CASE AUTH/2046/9/07 *NO BREACH OF THE CODE*

TAKEDA v GLAXOSMITHKLINE

Press release on global corporate website

Takeda alleged that a press release placed on GlaxoSmithKline's global corporate website on 30 July which was headed 'GlaxoSmithKline presents Avandia data to [Food and Drugs Administration] FDA' was in breach of the Code including Clause 2. It was dated 30 July, bore the address for GlaxoSmithKline US and summarised the data regarding Avandia and increased risk of cardiovascular ischaemic events. The data was presented to an advisory committee of the FDA on 30 July 2007. The press release stated that GlaxoSmithKline believed that a full and scientific evaluation of all the data did not confirm the safety questions originally raised. The press release included important safety information about Avandia which referred to the FDA and company contact details for the UK and US media.

Takeda was concerned that the press release was placed on both the global website (www.gsk.com) as well as the US website (www.usa.gsk.com). The global website was however specifically directed towards a UK audience as evidenced by the following: the website was registered in the UK with US citizens being directed to a US website; there was no mention of any UK-specific website on the home page; for career opportunities in the UK one was directed to the global website; a Google search for GSK.co.uk directed one to www.gsk.com and the London Stock Exchange Share Price was given on the home page.

The press release was clearly directed towards a UK audience as at the end of it there were three London contact telephone numbers.

Thus GlaxoSmithKline in the UK was responsible and accountable for any information placed on the global website by the US affiliate.

Takeda did not accept GlaxoSmithKline's submission that the press release related to 'financial information' as there was no mention of any financial information. During inter-company dialogue the GlaxoSmithKline website was amended such that the information was 'labelled' as information for business journalists and analysts/investors. Takeda did not accept this and believed that all material in press releases should be in line with the Code and the spirit of the Code.

The Panel noted that the press release had been placed on the corporate website by GlaxoSmithKline US. It had been sent to UK financial media. The press release covered the FDA Advisory Committee which had occurred in the US and related to the US regulatory authorities. The data would obviously be of interest worldwide. The important safety information provided at the end of the press release related to the use of Avandia in the US.
The Panel noted that there had originally been two closely similar versions of the press release on the website. That accessed via 'Avandia News' did not originally feature a heading stating the intended audience. This was remedied by GlaxoSmithKline during inter-company dialogue.

GlaxoSmithKline was a UK headquartered company. It was not unreasonable for UK corporate contact details for the UK media to be included on the press release. The press release was issued in the UK to business/financial journalists, investors and analysts only. The issue would be relevant to such an audience.

The Panel noted that information or promotional material about prescription only medicines which was placed on the Internet outside the UK would be regarded as coming within the scope of the Code if it was placed there by a UK company or at the instigation or with the authority of such a company and if it made specific reference to the availability or use of the medicine in the UK.

The Panel considered that information about a prescription only medicine had been placed on the Internet by a UK company or an affiliate or at the instigation or with the authority of such a company. The Panel noted that the press release at issue referred to Avandia which was available in the UK. It included general information about Avandia but did not specifically refer to its availability or use in the UK. On the contrary the inclusion of important safety information related to the use of the product in the US. The press release related to a particular meeting of the FDA Advisory Committee and was issued as a corporate press release. The Panel did not consider that the press release came within the scope of the Code as alleged. The other allegations made by Takeda were as a consequence ruled not to be in breach of the Code, including of Clause 2.

Takeda UK Limited complained about a press release concerning Avandia (rosiglitazone) placed on the GlaxoSmithKline global corporate website on 30 July. Takeda supplied Actos (pioglitazone).

The press release was headed 'GlaxoSmithKline presents Avandia data to [Food and Drugs Administration] FDA'. It was dated 30 July and was issued on paper bearing the address for GlaxoSmithKline US. It summarised the Avandia scientific evidence available to address the question of increased risk of cardiovascular ischaemic events. The

data was presented to an advisory committee of the FDA on 30 July 2007. The press release stated that GlaxoSmithKline believed that a full and scientific evaluation of all the data did not confirm the safety questions originally raised. The press release included important safety information about Avandia which referred to the FDA and contact details for the UK media and the US media.

COMPLAINT

Takeda alleged that the press release was in breach of the Code. In addition, as the press release was placed on the Internet with global (which by definition also included European) access, it could also be considered to be in breach of the European Federation of Pharmaceutical Industries and Associations (EFPIA) Code of Practice on the Promotion of Medicines, as some of the statements and claims made within it were not in line with the Avandia summary of product characteristics (SPC).

