CASE AUTH/2107/3/08

BAXTER HEALTHCARE v JOHNSON & JOHNSON WOUND MANAGEMENT

Promotion of Quixil fibrin sealant

Baxter Healthcare alleged that Johnson & Johnson Wound Management's use of a regulatory authority safety alert for Trasylol (aprotinin) in its promotion of Quixil (human fibrin sealant) was misleading.

Baxter explained that in November 2007, worldwide marketing of Trasylol was suspended because of safety concerns – aprotinin was one component of Tisseel Kit fibrin sealant, marketed by Baxter. Immediately following this action, the European Medicines Evaluation Agency (EMEA) issued a statement explaining the reasons for the action, and made it clear that fibrin sealants containing aprotinin were not affected by this alert.

Early in December 2007, Baxter began to receive enquiries regarding the licence status of Tisseel and the appropriateness of its use; Baxter alleged that one customer from a cardiac surgery centre was told by the Johnson & Johnson representative to stop using Tisseel and switch to Quixil because Quixil did not contain aprotinin. Baxter immediately wrote to Johnson & Johnson expressing its dissatisfaction with this turn of events, and asked the company to let Baxter know what action had been taken to ensure this was not repeated. No response was received to this letter.

It subsequently became evident that Johnson & Johnson's salesforce had been officially briefed on the aprotinin withdrawal, however Johnson & Johnson refused to supply a copy of this briefing material – the company offered to show it at a meeting but would not send a copy to Baxter.

Baxter further noted that Johnson & Johnson had written to consultant haematologists informing them that there was a fibrin sealant available that did not contain aprotinin. Given the clear statement from the EMEA that this concern did not relate to fibrin sealants Baxter alleged that this was further misleading promotion of Quixil. Baxter had not got a copy of this letter, and given that use of Quixil was almost exclusively limited to surgical operations Baxter questioned the appropriateness of such a letter to anyone other than a surgeon.

Baxter alleged that it was clear that the briefing and the strategy were global initiatives based on a common theme, namely that fibrin sealants that contained aprotinin were less safe than those that did not. A banner stand for Quixil, used in the UK, included the statement 'Aprotinin free'.

The Panel noted that on 21 November 2007, the EMEA issued a questions and answers document on its recommendation to suspend the marketing authorizations for aprotinin-containing medicines. The first paragraph of the document stated that the Agency's Committee for Medicinal Products for Human Use had concluded that the benefits of systemic formulations of these medicines no longer outweighed their risks and had recommended that all marketing authorizations for these medicines should be suspended throughout Europe. The Agency defined systemic formulations as those which affected the whole body, such as infusions (drips). The document clearly stated in a section headed 'What is Aprotinin?' that 'Aprotinin can also be used locally during surgery, in sealants (glues), to help stop bleeding. These medicines are not affected by this recommendation'.

On 29 November 2007, the MHRA issued a statement entitled 'Aprotinin (Trasylol): Suspension of UK marketing authorisations (licences)'. Unlike the EMEA document the MHRA statement did not differentiate between aprotinin and aprotinin-containing medicines or systemic and local formulations but in that regard the Panel considered that the title of the document made it clear that the statement related solely to Trasylol.

The Panel noted that Johnson & Johnson had acknowledged that there was potential for confusion as to exactly what medicines had been suspended from use. The company had stated that it wanted to ensure that its customers knew that although Trasylol was affected by the suspension of its marketing authorization, there was no effect on Quixil or indeed any fibrin sealant.

The Panel disagreed with Johnson & Johnson's submission that, from as early as 13 November 2007, it had made it clear to its representatives that the regulatory status of Trasylol did not affect fibrin sealants. An email to representatives of 13 November stated 'The potential opportunity for Quixil to be used as an alternative [to Trasylol] is due *not necessarily* (emphasis added) to [Tisseel] containing aprotonin but due to the use of Trasylol as a systemic haemostat'. The Panel considered that this statement would lead the representatives to think that the aprotinin contained in Tisseel *might* be a problem. The email did not clearly distinquish between Trasylol and fibrin sealants as submitted.

