BAYER SCHERING PHARMA v LILLY

Alleged promotion of unlicensed indication

Bayer Schering Pharma complained about the possible promotion by Lilly of Cialis (tadalafil) of an unlicensed indication based on market research monitoring reports.

Bayer Schering alleged, inter alia, that the promotion of an unlicensed indication and an unlicensed dosage brought discredit to and reduced confidence in the industry in breach of Clause 2; it was misleading to imply that an unlicensed indication was consistent with the summary of product characteristics (SPC) and Lilly's refusal to supply information as requested and to regard the matter as closed without discussing conciliation was not consistent with maintaining high standards.

The Panel noted that the sole evidence provided by Bayer Schering comprised detail recall data from a small number of doctors. Three separate entries referred to Cialis and its cardiovascular effect. The Panel noted Lilly's submission about the survey's methodology and weight to be attached to such evidence.

The Panel accepted that it was difficult to know precisely what representatives were saying to health professionals. This was one reason why the Code required briefing material to be prepared.

The promotional and briefing materials provided neither referred to a possibility that Cialis had a positive cardiovascular effect nor to doses other than 10mg and 20mg. The Panel was nonetheless concerned that physicians recalled that smaller doses of Cialis were protective but did not consider that this was consistent with the material provided by Lilly.

The Panel noted that Bayer Schering had to establish its case on the balance of probabilities. Bayer Schering had referred to the '*possibility* that Cialis had been, and was being, promoted outside its licence in relation to cardiovascular conditions' (emphasis added). The Panel considered that Bayer Schering had not provided sufficient evidence to establish that, on the balance of probabilities, this was so. The Panel ruled no breach of the Code.

With regard to the alleged breach in relation to Lilly's refusal to supply information as requested or discuss conciliation, the Panel considered that there was no breach. There was no obligation for companies to discuss conciliation. There was only a requirement for the complainant to attempt inter-company dialogue prior to submitting a complaint to the Authority.

Bayer Schering Pharma complained about the promotion of Cialis (tadalafil) by Eli Lilly and Company Limited. Bayer Schering supplied Levitra (vardenafil).

COMPLAINT

Bayer Schering's principal concern was the possible promotion of Cialis for an unlicensed indication based on market research agency monitoring reports (provided) for March and September 2007 which indicated the possibility that Cialis had been (and was being) promoted in relation to cardiovascular conditions. Bayer Schering had asked Lilly to provide briefing materials for its representatives and speakers so that it could rule out Lilly's direct or indirect involvement in such practice. Unfortunately Lilly rejected inter-company correspondence on this matter and left Bayer Schering in a position unable to continue inter-company dialogue directed at assessing and resolving this matter. Since then Bayer Schering had received a further detail recall from December 2007 (provided). This appeared to indicate a continuance of the recall pattern evidenced by the earlier monitoring. In view of the documented recall pattern of health professionals referring to the use of Cialis for an unlicensed indication Bayer Schering alleged this matter might potentially be serious and should not be ignored, however, as a consequence of Lilly's refusal to engage it could not investigate this matter any further through its preferred route of inter-company dialogue. In the circumstances Bayer Schering referred the matter to the Authority.

Bayer Schering alleged breaches of:

Clause 3.2, promoting a medicine within [sic] the terms of its marketing authorization;
Clause 2, promotion of an unlicensed indication and an unlicensed dosage brought discredit to and reduced confidence in the industry;
Clause 7.2, it was misleading to imply by promotion that an unlicensed indication was consistent with the summary of product characteristics (SPC) and
Clause 9.1, Lilly's refusal to supply information as requested and to regard the matter as closed without discussing conciliation was not consistent with maintaining high standards.

RESPONSE

Lilly strenuously denied the allegation and remained confident that representatives had not promoted Cialis outside of the product licence, as set out in inter-company correspondence dated 13 December. This was supported by a number of factors. Firstly, all material used by representatives was certified in accordance with the Code. Secondly, all representatives' training material was certified as per Clause 15.9, and thirdly,

all slide presentations at Lilly promotional meetings produced by external speakers were reviewed for medical accuracy.

Lilly provided a summary of all relevant Cialis promotional material from 2007, an explanation of how it was used and associated briefing documents. Lilly considered several of these items, specifically the Cialis detail aids, objection handlers and associated briefing material to be company proprietary and hence company confidential. These materials were not left with physicians and therefore not used independently of the representative. Lilly requested that all material remained confidential and not be disclosed to Bayer Schering. The sharing of any material would provide Bayer Schering with commercial information which was beyond that necessary to resolve the complaint.

Lilly stated that the basis of Bayer Schering's original allegation was anonymous market research data from 12 GPs in September 2007 and 3 hospital doctors in March 2007. In Bayer Schering's correspondence to the Panel, it had included a further survey of an additional 4 hospital physicians, conducted in December 2007, not previously provided to Lilly and of which it was unaware. This type of market research was a paper based questionnaire that was mass mailed by the agency. Doctors were asked to complete the survey, sign and return, upon which they were sent a gift token. There were a number of problems with this methodology. Firstly, the quality of the data was solely dependant on the accurate memory of the doctor and there was generally no additional supporting evidence or validation. Secondly, there was no guarantee that the form had been completed by a health professional. Thirdly, there was no targeting exercise to verify that physicians surveyed had actually been detailed in the last week. Finally, as the unique identifiers had been removed, it could not be concluded that these individuals were indeed unique. This was particularly important in this case where two identical comments, reported in March and December, were allegedly made by two separate specialist registrars in genitourinary medicine, which was a relatively small speciality. Lilly requested that the agency verified that these individuals were indeed not one and the same whilst maintaining confidentiality.