'Avandia is the most widely studied oral anti-diabetic medicine for the treatment of Type 2 diabetes. The extensive data base for Avandia includes…'

The press release referred to an 'extensive data base' which included 116 clinical trials in over 52,000 patients. Of the 116 clinical trials mentioned, 113 were neither named nor referenced. For the three that were, Takeda noted that DREAM was conducted in patients who had raised blood glucose levels but were not medically classified as having type 2 diabetes, (and so not in accordance with the Avandia SPC), ADOPT was conducted in newly diagnosed type 2 diabetics who were drug naïve (so again, not in accordance with the Avandia SPC) and RECORD, which was described in the press release as 'specifically studying cardiovascular effects' only had an interim analysis currently available, so no final conclusions could be drawn from it. Similarly, the 'Study in a high risk cardiovascular-risk population: PPAR' was conducted in patients with metabolic syndrome (so once again not in accordance with the Avandia SPC).

Takeda alleged that the lack of referencing and the inclusion of studies outside the licence for Avandia which as monotherapy was indicated for type 2 diabetics who were inadequately controlled by diet and exercise, and for whom metformin was inappropriate because of contraindication or intolerance, rendered any claims with respect to 'The extensive database…' in breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.6 and 7.9.

'Across the extensive dataset for Avandia, there is no consistent or systematic evidence that Avandia increases the risk of heart attack or cardiovascular death in comparison with other antidiabetic medicines'

Takeda alleged that this claim was not consistent with the Avandia SPC which mentioned under section 4.8 Undesirable effects, cardiac ischaemia as being a common side effect for rosiglitazone monotherapy, rosiglitazone in combination with metformin, rosiglitazone with sulphonyurea, and rosiglitazone with metformin and a sulphonyurea. Further there was also a statement that 'In a retrospective analysis of data from pooled clinical studies, the overall incidence of events typically associated with cardiac ischaemia was higher for rosiglitazone containing regimens 1.99% versus comparators, 1.51%'.

In the discussion at the FDA Advisory Committee on the 30 July 2007, the Committee after reviewing all the data from the FDA as well as that provided by GlaxoSmithKline voted 20:3 that in its opinion rosiglitazone was associated with an increase of myocardial ischaemia and infarction compared to placebo. Importantly, the press release made no mention of any comparison between rosiglitazone with placebo, and only referred to 'antidiabetic medicines', which as noted above was false, misleading and did not reflect all the available evidence. Breaches of Clauses 7.2 and 7.3 were alleged.

Consequently the above claim regarding cardiovascular safety was inconsistent with the SPC, was not accurate, balanced, fair, objective, was misleading, not capable of substantiation, did not give references, did not reflect all the evidence available regarding side effects and did not encourage the rational use of Avandia in breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9 and 7.10. In addition Takeda alleged that the claim was in breach of Clause 2.

Following the above claim, specific mention was made of cardiovascular events with which Takeda also had concerns.

'Myocardial ischaemia: There was no statistically significant increase in myocardial ischaemia in ADOPT, GlaxoSmithKline's long term comparator study.'

This was just one study, yet the extensive database referred to above contained 116 clinical trials for which no mention was made. The claim in any case relating to myocardial ischaemia, was contrary to the information given in section 4.8 of the SPC (as referred to above). The ADOPT study was conducted in newly diagnosed type 2 diabetics who were treatment naïve and so not in accordance with the Avandia SPC. In addition, ADOPT was neither specifically designed nor powered to evaluate myocardial ischaemia nor indeed any other cardiovascular outcome. Breaches of Clauses 3.2, 7.2, 7.3, 7.4, 7.9 and 7.10 were alleged.

'Heart attack: the number of heart attacks across the sources of data is small, the data are inconsistent, and the totality of the evidence does not show a difference between Avandia and the most commonly prescribed anti-diabetic agents. In three epidemiological database studies, the risk of heart attack was similar for Avandia compared to the other anti-diabetic agents, and in one database study comparing Avandia to Actos there was no difference.'

The comparison between Avandia and Actos was incorrect because in the documents provided by the

FDA, and indeed in GlaxoSmithKline's own submission to the FDA, Takeda noted that there was a study which showed that Actos was associated with a lower risk of heart attack compared to Avandia. Takeda alleged that the claim was false, misleading and disparaged other medicines in breach of Clauses 7.2, 7.3, 7.4, 7.6 and 8.1.