On 4 December 2007, a further briefing by

Johnson & Johnson to its representatives on the updated guidance from the MHRA with regard to Trasylol, did not differentiate between systemic and local use of aprotinin nor did it distinguish between aprotinin as in Trasylol or aprotinin-containing medicines such as Tisseel. The briefing material did not refer to the EMEA's statement, which pre-dated the MHRA's statement, namely that sealants, or glues, were not affected by the suspension of the Trasylol licences. Representatives were asked to reassure customers that Quixil did not contain bovine aprotinin and if customers asked about other aprotinin-containing products, they were to be reassured that Quixil was the only fibrin sealant on the market that did not contain bovine aprotinin.

The Panel considered that the briefing material implied that because it did not contain aprotinin, there was a benefit for Quixil compared with aprotinin-containing sealants ie Tisseel. No data had been submitted to this effect. The Panel considered that by not explicitly informing representatives that the MHRA statement was Trasylol specific and referring to the EMEA statement that sealants or glues were not affected, the briefing material did not reflect the situation clearly and was misleading by implication and following it was likely to lead to a breach of the Code. The Panel ruled a breach of the Code.

The Panel noted that the letter sent in early January 2008 by Johnson & Johnson, explaining the situation to its customers, was headed 'Quixil Solutions for Sealant (Human Fibrin Sealant)'. This letter emphasised that the marketing suspension and license suspensions of Trasylol were Trasylol specific and did not affect surgical sealants. It also stated that Quixil did not contain aprotinin and there was no implied comparison with sealants which did. The Panel did not consider that the letter was misleading as alleged and no breach of the Code was ruled.

Unlike the letter the exhibition banner did not include information about the current situation with Trasylol. It featured five bullet points about Quixil the final one of which was 'Completely free of animal sourced components – Aprotinin free'. The Panel considered that such a claim implied a benefit for Quixil compared with sealants which contained aprotinin; readers would assume that there was some positive reason for the claim to be made. There was no data to show a clinical benefit for aprotinin- free sealants compared with those that contained aprotinin. The Panel considered that, in the light of the representatives' briefing material discussed above, the balance of probabilities was that the claim would be used to imply a clinical advantage for Quixil which was misleading. A breach of the Code was ruled.

Baxter Healthcare Ltd complained about the promotion of Quixil Solutions for sealant (human fibrin sealant) by Johnson & Johnson Wound Management.

COMPLAINT

Baxter alleged that Johnson & Johnson's use of a regulatory authority safety alert for another product in its promotion of Quixil was misleading in breach of Clause 7.2 of the Code.

Baxter explained that in November 2007, worldwide marketing of Trasylol (aprotinin) was suspended because of safety concerns – aprotinin was one component of Tisseel Kit fibrin sealant, marketed by Baxter. Immediately following this action, the European Medicines Evaluation Agency (EMEA) issued a statement which explained the reasons for the action, and made it clear that fibrin sealants containing aprotinin were not affected by this alert.

Early in December 2007, Baxter began to receive medical information enquiries regarding the licence status of Tisseel and the appropriateness of its use. Baxter alleged that in particular, one customer from a cardiac surgery centre was told by the Johnson & Johnson representative to stop using Tisseel and switch to Quixil because Quixil did not contain aprotinin. Baxter immediately wrote to Johnson & Johnson expressing its dissatisfaction with this turn of events, and asked the company to let Baxter know what action had been taken to ensure this was not repeated. No response was received to this letter.

In subsequent correspondence it became evident that Johnson & Johnson's salesforce had been officially briefed on the aprotinin withdrawal, however Johnson & Johnson refused to supply a copy of this briefing material – the company offered to show it at a meeting but would not send a copy to Baxter.

During this email exchange Baxter found out that Johnson & Johnson had written to consultant haematologists informing them that there was a fibrin sealant available that did not contain aprotinin. This letter came to light at a Baxter haematology advisory board meeting, when a customer mentioned receiving the letter and being rather surprised by it. Given the clear statement from the EMEA that this concern did not relate to fibrin sealants Baxter alleged that this was further misleading promotion of Quixil. Baxter had been unable to obtain a copy of this letter, and given that application of Quixil was almost exclusively limited to surgical operations Baxter questioned the appropriateness of such a letter to anyone other than a surgeon.