From the three surveys (total of 19 physicians), one respondent from general practice indicated that they recalled attending a meeting where 'New data on the reduction in CVD' was associated with tadalafil. There was no information to suggest that this was a Lilly promotional meeting or that Lilly was in anyway involved. A specialist registrar in genitourinary medicine, indicated that they recalled that 'small doses of Cialis protect vessels in high cardiovascular risk patients'. Again there was no additional detail to suggest that this message was delivered proactively by a Lilly representative. A second specialist registrar in genitourinary medicine, reported a similar message 'Low doses of Cialis protected cardiovascular system'. Therefore, in total, three physicians out of 19 surveyed made an association between Cialis and cardiovascular disease. However, this portion might represent a distorted and biased interpretation of the data, with little significance, as Lilly had no information as to the total number of agency market research waves conducted by Bayer Schering during 2007.

Lilly submitted that, although smaller dosage forms were licensed, only the standard doses of Cialis (10mg and 20mg) were available in the UK, so any allegation that Lilly promoted 'low doses' would not make commercial sense. There were a number of alternative reasons, all compliant with the Code as to why these three physicians would report an association between Cialis and cardiovascular disease. It had long been recognised that erectile dysfunction was often a consequence of general vascular disease or atherosclerosis, with patients therefore predisposed to conditions such as heart attacks, peripheral vascular disease and stroke. Atherosclerosis, or the laying down of plaque in the arterial wall, was thought to be linked to low grade inflammation of the vessel wall among other factors. The link between the enzyme PDE5 and dysfunction of the lining of the arteries (the endothelium) contributing to this inflammation was of huge scientific interest and increasing debate at congresses and meetings. In a literature search of 2007, there were 46 publications with 'tadalafil' and 'cardiovascular' identified as key words (Lilly's search was limited to English text and human subjects). Twenty articles in 2007, applying the same limitations, contained the keywords 'tadalafil' and 'endothelium'. Physicians therefore had wide access to such information on tadalafil and other PDE5 inhibitors, outside of any representative, through publications, independent scientific conferences and meetings, Lilly medical advisory boards, or in response to request for such data made to the Lilly medical/scientific services.

Whilst Lilly acknowledged that the comments of such physicians might be real, it remained confident that the source of this information was not a Lilly representative as suggested by Bayer Schering. Lilly submitted that the actions of its representatives were not in breach of Clauses 3.2 or 7.2. As previously stated, all of the tadalafil promotional material was on-licence.

In response to the alleged breach of Clause 9.1, Lilly agreed that inter-company dialogue took place as per correspondence (provided). It was noteworthy however that the case presented to the Panel differed from the original inter-company complaint (ie 3 months of market research vs 2 months). In addition, the nature of this complaint meant that robust evidence substantiating Bayer Schering's complaint was absent and hence any request for Lilly to provide company confidential documents such as sales material and briefing documents, was deemed disproportionate. Lilly hoped this reassured that all reasonable measures had been taken to address Bayer Schering's concerns and hence did not consider its previous actions to have breached Clause 9.1.

PANEL RULING

The Panel noted the parties' submission regarding agency monitoring reports and inter-company dialogue. The Panel noted that the monitoring reports

for March and September 2007 had been the subject of inter-company dialogue. A new report for December 2007 was also the subject of the current complaint and raised a closely similar matter. The Panel noted the Director's decision that inter-company dialogue had been unsuccessful.

The sole evidence provided by Bayer Schering comprised detail recall data from a small number of doctors. Three separate entries referred to Cialis and its cardiovascular effect. The Panel noted Lilly's submission about the survey's methodology and weight to be attached to such evidence.

The Panel accepted that it was difficult to know precisely what representatives were saying to health professionals. This was one reason why the Code required briefing material to be prepared.

None of the promotional or briefing materials provided referred to a possibility that Cialis protected vessels in high CV risk patients. Nor were doses other than 10mg and 20mg mentioned. The Panel was nonetheless concerned that physicians recalled that smaller doses of Cialis protected vessels but did not consider that this was consistent with the material provided by Lilly. There was no evidence that the entries referred to comments made by Lilly representatives.

The Panel noted that Bayer Schering had to establish its case on the balance of probabilities. Bayer Schering had referred to the '*possibility* that Cialis had been, and was being, promoted outside its licence in relation to cardiovascular conditions' (emphasis added). The Panel considered that Bayer Schering had not provided sufficient evidence to establish that Lilly was, on the balance of probabilities, promoting Cialis outside its licence as alleged. The Panel ruled no breach of Clauses 3.2 and 7.2. The Panel also ruled no breach of Clause 2.

With regard to the alleged breach of Clause 9.1 in relation to Lilly's refusal to supply information as requested or discuss conciliation, the Panel considered that there was no breach. There was no obligation for companies to discuss conciliation. There was only a requirement for the complainant to attempt inter-company dialogue prior to submitting a complaint to the Authority (Paragraph 5.2 of the Constitution and Procedure).

Complaint received 31 January 2008

Case completed 26 March 2008