'CV death:the long-term trials provide no evidence of increased CV death or all cause mortality with Avandia compared to the most commonly prescribed oral antidiabetics.'

This was in contrast to the findings and conclusions in the New England Journal of Medicine meta-analysis which included 42 studies with a duration of more than 24 weeks. In this peer-reviewed journal the authors stated in the results section that 'in the rosiglitazone group as compared with the control group, the odds ratio for death from cardiovascular causes was 1.64 (95%Cl 0.92 to 2.74; P= 0.06) and that this achieved borderline significance'. So although GlaxoSmithKline might state that there was no increase in CV death, it did not reflect the conclusions of health professionals working in the field of diabetes, and the claim did not refer to rosiglitazone's increased risk of cardiac ischaemia compared with placebo as referred to in the SPC. Breaches of Clauses 3.2, 7.2, 7.3 and 7.4 were alleged.

'Stroke: Across the data sources, fewer strokes are observed with Avandia than with other anti-diabetic medicines, although the differences in the long-term trials were not statistically significant.'

Takeda did not know of any rosiglitazone studies where the incidence of stroke had been evaluated as a primary endpoint. Claims regarding the beneficial effects of Avandia in this respect therefore could not be made especially when it would seem according to the press release that the differences in long-term trials were 'not statistically significant'. This was inaccurate, false and misleading. Breaches of Clauses 3.2, 7.2, 7.3 and 7.4 were alleged.

'GlaxoSmithKline continues to support Avandia as safe and effective when used appropriately'.

The Code cautioned the use of the word 'safe' and stated that it must not be used without qualification (Clause 7.9). Describing Avandia as 'safe' was a claim that could not be made in the context of an FDA Advisory Committee meeting which was arranged specifically to look at its cardiovascular safety and where most (20:3) of the committee voted that rosiglitazone was associated with an increased risk of cardiac ischaemia. Furthermore as the information in this press release was so misleading, inaccurate and biased, Takeda questioned whether it would be possible for healthcare providers or patients who read it to use Avandia 'appropriately' based on the information given, which did not encourage the rational use of a medicine. Breaches of Clauses 2, 7.9 and 7.10 were alleged.

The last part of the press release contained:

'Important Safety Information for Avandia …'

Takeda stated that this section was specifically directed towards patients and was not in line with either the UK or the European patient information leaflet (PIL) for Avandia. In particular Takeda noted that it did not list all the possible side effects as given in section 4 of the PIL. At the very least it should list the thirteen 'very common side effects' from the PIL, and more specifically the 'very common cardiovascular side effects' which included 'chest pain resulting from reduced blood supply to the heart muscle' as well as a 'small increase in total cholesterol levels' and 'increased levels of fats in the blood'.

Breaches of Clauses 3.2, 7.2, 7.9 and 7.10 were alleged. Takeda further alleged that as this section was directed towards patients then it was also in breach of Clause 2.

Finally as this piece clearly promoted Avandia to patients in the UK and Europe, it was in breach of Clauses 20.1 and 20.2 not least as it was misleading with respect to the safety of the product.

Takeda was concerned that the press release was placed on both the global website (www.gsk.com) as well as the US website (www.usa.gsk.com). The global website was however specifically directed towards a UK audience as evidenced by the following: the website was registered in the UK with US citizens being directed to a US website; there was no mention of any UK-specific website on the home page; for career opportunities in the UK in GlaxoSmithKline one was directed to the global website; a Google search for GSK.co.uk directed one to www.gsk.com and the London Stock Exchange Share Price was given on the home page.

Regarding the press release itself, clearly the announcement was directed towards a UK audience as at the end of it there were three London telephone numbers given for the UK media to contact for further information.

Clause 21.2 stated that 'Information or promotional material about medicines covered by Clause 21.1 above which is placed on the Internet outside the UK will be regarded as coming within the scope of the Code if it was placed there by a UK company or an affiliate of the UK company. Thus GlaxoSmithKline in the UK was responsible and accountable for any information placed on the global website by the US affiliate.

Finally Takeda noted the following case precedents: Case AUTH/1937/1/07 where no breach was ruled as it was made quite clear that the information provided on the website was not directed towards a UK audience and Case AUTH/1527/10/03 where the Panel stated that 'If such material had been placed on the website by an affiliate of a UK company it could nonetheless, be caught by Clause 21.2 and thus come within the scope of the Code.'