Baxter alleged that it was clear that the briefing and the strategy were global initiatives based on a common theme, namely that fibrin sealants that contained aprotinin were less safe than those that

did not. A banner stand for Quixil, used in the UK, included the statement 'Aprotinin free'.

RESPONSE

Johnson & Johnson explained that control of haemostasis was a critical element to ensure successful surgery. Many different approaches to achieving this goal existed including surgical and anaesthetic techniques, local haemostatic devices and pharmacological agents. The health professionals involved in this therapy area included surgeons, other operating theatre staff, pharmacists, haematologists and blood transfusion experts.

The pharmacological agents used as supportive treatments in the control of haemostasis in surgery included fibrin sealants, such as Tisseel and Quixil. Fibrin sealants were not simple chemical entities. Their main components were derived from human plasma. In simple terms, fibrin sealants consisting of a component that was mainly fibrinogen, a component that was mainly thrombin and they might also contain an antifibrinolytic. The antifibrinolytic in Tisseel was bovine aprotinin and that in Quixil was tranexamic acid. When required by the surgeon, these agents were admixed and applied topically to the wound site and formed a stable clot thereby reducing blood loss. Both Tisseel and Quixil were licensed as supportive treatments where standard surgical techniques were insufficient for improvement of haemostasis. Each, in turn, had certain restrictions and warnings on its use but each was effectively licensed for improvement of haemostasis in a range of surgical procedures.

Aprotinin, the active ingredient in Trasylol, was another such medicine which, until its licences were suspended on 7 December 2007 by the MHRA, was licensed to reduce blood loss in certain patients undergoing coronary artery bypass graft surgery. It was also known to be used to reduce blood loss in other unlicensed indications. It was administered intravenously. The MHRA on its website on 29 November 2007 stated, *inter alia*, that a full review of the balance of risks and benefits of aprotinin was underway and that the licences of aprotinin would be suspended from 7 December until further notice. This action had followed results of a study that had been terminated because of an excess of mortality in the aprotinin arm (relative risk of 1.5 compared with both tranexamic acid and aminocaproic acid). Johnson & Johnson noted that the marketing authorization holders for Trasylol, had already voluntarily suspended global marketing of the product (on 6 November 2007) due to safety concerns.

Following the worldwide marketing suspension on 6 November and the MHRA statement on 29 November 2007, health professionals told Johnson & Johnson's representatives about their concerns regarding aprotinin (Trasylol) and of other aprotinin-containing products; Tisseel was specifically mentioned. In many cases, these concerns did not distinguish between aprotinin containing products applied topically in the form of fibrin sealants and aprotinin administered intravenously in the form of Trasylol, a distinction also not made by the MHRA in its statement of 29 November 2007. For example, a consultant surgeon told one of Johnson & Johnson's sales staff that the medical director had emailed all surgeons explaining 'under no circumstances are they to use any product containing aprotinin'. This surgeon viewed this instruction to extend to Tisseel. On 29 November 2007 a cardiac surgeon, who referred to the MHRA alert on aprotinin (Trasylol), told a representative his unit might now have to reconsider the use of fibrin sealants as a supportive treatment.

The potential for confusion of the aprotinin (Trasylol) safety concerns extending to aprotinin containing fibrin sealants was also shown by the EMEA stating in its 'Questions and Answers' document of 21 November 2007 that aprotinin-containing medicines used locally during surgery in sealants were not affected.

Given the confusion concerning the safety of aprotinin in any form and the potential therefore for health professionals to consider that the safety of all fibrin sealants might be affected by the aprotinin (Trasylol) safety concerns, Johnson & Johnson considered it important to reassure its customers that Quixil did not contain bovine aprotinin, especially as Quixil could be an alternative supportive treatment for the improvement of haemostasis in situations where aprotinin (Trasylol) had been used (both in Trasylol's licensed and unlicensed uses). Accordingly Johnson & Johnson felt obliged, firstly, to ensure its staff understood the regulatory situation of aprotinin (Trasylol) and explained the situation to their customers correctly and, secondly, to communicate directly to its customers on the point that the aprotinin (Trasylol) action had no direct effect on Johnson & Johnson's product or indeed on any fibrin sealant.

