients with type 1 diabetes (Albright *et al*, 2004, Garg *et al*, 2004). The clinical experience should and must be considered when the duration of action of Lantus was discussed. In fact Sanofi-Aventis had acknowledged this when it stated 'the experimental model might not reflect real-life conditions of patients with type 1 diabetes'.

Novo Novartis noted that in its previous submissions it provided detailed information which made the overall 24-hour control claim questionable in type 2 diabetes as well.

Turning to the MHRA guideline, Novo Nordisk noted that Sanofi-Aventis appeared to have avoided addressing this point.

Sanofi-Aventis concluded 'In summary, the evidence presented with the initial complaint firmly demonstrated that Lantus remained effective at maintaining glycaemic control for *up to 24 hours* at doses as low as 0.3 U/kg' (emphasis added). Novo Nordisk fully agreed with Sanofi-Aventis that a claim of 'up to 24-hour duration' would more accurately reflect the properties of Lantus than the current all encompassing claim.

On the basis of the above, Novo Nordisk alleged that the '24 hour control' claim used by Sanofi-Aventis was in breach of Clauses 7.2, 7.4 and 9.1 of the Code.

Novo Nordisk noted Sanofi-Aventis' comment that it was discourteous to primary care clinicians in relation to their knowledge about the dosing of insulin. Novo Nordisk stressed that its comment had been taken out of context. Novo Nordisk agreed with the Panel that insulin dose was an important consideration and that health professionals would be well aware of this fact. The point Novo Nordisk was endeavouring to make was that data from clamp studies were difficult to translate into a clinical setting, since there was no consensus on the definition and interpretation of clamp study results amongst diabetologists.

APPEAL BOARD RULING

The Appeal Board noted that on poster LAN 07/1038 and the leavepiece the claim '24 hour glycaemic control' appeared as a strapline beneath the Lantus product logo. 'Once daily 24-hour glycaemic control' appeared in a similar position on poster LAN05/215. On the leaflet 'Once Daily 24-Hour' appeared as part of the product logo. In the patient booklet there were a number of references to Lantus working for 24 hours.

The Appeal Board noted that of the data provided in substantiation of the claims at issue, the only data available when the complaint was made was Lepore *et al*. Lepore *et al* had studied the pharmacokinetic and pharmacodynamic effects of Lantus in 20 patients using an isoglycaemic 24-hour clamp technique. The authors had thus examined duration of action of Lantus, not its efficacy in terms of glycaemic control.

In the Appeal Board's view, in the context of diabetes, 'control' referred to glycaemic control ie the maintenance of blood glucose between set parameters. The Appeal Board noted that Lantus was a basal insulin designed to provide a background, constant suppression of blood glucose. Section 5.1 of the SPC included a graph comparing the activity profile in patients with type 1 diabetes of insulin glargine and NPH insulin. The graph showed that the activity profile of insulin glargine was smooth, peakless and almost constant between 9 and 24 hours (which was when the observation period ended).

The Appeal Board noted that in response to a question, the Sanofi-Aventis representatives submitted that no type 1 diabetic would be controlled solely on Lantus and only about half of type 2 diabetics would be controlled on a combination of Lantus and oral agents. Most diabetics would thus require short-acting insulin, in addition to Lantus, to cope with daily glucose peaks resulting from meals. The Appeal Board thus considered that a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control.

The Appeal Board considered that claims for 24-hour control or 24-hour glycaemic control were not capable of substantiation and were exaggerated and misleading in that regard. The Appeal Board ruled breaches of Clauses 7.2 and 7.4. The appeal was successful on this point. The Appeal Board did not consider that Sanofi-Aventis had failed to maintain high standards and no breach of Clause 9.1 was ruled. The appeal was unsuccessful on this point.

2 'Joe's Rough Guide to Diabetes' book

COMPLAINT

Novo Nordisk noted that this book was authored by Joseph JM Fraser and published by Wiley. The logo of Sanofi-Aventis was on the back of the publication; therefore Novo Nordisk alleged that this book was sponsored by the company. However the publication did not state the extent of the involvement of Sanofi-Aventis in this process and thus it was alleged to be in breach of Clause 9.10 of the Code.

