CASE AUTH/2815/12/15

ABBVIE v PIRAMAL

Sevoflurane Material

AbbVie complained about a leaflet detailing a drop test of Sevoflurane Piramal screw top glass bottles produced by Piramal Healthcare UK.

AbbVie alleged that the leaflet was in breach of the Code as the cost of sevoflurane and the date on which the leaflet was drawn up was not stated and there was no statement about the need to report adverse events. AbbVie further alleged that Piramal had not maintained high standards and by not including the adverse event reporting statement which prejudiced patient safety had brought the industry into disrepute in breach of Clause 2.

The detailed response from Piramal is given below.

The Panel noted Piramal's submission that the leaflet was not promotional because it focussed on the packaging of sevoflurane and did not seek to promote the therapeutic value, safety or efficacy of the medicine. The Panel considered, however, that a licensed medicine was the sum of its parts, and packaging (in this case the robustness of the glass bottles) might be a reason why a health professional or other relevant decision maker would choose one medicine over another. Reference was made to sevoflurane Piramal's 5 year shelf life. The Panel noted in that regard the application of the Code; it was not limited to information or claims of a medical or scientific nature. In the Panel's view, a claim about any aspect of a medicine would be caught by the definition of promotion. The Panel thus considered that the leaflet promoted sevoflurane.

The Panel noted that the Code required promotional material to include the cost (excluding VAT) of a medicine. The Panel noted that the SPC and patient information leaflet appeared to have been reproduced in the leaflet; the cost of sevoflurane was not included. The Panel therefore ruled a breach of the Code.

This obligatory statement about adverse event reporting did not appear in the leaflet at issue and the Panel therefore ruled a breach of the Code. Similarly, the Panel ruled a breach of the Code as the leaflet did not include the date on which it was drawn up or last revised.

The Panel considered that high standards had not been maintained and a breach of the Code was ruled.

The Panel noted its rulings above and although it was concerned that the adverse event reporting statement had not been included in the leaflet, it considered that an additional ruling of a breach of Clause 2 would be disproportionate; a ruling of a breach of Clause 2 was used as a sign of particular censure and reserved for such use and no breach of that clause was ruled.

AbbVie Ltd complained about the promotion of sevoflurane by Piramal Healthcare UK Ltd. The piece at issue was a leaflet detailing a drop test of Sevoflurane Piramal screw top glass bottles (ref MKT-SEV-025). The drop test was conducted to investigate the incidence of breakage on four different floor types commonly found in hospitals. Information for health professionals and patient information was on pages 5 and 6 of the leaflet.

Sevoflurane was indicated for induction and maintenance of general anaesthesia in adult and paediatric patients for inpatient and outpatient surgery. AbbVie also marketed sevoflurane.

COMPLAINT

AbbVie noted that Piramal's primary defence was that the material was non-promotional and therefore did not fall within the scope of the Code. In AbbVie's view, the material was promotional and contained significant issues and omissions that potentially compromised patient safety.

Definition of promotion and application to the materials

AbbVie noted that Clause 1.2 defined promotion as any activity by a pharmaceutical company which promoted the 'purchase, recommendation, sale, supply or use of its medicines'. Piramal's actual or presumed intention, taking into account the totality of the information and circumstances, plus the likely perception of the average physician was relevant. In AbbVie's view, the leaflet was intended to influence the sale, supply or use of Piramal's sevoflurane; the material was not primarily designed to provide medical or financial information and so displayed an actual or presumed promotional intent. Further, AbbVie considered that anything which promoted the 'use' of the product (eg handling, bottle safety and integrity of packaging as in the leaflet at issue) amounted to promotion and fell within the scope of the definition in Clause 1.2. AbbVie alleged breaches as follows:

- The cost of sevoflurane was not stated in breach of Clause 4.2.
- The date on which the leaflet was drawn up was not stated in breach of Clause 4.9.
- There was no statement about the need to report adverse events in breach of Clause 4.10.

AbbVie further alleged that Piramal had not maintained high standards in breach of Clause 9.1.

AbbVie further alleged that Piramal had brought the industry into disrepute by not providing the appropriate safety information in that the adverse event reporting statement was not included. In AbbVie's view this prejudiced patient safety in breach of Clause 2.

Inter-company dialogue

AbbVie explained that during inter-company dialogue Piramal had that the leaflet was not promotional. However, in AbbVie's view it was clearly promotional; it highlighted the glass packaging of sevoflurane which could not be separated from the product itself. In AbbVie's view, the purpose of the item was to increase the purchase, recommendation, sale, supply or use of sevoflurane. Further, the leaflet used promotional language, eg 'Glass represents Quality and Trust' and 'Glass – by choice'.