A copy of the representatives' briefing document was supplied. This gave the regulatory status of aprotinin (Trasylol) and instructed staff to determine how individual hospitals were interpreting this. They were then asked to determine whether this was likely to affect Quixil and to reassure customers that Quixil did not contain bovine aprotinin. They were told not to discuss any aprotinin-containing product other than Trasylol and, should a customer ask about other aprotinin containing products, to refer them to the manufacturer concerned.

In early January 2008, Johnson & Johnson sent a promotional letter to approximately 28,000 of its customers that referred to the aprotinin (Trasylol) safety concerns and the recent regulatory action. These customers consisted mainly of surgeons and pharmacists but included 160 haematologists and 2,100 clinical directors. This letter noted that these regulatory actions were Trasylol specific and did not

affect fibrin sealants, a distinction the company made clear to its sales representatives as early as 13 November 2007.

The email chain referred to by Baxter culminated in an email to Johnson & Johnson dated 15 January 2008 which referred not only to a regulatory safety alert for another product but also to Johnson & Johnson's concerns about possible inappropriate hospitality extended by Baxter staff. Johnson & Johnson would not address this latter matter further in this response.

The email correspondence did continue beyond 15 January 2008. On 16 January 2008, Johnson & Johnson repeated its request for a meeting between the senior medical staff of the companies.

Johnson & Johnson was prepared to show Baxter a copy of its representative' briefing material in order to reassure it of Johnson & Johnson's version of events. Johnson & Johnson did not want to give a hard copy or email copy of this to Baxter as the company was concerned that it would be given to Baxter's marketing and sales departments allowing them to see how Johnson & Johnson addressed its sales staff thereby potentially compromising its commercial competitiveness.

Johnson & Johnson noted that it had repeatedly and unsuccessfully requested the identity of the representative or the hospital concerned. Johnson & Johnson found this surprising since the representative was its member of staff. The effect of this was that Johnson & Johnson was prevented from following up the specifics of Baxter's complaint with the representative concerned.

Johnson & Johnson noted that Baxter had alleged that Johnson & Johnson's use of a regulatory authority safety alert for another product was misleading promotion of Quixil in breach of Clause 7.2. Clause 7.2 stated, *inter alia*, that 'Information, claims and comparisons ... must not mislead either directly or by implication...'.

Johnson & Johnson acknowledged that it used the regulatory authority safety alert to brief its representatives on the issues and the alert was also referred to in a promotional letter sent to appropriate customers. Johnson & Johnson considered that its use of this safety alert was appropriate and was not misleading and it thus denied any breach of Clause 7.2 concerning its use.

Johnson & Johnson noted that although Baxter had referred to the behaviour of one of its staff there was no specific allegation of a breach of the Code in this regard. As stated earlier, Johnson & Johnson was unable to take this aspect of Baxter's complaint further since Baxter would not provide the necessary information. Johnson & Johnson was satisfied that its representatives' briefing material was not misleading and did not advocate a course of action that would bring them into conflict with the Code.

Additionally, Johnson & Johnson noted Baxter's reference to a Quixil banner stand in use in the UK and denied that this banner was misleading in breach of Clause 7.2.

Johnson & Johnson further noted that Baxter referred to activities undertaken in countries outwith the UK. Given the scope of the Code, Johnson & Johnson had not addressed these issues.

PANEL MINUTE

The Panel noted that on 21 November 2007, the EMEA issued a questions and answers document on its recommendation to suspend the marketing authorizations for aprotinin-containing medicines. The first paragraph of the document stated that the Agency's Committee for Medicinal Products for Human Use (CHMP) had concluded that the benefits of systemic formulations of these medicines no longer outweighed their risks and had recommended that all marketing authorizations for these medicines should be suspended throughout Europe. The Agency defined systemic formulations as those which affected the whole body, such as infusions (drips). The document clearly stated in a section headed 'What is Aprotinin?' that 'Aprotinin can also be used locally during surgery, in sealants (glues), to help stop bleeding. These medicines are not affected by this recommendation'.

On 29 November 2007, the MHRA issued a statement entitled 'Aprotinin (Trasylol): Suspension of UK marketing authorisations (licences)'. Unlike the EMEA document the MHRA statement did not differentiate between aprotinin and aprotinin-containing medicines or systemic and local formulations but in that regard the Panel considered that the title of the document made it clear that the statement related solely to Trasylol.