Novo Nordisk alleged that a table of data within the book itself contained inaccurate information regarding the onset of action, the peak of action and duration of action of some insulin preparations:

- *onset of rapid-acting analogues:* the book stated 5-15 minutes however SPCs of each rapid-acting analogue stated 10-20 minutes.
- *onset and duration of action of intermediate-acting insulins:* the book stated 2-4 hours and 12-18 hours respectively however the SPC of Insulatard (Novo Nordisk's intermediate-acting insulin preparation) stated within 1½ hours and approximate 24 hours.
- *Long-acting insulins:* the book stated 24 hours of action for Lantus (neither approximately nor up to, but exactly 24 hours) while the SPC of Lantus stated *'The time course of action of insulin and insulin analogues such as insulin glargine may vary*

considerably in different individuals or within the same individual.' However in case of Levemir, which was the only direct competitor, the book stated that it started to work in 1 to 2 hours, had a peak at 6-8 hours and a duration of 6-23 hours. These claims contradicted the Levemir SPC which stated *'For doses in the interval of 0.2-0.4 U/kg, Levemir exerts more than 50% of its maximum effect from 3-4 hours and up to approximately 14 hours after dose administration' and 'maximum serum concentration is reached between 6 and 8 hours after administration'.* More importantly the SPC also stated that *'the duration of action is up to 24 hours depending on dose'.*

Novo Nordisk noted that during inter-company discussion, Sanofi-Aventis had stated that its only involvement has been to purchase copies to provide health professionals (as an educational service, not as a promotional item) and considered it as a valuable resource with considerable educational value for this audience. In this case, it would further increase the need for providing accurate, fair and balanced information. This book clearly failed to provide such basic information.

Novo Nordisk's major concern regards the fact that Sanofi-Aventis considered the content was fair and accurate and of significant educational merit when it clearly tried to highlight differences between two insulin preparations (insulin glargine and insulin detemir) that were in direct competition with each other in the market.

Based on this Novo Nordisk alleged that the book was in clear breach of the Code regarding Clauses 14.3 and 18.2 and therefore it had requested that Sanofi-Aventis withdrew this publication from distribution. Novo Nordisk queried whether the dissemination of such misleading information under the guise of an educational aide warranted the issue of a corrective statement to the recipients of this book relating to the claims/'facts' contained therein.

RESPONSE

Sanofi-Aventis submitted that neither it nor its agents had been involved in the initiation, creation, support to the author, editorial control or any other aspect of the production of this book. The publishers approached Sanofi-Aventis with the completed book to see if the company would be interested in purchasing it when it was published.

The book provided an excellent overview of the problems that adolescents might encounter in facing up to a future with diabetes, and as such was a valuable, educational resource for health professionals in order to increase their understanding of the unique aspects that teenage life introduced to diabetes care. It was therefore decided that this was appropriate to supply as an educational resource in accordance with Clause 18.2 of the Code. The email briefing sent to sales representatives regarding the booklet reflected this view.

Sanofi-Aventis was disappointed therefore that Novo Nordisk had ignored the value that this book could bring through its 42 pages of perspective on life through the eyes of a diabetic teenager, choosing instead to focus on a single point. This point was that the speed of onset of action of one class of insulins which was stated to be 5-15 minutes, compared to the SPCs which collectively described 10-20 minutes. This statement in the book was not even made in reference to an individual product, rather to a class as a whole.

Sanofi-Aventis submitted that all other information contained in this book was accurate and in accordance with the SPCs, including the detail which Novo Nordisk noted regarding Lantus and Levemir. The data was presented in a simple tabular fashion, and did not specifically highlight the differences between these two products as alleged. Contrary to the allegations, Sanofi-Aventis submitted that, on balance, this book was factual and accurate and not misleading, and that its provision was in keeping with the requirements of Clause 18.2 of the Code. It greatly helped health professionals in improving their understanding of adolescent patients' problems. Contrary to the allegations this was a positive action made in the spirit of the Code to improve patient care.

Following a request for a response to the alleged breach of Clause 14.3, Sanofi-Aventis submitted that the book was approved according to its standard procedures and as required by that clause.