AbbVie stated that the leaflet also looked and felt promotional; it was glossy and colourful marketing-style communication. Non-promotional material must not contain product claims.

AbbVie noted that Piramal had stated during inter-company dialogue that the Code allowed for the summary of product characteristics (SPC) to be provided in lieu of the specific particulars listed in the 'obligatory information for inclusion in promotional materials' section above. Clause 4.2 made it clear that the legal classification and cost must also be included and those particulars were not in the SPC. As noted above, the cost was not stated in the leaflet.

Piramal failed to acknowledge that the leaflet was promotional and stated that it was being revised, however it had not stated explicitly that it was no longer used in the UK. Piramal provided no written undertaking that the claims to which this complaint related would not be repeated and AbbVie considered that inter-company dialogue had been unsuccessful.

In summary, AbbVie alleged breaches of Clauses 2, 4.2, 4.9, 4.10 and 9.1 of the Code and a breach of the MHRA Blue Guide.

RESPONSE

Piramal submitted that there was no basis for the allegations and responded to each of the points raised by AbbVie.

Piramal provided the background surrounding the preparation and use of the item; Piramal submitted that the item should be considered in context in order to assess the validity of AbbVie's allegations. Secondly, Piramal included its observation with respect to the allegedly promotional nature of the item in the context of Clause 1.2 and applicable law. Lastly, it addressed each of AbbVie's allegations.

Piramal submitted that it was particularly mindful of its over-arching obligation to ensure regulatory compliance of all external communications. Each external communication was subject to rigorous review according to established processes and procedures. Piramal submitted that its established review policy took full account of the requirements set out in law and in voluntary industry codes of practice. Piramal submitted that it was fully committed to compliance and good governance. Compliance with the promotional and advertising rules for medicines was no exception.

Piramal was disappointed to learn of AbbVie's characterisation to the effect that its materials fell short of the acceptable industry standard. Piramal considered AbbVie's allegations and characterisation to be wholly unfounded.

Background information

Piramal submitted that Sojourn Sevoflurane 100% Inhalation Vapour Liquid (UK PL 29595/0002) was authorised in the UK and twenty seven other EU member states through the decentralised procedure; the UK was the reference member state.

Pursuant to the requirements set out in Article 11 of Directive 2001/83 and the Commission's Guidance on SPC, Piramal, as the marketing authorization holder, must provide information in Section 6.5 on the nature and contents of the primary packaging container of the medicine. Section 6.5 of the SPC read as follows:

> 'Type III, 250 ml amber coloured glass bottles with two component screw cap made up of the outer black phenolic cover and inner translucent low density polyethylene cone. The pack is provided with an LDPE yellow-coloured collar.'

The UK Public Assessment Report gave the following description on the assessment of the container-closure system:

> 'The finished product is supplied in Type III, 250 ml amber-coloured, glass bottles, with two component screw caps made up of outer black phenolic covers and inner translucent low-density polyethylene (LDPE) cones. The pack is provided with an LDPE yellow-coloured collar.
>
> Satisfactory specifications and Certificates of Analysis for all packaging material have been provided for all packaging used. All primary packaging complies with the requirements of Directive 2002/72/EC. In addition, the glass bottles are compliant with the Type III requirements of European Pharmacopoeia monograph 3.2.1 "Glass containers for pharmaceutical use".

In the UK, there were three sevoflurane containing products marketed by AbbVie, Baxter and Piramal as treatment options or alternatives for the induction and maintenance of general anaesthesia in adults and children.

Piramal submitted that the leaflet was used at a European conference in Berlin in May 2015 as a detail aid, and was developed by the marketing team in April 2015 for that purpose. It was used as an informative memory aid for Piramal's sales

personnel and was not intended for publication or distribution in both the UK and EU markets. The information contained in the item reflected an independently conducted research study about glass breakage.

The material provided factual information about the drop test which Piramal had undertaken. The test was conducted in accordance with the standards recommended by the International Safe Transit Association (ISTA) which was accredited by the American National Standards Institute. Testing was performed by a laboratory which was certified by ISTA and accredited by the American Association for Laboratory Accreditation. The test was designed to demonstrate susceptibility (or otherwise robustness) of the primary package constructed from Type III glass to breakage on common hospital floor coverings ie carpet, rubber, linoleum and vinyl composite tile.

The published material provided the test method, the test results and the conclusion.