The Panel noted that Johnson & Johnson had acknowledged that there was potential for confusion as to exactly what medicines had been suspended from use. The company had stated that it wanted to ensure that its customers knew that although Trasylol was affected by the suspension of its marketing authorization, there was no effect on Quixil or indeed any fibrin sealant.

The Panel disagreed with Johnson & Johnson's submission that, from as early as 13 November 2007, it had made it clear to its representatives that the regulatory status of Trasylol did not affect fibrin sealants. An email to representatives of 13 November stated 'The potential opportunity for Quixil to be used as an alternative [to Trasylol] is due *not necessarily* (emphasis added) to [Tisseel] containing aprotonin but due to the use of Trasylol as a systemic haemostat'. The Panel considered that this statement would lead the representatives to think that the aprotinin contained in Tisseel *might* be a problem. The email did not clearly make the

distinction between Trasylol and fibrin sealants as submitted. Representatives were instructed to refer questions regarding Tisseel to Baxter as Johnson & Johnson could not comment.

On 4 December 2007, Johnson & Johnson further briefed its representatives on the updated guidance from the MHRA with regard to Trasylol. The powerpoint presentation did not differentiate between systemic and local use of aprotinin nor did it distinguish between aprotinin as in Trasylol or aprotinin-containing medicines such as Tisseel. The briefing material did not refer to the EMEA's statement, which pre-dated the MHRA's statement, namely that sealants, or glues, were not affected by the suspension of the Trasylol licences. Representatives were asked to reassure customers that Quixil did not contain bovine aprotinin and if customers asked about other aprotinin-containing products, they were to be reassured that Quixil was the only fibrin sealant on the market that did not contain bovine aprotinin. A slide headed 'Your briefing instructions' stated that representatives should be prepared to engage on this topic with appropriate customers and should be familiar with the MHRA guidance on Trasylol. Representatives then had to establish whether the customer expected this to affect Quixil, and if so why, and then reassure customers that Quixil did not contain bovine aprotinin. Representatives could not discuss other aprotinin-containing products except Trasylol. If customers asked about such products representatives were to reassure them that Quixil was the only fibrin sealant on the market which did not contain bovine aprotinin.

The Panel considered that the briefing material implied that because it did not contain aprotinin, there was a benefit for Quixil compared with aprotinin-containing sealants ie Tisseel. No data had been submitted to this effect. The Panel considered that by not explicitly informing representatives that the MHRA statement was Trasylol specific and referring to the EMEA statement that sealants or glues were not affected, the briefing material did not reflect the situation clearly and was misleading by implication and following it was likely to lead to a breach of the Code. The Panel noted that Baxter had not alleged a breach of Clause 15.9 of the Code which related to briefing material although this was not surprising as Baxter had not seen the briefing material. Although Clause 15.9 would have been more relevant, given that the briefing material was misleading, the Panel ruled a breach of Clause 7.2 of the Code.

The Panel noted that the letter sent in early January 2008 by Johnson & Johnson, explaining the situation to its customers, was headed 'Quixil Solutions for Sealant (Human Fibrin Sealant)'. This letter emphasised that the marketing suspension and license suspensions of Trasylol were Trasylol specific and did not affect surgical sealants. It also stated that Quixil did not contain aprotinin and there was no implied comparison with sealants which did. The Panel did not consider that the letter was misleading as alleged and no breach of Clause 7.2 of the Code was ruled.

Unlike the letter the exhibition banner did not include information about the current situation with Trasylol. It featured five bullet points about Quixil the final one of which was 'Completely free of animal sourced components – Aprotinin free'. The Panel considered that such a claim implied a benefit for Quixil compared with sealants which contained aprotinin; readers would assume that there was some positive reason for the claim to be made. There was no data to show a clinical benefit for aprotinin- free sealants compared with those that contained aprotinin. The Panel considered that, in the light of the representatives' briefing material discussed above, the balance of probabilities was that the claim would be used to imply a clinical advantage for Quixil which was misleading. A breach of Clause 7.2 the Code of was ruled.

Complaint received **18 March 2008**

Case completed **30 April 2008**