Takeda did not accept GlaxoSmithKline's argument that the press release related to 'financial information' but as there was no mention of any financial

information at all. During inter-company dialogue the GlaxoSmithKline website was amended such that the information was 'labelled' as information for business journalists and analysts/investors. Takeda did not accept this and believed that all material in press releases should comply with the letter and spirit of the Code.

RESPONSE

GlaxoSmithKline strongly disagreed that this press release breached the ABPI Code or the EFPIA Code. The press release was entitled 'GlaxoSmithKline presents Avandia data to FDA' and was a true, fair and balanced summary, to the business and financial media, of the company's presentation to an FDA Advisory Committee meeting on Avandia in the US and was clearly stated as such. The presentation was publicly available on the FDA's website. GlaxoSmithKline provided two versions of this reference; one was what was seen on the computer screen while the other was what was printed when a hard copy was requested using standard print function. The difference between these two was that GlaxoSmithKline's logo and disclaimer did not appear on the latter.

Background

GlaxoSmithKline was committed to patient safety and the full transparency of its scientific information which was publicly available on the Clinical Trials Register (CTR) on the GlaxoSmithKline corporate website.

In 2006, as part of ongoing safety surveillance, GlaxoSmithKline pro-actively conducted a meta-analysis to investigate whether rosiglitazone might be associated with myocardial ischaemia. A very broad definition of myocardial ischaemia that included events such as shortness of breath and chest pain was used and the results suggested an increased risk of myocardial ischaemia. In order to further test this hypothesis GlaxoSmithKline conducted a large observational study in which the risk associated with rosiglitazone was similar to other antidiabetic agents. These data were submitted to the appropriate regulatory authorities and were reflected in the European SPC since October 2006.

Nissen and Wolski (2007) accessed GlaxoSmithKline's CTR database and conducted a meta-analysis of some of the data. The paper, published in the New England Journal of Medicine, generated an enormous amount of media interest, including the financial media. This was followed by editorials and other publications which continued to generate intense media interest. The intense media interest brought forward a planned review of rosiglitazone by the FDA, as the data was conflicting and inconsistent. This became a spotlight for lay, healthcare and financial media.

Meta-analysis was only one method used to assess the clinical data and the results were subject to significant confounding, particularly in this case when glycaemic endpoint studies were used to test a cardiovascular hypothesis, utilising predominantly adverse event reports. GlaxoSmithKline conducted a range of other studies and analyses to answer questions raised from the meta-analyses. As the results of these studies were significantly at odds with the meta-analysis data, their publication was considered of material importance with respect to the GlaxoSmithKline share price.

The press release was focused on rosiglitazone and was an accurate summary of the data presented to the FDA Advisory Committee meeting.

Over 50% of GlaxoSmithKline's investor base was in the UK market, and so there was a considerable investor and press following of the company. The company communicated with investors/press through a variety of means, including dissemination of press releases and stock exchange announcements.

If an announcement was deemed 'material' it would be issued via the London and New York stock exchanges. If it was not deemed 'material' but was deemed newsworthy (as in this case) a press release would be issued. Press releases were issued to subscribed lists of journalists/investors and analysts.

Whilst there were no formal disclosure obligations surrounding a press release, best practice ensured that company followers (investors, analysts and journalists) could access the information. Newswire reporting helped GlaxoSmithKline to disseminate information widely, but this was editorialised. To ensure that GlaxoSmithKline's position, in full, was available it published the press releases on the corporate website.

The issues surrounding Avandia had been material to the company, as evidenced by the fall in market value and share price reaction since the publication of the Nissen and Wolski analysis in May. At the time of this press release, the shares had fallen 17% with a resultant loss of approximately £12bn in market capitalisation.

Given this background, the FDA Advisory Committee meeting was critical, not least as there was a vote to remove the product from the market. Beforehand, and on the day of the meeting, there was significant interest from investors and journalists on the content and possible outcomes of the meeting, including specifically what GlaxoSmithKline would present.

The Advisory Committee meeting was clearly newsworthy for the company and of business relevance. Therefore a press release was issued to business journalists to provide them with a summary of information that was to be presented by the company at the meeting. The resulting vote from the meeting was issued as a stock exchange announcement later the same day.

In the UK, GlaxoSmithKline confirmed that the press release was issued to business/financial journalists, investors and analysts only. The GlaxoSmithKline 'UK' media contacts identified on the press release were responsible for managing communication with primarily business/financial journalists.