Nothing in the material purported to convey information about the clinical safety, efficacy or therapeutic use of sevoflurane, nor was a comparator product referred to either expressly or by implication.

New data had since become available and Piramal decided to withdraw the item. A new version would be developed to take account of the new data to ensure that the information reflected the current and up-to-date scientific development. Piramal stated that it informed AbbVie about its decision in November 2015.

Although the material had been subject to Piramal's internal review process, it had never been published or distributed or otherwise used externally in the UK market, nor had Piramal consented to its use by any third party, including its agents, contractors etc.

Piramal submitted that it was therefore surprised and concerned to learn from AbbVie that the material had come into the possession of individuals in the UK outside of Piramal as it had never intended to release the leaflet for external use. Piramal noted that AbbVie had not responded to its repeated requests for information on how it came into possession of the leaflet. Copies of correspondence with AbbVie were provided.

Piramal submitted that AbbVie's allegations therefore concerned material which had either been or was currently being withdrawn globally for reasons that were unrelated to the complaint, and which had never been circulated outside Piramal in the UK with its consent and which was the subject of a possible legal action arising from the unauthorised disclosure of the materials to a third party.

The allegedly promotional nature of the materials

Piramal submitted that AbbVie had consistently objected to the leaflet being used because in its view it was in breach of various clauses of the Code and the relevant guidance published by the MHRA.

(i) Packaging promotion

Piramal submitted that the leaflet did not promote sevoflurane; it had been prepared to factually describe the quality of the primary packaging material used. It could not be viewed as promotional by conveying the effect of promoting or inducing the prescription, supply, sale or consumption of Piramal's sevoflurane.

The position of the Code was consistent with that set out in Title VIII of Directive 2001/83 with regard to what was considered to be advertising. Advertising of medicines included any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicines. As the Court of Justice of the EU articulated in its decision in the Merck Sharp & Dohme Case (C-316/09), the key basis for distinguishing non-promotional information from advertising was the purpose of the communication. As soon as the communication was intended to promote the prescription, supply, sale or consumption of medicines, it would qualify as advertising.

Piramal submitted that the leaflet provided factual information about the primary packaging used for containing the liquid sevoflurane, consistent with Section 6.5 of the SPC.

The item focussed on the provision of additional factual information about the packaging material used to safely contain and preserve the quality and integrity of sevoflurane. If provision of information on primary packaging was properly characterised as promotion, Piramal accepted that the material was promotional in nature in respect of the primary packaging. However, it did not promote a medicine as envisaged by the Code and in the manner that had been interpreted by the courts in accordance with applicable legislation, as discussed below.

In a broader context, according to the established case-law of the European Court (Novo Nordisk Case C-249/09), claims in advertisements for health professionals who had a higher level of scientific knowledge than the public, did not have to be 'included in or be derivable from' information in the SPC. They could also contain additional information provided that the claims:

a) confirmed or clarified and were compatible with the details in the SPC and did not distort the latter;
b) were not misleading and encouraged the rational use of the medicine by presenting it objectively and without exaggerating its properties (see below) and
c) were accurate, up-to-date, verifiable and sufficiently complete to enable the health professional to form his/her own opinion of the therapeutic value of the medicine.

Even if the leaflet was considered as promotional or advertising as suggested by AbbVie, Piramal denied that it breached the Code and the UK Advertising Regulations that sought to implement the requirements in Directive 2001/83/EC. In that case, the leaflet complied with the particulars listed in the

approved SPC. Moreover, nothing in the material encouraged the irrational use of a medicine by not presenting the nature of the primary packaging objectively or otherwise exaggerating the properties of the packaging material, nor could the content of the material be considered misleading.

For the above reasons, as a general matter, Piramal submitted that it could not identify a proper factual basis to suggest that the material was in breach of the Code or the UK Advertising Regulations.

(ii) 'Promotion' under Clause 1.2 of the Code and applicable law

Consistent with the position set out in EU law, the term 'promotion' was defined in Clause 1.2 as:

> 'any activity undertaken by a pharmaceutical company or with its authority which promotes the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines'.

Having regard to the general EU law position, Piramal now provided reasons as to why the leaflet was not considered to be promotion of a medicine within the context of the Code.

Piramal submitted that as a preliminary point, and without prejudice to the specific points made herein the leaflet could not, on any interpretation, be considered promotional within the meaning of Clause 1.2, as it was not made available to UK health professionals by Piramal or with its authority. As explained, it had never been distributed in the UK. Piramal submitted that even if it had been so distributed in the UK as alleged by AbbVie (and Piramal respectfully disagreed), there was no proper basis to suggest that it breached the requirements set out in the Code or the UK Advertising Regulations.