PANEL RULING

The Panel noted that the back cover of the book included the Sanofi-Aventis logo and a statement 'Because health matters'. Sanofi-Aventis had no role in the initiation, creation or production of the book. It had purchased copies of the book which cost less than the maximum £6 plus VAT permitted for promotional aids. The book was aimed at teenagers with diabetes. The foreword was written by a consultant paediatrician who suggested that the book ought to be available to every young diabetic and to anybody involved in helping young people to grow up with diabetes.

The Panel considered that the purpose of the book was not entirely clear. Sanofi-Aventis' written submission stated that it was provided to health professionals to increase their understanding of teenage life with regard to diabetes care ie as an educational resource for the health professional. The representatives' briefing material stated that it was a mixture of practical advice and personal experience; a great read for anyone but was particularly relevant to adolescents and young adults. The book was part of the support the company wanted to offer to adolescent patients. It was to be used in centres dealing with high numbers of adolescents and young people. The Panel thus considered that representatives had been instructed to use the book as a gift intended for use by patients.

The Panel noted that the supplementary information to Clause 18.2 of the Code, Gifts to or for Use by Patients stated that some items distributed as promotional aids were intended for use by patients and these were not generally unacceptable provided they met the

requirements of Clause 18.2, for example, puzzles and toys for a young child to play with during a visit to the doctor. No gift or promotional aid for use by patients must be given for the purpose of encouraging patients to request a particular medicine.

With regard to the provision of books as promotional aids to health professionals, the relevant supplementary information to Clause 18.2 Gifts stated 'Certain independently produced medical/educational publications such as textbooks have been held to be acceptable gifts under Clause 18.2. The content of publications used in this way has to be considered carefully and must comply with the Code as regards any references to the donor's or competitors' products. It might be possible to give certain medical/educational publications in accordance with Clause 18.4 – Provision of Medical and Educational Goods and Services'.

The Panel noted that neither Novo Nordisk nor Sanofi-Aventis referred to Clause 18.4 of the Code.

The Panel noted that Clause 9.10 required that material relating to the medicines sponsored by a company must clearly indicate that it had been sponsored by that company. Sanofi-Aventis had purchased copies (at £1.25 per copy) to supply to health professionals.

The Panel did not know whether the book would have existed if Sanofi-Aventis had not purchased 20,000 copies to distribute as gifts. The Panel was concerned that the logo appeared on the book without a clear explanation as to Sanofi-Aventis' involvement. The Panel considered that on the information before it as Sanofi-Aventis had not contributed to the expenses of producing the book, it had not sponsored it as set out in Clause 9.10 of the Code and no breach of that clause was ruled.

The Panel examined the table of data at issue which was headed 'Insulins' and which set out the trade names for various types of insulin eg rapid acting analogue. Information was given in columns headed 'Starts To Work In', 'Peak Action' and 'Duration'. The bottom of the table stated 'Please remember these are approximate figures. Please consult your diabetes team if you want information on any particular insulin and advice as to what is the best insulin for you'.

The Panel noted Novo Nordisk's concerns about the table which generally gave a range of values for a number of insulins and clearly advocated discussion with the diabetes team. There was a direct comparison of Levemir and Lantus. The Levemir SPC stated that it was a long acting insulin analogue used as a basal insulin and that when Levemir was used as part of basal-bolus insulin regimen it should be administered once or twice daily depending on patients' needs. The duration of action was up to 24 hours. The chart in question stated that the duration of action of Levemir was '6 to 23 hours' which was not accurate. That section was the only part of the table that included information for each of the products mentioned rather than a range. The Panel queried whether the book met the requirements of the Code, particularly Clause 7.2.

The Panel noted that the only clauses cited by Novo Nordisk were 14.3 and 18.2.

The Panel did not consider that, on the information before it, the book was unacceptable either as a promotional aid for health professionals or as a gift for use by patients. Clause 18.2 of the Code required that promotional aids were inexpensive and relevant to the recipient's employment. The book was well within the cost limitation for promotional aids and relevant, and thus no breach of Clause 18.2 was ruled.

The Panel noted Sanofi Aventis' submission that the book had been approved as required by Clause 14.3 of the Code and thus ruled no breach of that clause.

Complaint received	**30 July 2007**
Case completed	**10 January 2008**