The press release was placed on the GlaxoSmithKline corporate website by the US arm of the company, on 30

July 2007 after 13.36hrs UK time (in advance of the Advisory Committee meeting), to ensure that company followers (investors, analysts and financial journalists) were able to access the information. This ensured that GlaxoSmithKline's position, in full, was available. The events covered in the press release occurred in the US and were specific to the US regulatory authorities. The press release was prefixed with Philadelphia and used the GlaxoSmithKline ticker on the New York Stock Exchange. The corporate website, www.gsk.com, had the following statement: 'GlaxoSmithKline is quoted on the London and New York stock exchanges. The company's shares are listed on the New York Stock Exchange in the form of American Depositary Shares (ADSs) and these are evidenced by American Depositary Receipts (ADRs), each one of which represents two ordinary shares.'

The intended audience was financial and business media – this was stated across the top of the press release when accessed from the Media Centre, and as noted by Takeda, during inter-company dialogue, GlaxoSmithKline UK requested its corporate colleagues to further clarify the header of the press release when accessed via 'Avandia News' in the news section of www.gsk.com, in an attempt to resolve this matter at an inter-company level. The header read 'The information on this page is intended for **business journalists and analysts/investors** [emphasis added]. Avandia is in the news because of an article in the New England Journal of Medicine about cardiovascular risk' and UK medical and consumer media were not directed towards the press release by e-alerts or otherwise. UK health professionals were not alerted to it. UK healthcare and lay media were the responsibility of GlaxoSmithKline UK which took no part in the dissemination or posting of this corporate release. No UK medical or consumer media journalist received the press release either proactively or reactively

As mentioned above, there were two ways to access the press release on the GlaxoSmithKline corporate website, via the 'Media Centre' or via 'Avandia News'. The Media Centre front page and the press release (when viewed from this route) had an alert at the top stating 'These press releases are intended for business journalists and analysts/ investors. Please note that these releases may not have been issued in every market in which GlaxoSmithKline operates'. The Avandia News version did not have this alert, but the wording cited above was added during inter-company dialogue to further clarify the intended audience for the press release when accessed via the Avandia News page.

GlaxoSmithKline submitted that a press release clearly intended for business and financial media was not promotional and as such was not subject to the promotional aspects of the Code. It was fair and balanced and therefore fulfilled the requirements of the Code regarding company press releases and ethical requirements. GlaxoSmithKline reiterated that this press release had never been used promotionally.

The website to which the press release was posted was the GlaxoSmithKline global corporate website, which contained information about worldwide events. The press release was clearly intended for the media and was therefore allowable under Clause 20.2. This was in common with Takeda's own practice on its global website www.takeda.com. As such, this was not a promotional item and did not contain claims. The GlaxoSmithKline corporate site also complied with Clause 21. The press release was not promotional and so Clause 20.2 was relevant in this instance. Whilst the press release was examined by GlaxoSmithKline UK (as required by the Code in compliance with the supplementary information to Clauses 20.2 and 14.3), as GlaxoSmithKline was a UK headquartered legal entity, it did not specifically refer to the availability or use of the medicine in the UK and therefore was not considered to come within the scope of the Code.

GlaxoSmithKline noted that the supplementary information to Clause 20.2 stated that business releases should identify the business importance of the information. Given the high profile nature of the discussions of the Avandia cardiovascular discussions in the lay and business press and its effect on the GlaxoSmithKline share price, it believed the business importance was self evident.

This was clearly a corporate press release referring to events in the US. These events were in the public domain and the data mentioned in the press release was presented to the US regulatory body. As the press release reported on data presented to the US regulatory body, it was appropriate that it was based on the US licence which formed the reference point for this important news item; in that regard Takeda's reference to the European SPC was erroneous.

GlaxoSmithKline disagreed with the allegation that the press release did not comply with the EFPIA Code. The EFPIA Code did not cover non-promotional, general information about companies (such as information directed to investors or to current/prospective employees), including financial data, descriptions of research and development programmes, and discussion of regulatory developments affecting the company and its products. Also, in the EFPIA Code, Guidelines for Internet Websites Available to Healthcare Professionals, Patients and the Public in the EU, it stated 'General information on the company. Websites may contain information that would be of interest to investors, the news media and the general public, including financial data, descriptions of research and development programmes, discussion of regulatory developments affecting the company and its products, information for prospective employees, etc. The content of this information is not regulated by these guidelines or provisions of medicines advertising law.'

Given the above, GlaxoSmithKline submitted that the release was not promotional material under the scope of the Code. Additionally the Code made provision for such information to be made available and reviewed to ensure that it was balanced. As such GlaxoSmithKline respectfully suggested that there was no prima facie case to answer.