Clause 1.2 explicitly stated that 'promotion' did not include:

> 'factual, accurate, informative announcements and reference material concerning licensed medicines and relating, for example, to pack changes, adverse reaction warnings, trade catalogues and price lists, provided they include no product claims'

Whilst the term 'product claims' was not defined in the Code, the MHRA Blue Guide provided that a 'product claim' was:

> 'anything or any activity which was intended to encourage prescription or supply by healthcare professionals and use of medicines by the general public, generally by means of highlighting qualities of *the medicine*' (emphasis added).

Given the Code could not be applied or otherwise interpreted outside of the statutory framework, the 'product claim' referred to in Clause 1.2 ought to be considered as a 'product claim' for a medicine. In that case, the material did not seek to promote the therapeutic value, safety or efficacy of a medicine. Instead, it highlighted the qualities of packaging rather than sevoflurane as a therapeutic agent.

The claims (to which AbbVie had consistently objected) related to the nature and the quality of glass packaging, not a medicine. The item accordingly came within the exclusion contemplated by Clause 1.2.

Piramal agreed with AbbVie to the extent that the 'totality of the information' contained in the leaflet must be considered to inform an assessment of whether it had a promotional intent. Piramal also reiterated and emphasised its submission above that its intention underlying the production of the leaflet was to detail the quality of a particular form of packaging, rather than to make claims about the therapeutic value of a medicine.

Piramal rejected AbbVie's allegations that, by not including certain information which was required in connection with the promotion of a medicine, Piramal had breached Clauses 4.2, 4.9 and 4.10.

Piramal reiterated that in its view the leaflet could not be construed as promotion of sevoflurane. Piramal submitted that since the leaflet did not constitute promotional material of the kind that the Code sought to address, it was not obliged to include the information specified in Clause 4.

Piramal submitted that it was mindful of AbbVie's observations that some, but not all, of the information specified in Clauses 4.2, 4.9 and 4.10 had been included in the material. However, the voluntary inclusion of information stipulated under Clause 4 did not render the item promotional within the meaning of the Code and trigger the need to comply with the requirement of the Code to include all such information, given that the leaflet focussed on the packaging and not the medicine.

Piramal noted AbbVie's allegation that it had failed to maintain high standards as required under Clause 9.1.

Piramal stated that notwithstanding its view that it had not breached the Code and that the leaflet at issue did not constitute promotion within the meaning of the Code, it further noted that the supplementary information to Clause 9 indicated that the clause was intended to ensure that aspects such as sexual imagery or emoticons did not form part of medicine advertising, which attracted a higher standard than that of general commodity advertising. Piramal queried the validity of AbbVie's assessment on the applicability of Clause 9 to this case.

Piramal refuted that it had brought the industry into disrepute, contrary to Clause 2. Piramal submitted that AbbVie's allegation was plainly vexatious and wholly unfounded.

Piramal noted that a breach of Clause 2 was consistently reserved for behaviour and activities that were particularly egregious of the Code's

requirements and therefore attracted particular censure. In light of the totality of facts and circumstances in this case, Piramal submitted that a finding of a breach of Clause 2 was not warranted, nor would such a finding, in its view, be proportionate.

Piramal submitted that it fully appreciated and respected its obligations under the Code and applicable legislation with respect to promotion of sevoflurane. However, the leaflet did not constitute an advertisement of a medicine within the meaning of the Code and applicable legislation. The material provided specific information about the nature and quality of the primary packaging material based on a particular type of glass. The allegations made by AbbVie were therefore unfounded and should be dismissed.

Piramal submitted that for the reasons given above, the item was acceptable for the purpose of providing factual information about the glass used as primary packaging. Piramal had identified no proper basis to suggest that the material (even if it was distributed for use in the UK) breached the Code and the UK Advertising Regulations.

In keeping with its legal, regulatory and ethical obligations, Piramal noted that, in spite of telling AbbVie about its decision to withdraw the material, AbbVie submitted the complaint thereby expending the PMCPA's resources on investigating a case that would have no practical consequences and where the allegations were unfounded.

For the reasons given above, Piramal's submitted that AbbVie's complaint was baseless. Accordingly, Piramal requested that the Panel consider holding AbbVie fully accountable under Paragraph 7.2 of the Constitution and Procedure to pay an administrative charge for each matter alleged, but ruled by the Panel not to be in breach of the Code.

In response to a request for further information, Piramal referred to inter-company correspondence in which it informed AbbVie that the leaflet was being updated and as soon as the revision was complete, the revised version would replace the current piece in the near future.

Piramal stated that the leaflet was first used at a European conference in Berlin in May 2015 and had also been used in the UK. The leaflet has been withdrawn from use and external distribution in November 2015.

In response to a request for further information, Piramal apologized that its previous responses might not have fully addressed the Panel's request and appeared to be conflicting or unclear; it might have been in part due to its misunderstanding of the extent to which the Panel was concerned with use of the materials in question outside of the UK. Piramal clarified that the leaflet was developed for multi-country use and not specifically for use in the UK. Piramal further clarified that its only two products on the UK market were both inhaled anaesthetics used exclusively in secondary care and as a consequence its UK organization was very small and so was its team that interacted directly with UK health professionals or organizations. With such a small team, Piramal was very confident that instructions about use or non-use of materials were complied with and declarations from both team members supporting their use of the materials in question were provided.

Piramal submitted that the leaflet was last used in the UK in November 2015. Declaration of Piramal's UK country manager and regional manager received on 10 March 2016 regarding the use of the leaflet in the UK and an email from Piramal's marketing manager to the UK country manager, dated 11 December 2015, instructing him that none of the materials should be used, were provided.

Piramal hoped that the explanation clarified the position regarding use and withdrawal of the material in the UK, and submitted that every effort was made to ensure that the leaflet was removed from use in the UK to the extent it was able to once concerns relating to its use were raised by AbbVie.

Piramal submitted that it would evaluate whether the leaflet should be revised and subsequently used in the UK; the revised material would be in full compliance with UK law governing advertising of medicinal products and the Code and be consistent with the Panel's rulings.

PANEL RULING

The Panel noted that both in its initial response and in response to a request for further information, Piramal had stated that the leaflet at issue was used in the UK. It was thus subject to the Code. Declarations from members of staff showed that the material was last used in November 2015. Although the leaflet had been withdrawn in November 2015, during the course of inter-company dialogue that fact had not been made clear to AbbVie. From inter-company dialogue it appeared that the leaflet was being revised and that the revised version would replace the current version in due course. Indeed Piramal stated that the leaflet had been withdrawn to update its content in response to the Authority. The Panel thus considered that when AbbVie complained to the PMCPA in December 2015, it had reason to believe that the leaflet was still in use and that inter-company dialogue had been unsuccessful.

The Panel noted Piramal's submission that the leaflet was not promotional because it focussed on the packaging of sevoflurane and did not seek to promote the therapeutic value, safety or efficacy of the medicine. The Panel considered, however, that a licensed medicine was the sum of its parts, and packaging (in this case the robustness of the glass bottles) might be a reason why a health professional or other relevant decision maker would choose one medicine over another. Reference was made to Piramal's sevoflurane 5 year shelf life. The Panel noted in that regard the application of Clause 7, Information, Claims and Comparisons, was not limited to information or claims of a medical or scientific nature. In the Panel's view, a claim about any aspect of a medicine would be caught by the definition of promotion. The Panel thus considered

that the leaflet, which was developed for use at a European conference in Berlin but had also been used with customers and internally in the UK, promoted sevoflurane.

The Panel noted that AbbVie had alleged breaches of the MHRA Blue Guide. The Panel could only make rulings on the Code.

The Panel noted that Clause 4.2 required promotional material to include, as part of the prescribing information, the cost (excluding VAT) of a medicine. The Panel noted that the SPC and patient information leaflet appeared to have been reproduced on pages 5 and 6 of the leaflet; the cost of sevoflurane was not included. The Panel noted that a breach of Clause 4.2 had been alleged. Clause 4.2 listed the components of prescribing information and it was a requirement of Clause 4.1 that such be provided. As the cost of sevoflurane had not been stated the Panel ruled a breach of Clause 4.1.

Clause 4.9 stated that all promotional material must include the prominent statement 'Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to [relevant pharmaceutical company]'. This statement did not appear in the leaflet at issue and the Panel therefore ruled a breach of Clause 4.9.

Similarly the Panel ruled a breach of Clause 4.10 as the leaflet did not include the date on which it was drawn up or last revised as required by that clause.

The Panel noted its rulings above and considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted its ruling of a breach of Clause 4.9 above and although it was concerned that the adverse event reporting statement had not been included in the leaflet, it considered that an additional ruling of a breach of Clause 2 would be disproportionate. A ruling of a breach of Clause 2 was used as a sign of particular censure and reserved for such use. No breach of that clause was ruled.

Complaint received **22 December 2015**

Case completed **6 May 2016**