Notwithstanding its position that there was no prima facie case, GlaxoSmithKline addressed each of Takeda's

points individually. However in the context of a press release for business and financial media these statements could not be viewed under the Code in the same way as promotional claims, they were a balanced and truthful reflection of a company's presentation of data to the US regulatory authorities that had been examined in accordance with the supplementary information to Clauses 20.2 and 14.3 in the knowledge that the release dealt with a significant corporate newsworthy event occurring in the US with a probable material impact on the share price.

'Avandia is the most widely studied oral anti-diabetic medicine for the treatment of Type 2 diabetes. The extensive data base for Avandia includes…'

All of the 116 trials cited in the press release were publicly accessible on the GlaxoSmithKline CTR: http://ctr.gsk.co.uk. As no promotional claims were made, it was not necessary to cite each study individually as would be the case with promotional material. Given the focus of the FDA's review of cardiovascular outcome data which could only be fully determined through long-term studies, it was entirely appropriate that DREAM, ADOPT and RECORD be mentioned in the press release as they contained important safety data pertinent to the FDA hearing. The trials mentioned were an accurate reflection of how the data was presented at the FDA hearing. In the context of a safety discussion, it was important to consider the totality of the data. The regulatory authorities explicitly asked that all data be submitted for review including studies conducted on out of licence populations, such as DREAM.

The labelling for any medicine reflected the totality of the data regarding safety. For example, a study that included patients with heart failure was reflected in the SPC and was out of licence, yet contributed important information to the SPC and formed the basis of the contraindication in heart failure in Europe and the different warnings and contraindications that appeared in the US labelling.

GlaxoSmithKline noted that the ADOPT study, referred to by Takeda, was not an out of licence population in the US where the FDA Advisory Committee occurred. The US label indications were as follows

'Avandia is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus.

- Avandia is indicated as monotherapy.
- Avandia is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycaemic control. For patients inadequately controlled with a maximum dose of a sulfonylurea or metformin, Avandia should be added to, rather than substituted for, a sulfonylurea or metformin.
- Avandia is also indicated for use in combination with a sulfonylurea plus metformin when diet, exercise, and both agents do not result in adequate glycaemic control.'

For completeness GlaxoSmithKline provided the US prescribing information for Avandia.

Therefore GlaxoSmithKline strongly disagreed that this statement in the context of a press release relating directly to a company presentation to the US regulatory body that was in the public domain was in any way a breach of the multiple alleged breaches of the Code.

'Across the extensive dataset for Avandia, there is no consistent or systematic evidence that Avandia increases the risk of heart attack or cardiovascular death in comparison with other antidiabetic medicines'

GlaxoSmithKline disagreed with Takeda's allegation that this was a claim; it was a statement in an important and relevant press release to business media.

The press release was an accurate summary of the data presented and GlaxoSmithKline's position on that data to the FDA Advisory Committee meeting. This meeting focused on the safety data for rosiglitazone. It was important that the data was discussed in terms of the definitions used in clinical trials, from where the data originated. In the clinical trials presented by GlaxoSmithKline, the definition of cardiac ischaemia was broad and included symptoms, such as dyspnoea (shortness of breath). In the GlaxoSmithKline presentation, the number of myocardial infarctions or cardiovascular deaths on rosiglitazone was small, crossed '1' on the Forest plot, and hence was not significant. Therefore based on the data presented this was an acceptable statement to make at the FDA Advisory Committee.

Takeda alleged that this statement was not consistent with the UK SPC. As previously stated this press release was based entirely on events relating to the US and FDA Advisory Committee with share price relevance in the UK and US – it would not therefore be appropriate to base this information on the UK SPC (which differed from the US prescribing information).

Unfortunately Takeda had also selectively quoted and selectively highlighted the Avandia SPC. It had omitted that in section 4.8, with reference to cardiac ischaemia, there was the following note: 'The frequency category for the background incidence of these events, as taken from placebo group data from clinical trials, is 'common".

Comments on the FDA Advisory Committee vote were not included in the press release as its purpose was to summarise the data, and GlaxoSmithKline's position on it, to investors and business journalists that GlaxoSmithKline presented to the FDA Advisory Committee, and as mentioned above was issued before the meeting started. This fulfilled GlaxoSmithKline's corporate obligation to disclose information to investors that the company knew of and which might materially affect its share price. A subsequent stock exchange announcement posted later the same day after the Advisory Committee meeting had finished detailed the results of the Committee's votes and deliberations regarding the cardiovascular position of

Avandia. This reflected the position the Committee took and importantly reflected that the Committee declined to comment on comparative risk of Avandia to other oral anti-diabetic medicines. Takeda did not mention this in its complaint.

GlaxoSmithKline strongly refuted the allegation that the press release did not encourage the rational use of Avandia as the press release was not intended for prescribers, the purpose and source of the data within the press release was clearly stated, the information was a fair and balanced reflection of that data and a subsequent stock exchange announcement the same day detailed the Advisory Committee's findings.

GlaxoSmithKline also noted the following:

- The US licence did not list cardiac ischaemia as a common adverse event. GlaxoSmithKline reiterated that as the press release reported on data presented to the US regulatory body, therefore it was appropriate that it was based on the US licence.
- The FDA Advisory Committee queried whether the available data supported a conclusion that Avandia increased cardiac ischaemic risk in type 2 diabetes mellitus?If it did, was there evidence that this risk was greater than other available therapies for the treatment of type 2 diabetes mellitus?
  It did not vote specifically on myocardial infarction and myocardial ischaemia, but the broader definition as noted above. It did not vote definitively on the second part of the question at that stage. It also noted during the meeting that the comparison to placebo was not as relevant to clinical practice as the comparison to other treatments.
  The minutes stated that many committee members were reluctant to draw conclusions comparing the risk level of Avandia versus other available therapies, until additional [sic] has been reviewed (eg Takeda's study of pioglitazone).
- GlaxoSmithKline's analysis was versus comparator treatments and not placebo and hence comments on placebo were not included in the press release. Therefore it was entirely appropriate for the press release to reflect comparator treatments as it reflected GlaxoSmithKline's presentation of the data.
- The Advisory Committee made recommendations to the FDA. The FDA was currently reviewing the evidence and the deliberations of the Advisory Committee and had not yet decided upon what (if any) action would be taken with regard to labelling in the US.
- With regard to UK regulatory perspective, the Medicines and Healthcare products Regulatory Agency (MHRA) described the increased risk of myocardial infarction and cardiovascular death as 'small' and it stated that 'In September 2006, following a comprehensive review within Europe of the available data from clinical trials, the product information for prescribers and patients was updated to reflect more fully the risk of heart failure and to include a warning about the potential small increased risk of myocardial infarction in patients receiving rosiglitazone compared with those receiving placebo (dummy pills).'

The MHRA, together with EU regulatory agencies, was currently reviewing all the available data for the cardiovascular safety of rosiglitazone and pioglitazone.

Consequently GlaxoSmithKline did not believe that this statement, in the context of the above, breached the Code. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

'Myocardial ischaemia: There was no statistically significant increase in myocardial ischaemia in ADOPT, GlaxoSmithKline's long term comparator study'

GlaxoSmithKline again submitted this was not a claim but a statement made in the appropriate context outlined above.

Of all the trials that had been conducted on rosiglitazone, large scale, long-term clinical trials in patients with the disease were the most scientifically rigorous way of assessing the risk of myocardial ischaemia. ADOPT (A Diabetes Outcome Progression Trial) directly compared both the safety and effectiveness of Avandia with metformin and a sulphonylurea (glibenclamide) – two of the most commonly used medicines to treat type 2 diabetes, in over 4,300 patients studied for up to 6 years. Results showed that the overall risk of serious, cardiovascular events (CV death, myocardial infarction, and stroke, or major adverse cardiovascular events (MACE) endpoint prospectively defined) for patients on Avandia was comparable to metformin and a sulphonylurea (glibenclamide). These data were post-adjudicated by three independent cardiologists. ADOPT showed comparable rates of cardiovascular deaths between the agents under study. Although not powered to assess cardiovascular risk, it was the only trial on rosiglitazone to date that could add significantly to what was known about the safety profile of rosiglitazone. Clearly long-term prospective trials contributed significantly to the information about the safety of medicines. RECORD, which was designed to look at cardiovascular risk, had not reported y*et al*though an interim analysis showed no significant difference in cardiovascular risk compared with metformin or sulphonylureas, except for the well-known risk of cardiac failure, in which rosiglitazone was contraindicated.

In the context of a safety discussion, it was important to include all data sources and specifically long-term trials which provided more robust data on the safety and efficacy of a medicine.

As discussed above the ADOPT study was consistent with the US labelled population, and as such Takeda's reference to the European SPC not relevant.

GlaxoSmithKline did not believe that this statement in the context of a press release outlined above in any

way breached the Code. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

'Heart Attack: the number of heart attacks across the sources of data is small, the data are inconsistent, and the totality of the evidence does not show any difference between Avandia and the most commonly prescribed anti-diabetic agents. In three epidemiological database studies, the risk of heart attack was similar for Avandia compared to the other anti-diabetic agents, and in one database study comparing Avandia to Actos, there was no difference.'

The data were inconsistent which was why the FDA Advisory Committee was called to discuss them. As stated above, the MHRA described the increased risk of myocardial infarction and cardiovascular death as 'small'.

The Nested Case-Control study to which Takeda referred compared rosiglitazone with other anti-diabetic agents excluding pioglitazone, and separately compared pioglitazone with other anti-diabetic agents excluding rosiglitazone. There was no comparison of rosiglitazone with pioglitazone. This study was not a direct comparison of Actos and Avandia as stated by Takeda.

There was only one observational study, the Pharmetrics study, which was submitted to the FDA by GlaxoSmithKline. External sources presented other observational studies which directly compared rosiglitazone and pioglitazone, and showed no difference.

GlaxoSmithKline strongly disagreed that the press release gave false and misleading information regarding other medicines or disparaged other medicines. The press release focused on rosiglitazone. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

'CV death: the long term trials provide no evidence of increase CV death or all cause mortality with Avandia compared to the most commonly prescribed oral antidiabetics'

GlaxoSmithKline disagreed that in the context of a corporate press release relating to a US regulatory process this is a promotional claim under the terms of the Code.

The Nissen and Wolski meta-analysis showed a non-significant difference in the odds ratio for death from cardiovascular causes (95% CI, 0.98-2.74; P=0.06). Takeda erroneously cited this p value as having borderline significance; however independent interpretation and convention would state that no statistical difference was seen. Even using the results of this highly controversial meta-analysis, GlaxoSmithKline was correct to state that there was no evidence of increased CV death. It was important to note some of the methodological issues with this meta-analysis. Of particular importance to cardiovascular death, this meta-analysis did not contain patient level data and so it was not possible to adjudicate the cause of death and, by their own admission, the authors excluded several studies where no cardiovascular events were seen.

The most robust prospective analysis of rosiglitazone with respect to cardiovascular death was conducted by GlaxoSmithKline using adjudicated endpoints from the three long-term rosiglitazone outcome studies, DREAM, ADOPTand RECORD. When more than 14,000 patients across the three studies were evaluated, the hazard ratio for death was 0.84 (0.57-1.22). This data was reviewed as part of the Advisory Committee.

GlaxoSmithKline was extremely disappointed by Takeda's comments regarding the conclusions of health professionals working in the field of diabetes. This could only be anecdotal reports and these unsupported comments could not be seen as a robust interpretation of the entirety of the data as presented to the FDA. Nissen and Wolski had been widely criticised, for example the editor of The Lancet on 2 June 2007 stated that 'Until the results of RECORD are in, it would be premature to overinterpret a meta-analysis that the authors and [New England Journal of Medicine] editorialists all acknowledge contains important weaknesses'. In various letters to the New England Journal of Medicine, health professionals working in the field of diabetes criticised the methodology or conclusions of Nissen and Wolski. Furthermore, the conclusions of the meta-analysis had been disputed in Nature Clinical practice (Gerstein and Yusuf 2007).

To add further context to the discussion, Lago *et al* (2007) assessed the risk of heart failure and cardiovascular death in a meta-analysis of studies which specifically adjudicated cardiovascular endpoints or adverse events and found no difference between rosiglitazone and pioglitazone. 'The risk for congestive heart failure did not differ for rosiglitazone and pioglitazone (1·74, 0·97–3·14, p=0·07). The risk of cardiovascular death did not differ between both drug groups (1·01, 0·73–1·40, p=0·96)'.

GlaxoSmithKline additionally referred back to its response above regarding the absence of any comment on comparison with placebo.

GlaxoSmithKline strongly disagreed that this statement in the context of this press release breached the Code in anyway. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

'Stroke: Across the data sources, fewer strokes are observed with Avandia than with other anti-diabetic medicines, although the differences in the long-term trials were not statistically significant'

As stated previously this was not a promotional claim. This press release represented company data presented

to a FDA advisory committee, therefore it was entirely possible that data would be presented that was not published.

In GlaxoSmithKline's presentation to the FDA, the integrated clinical trials analysis (ICT) showed a significant decrease in stroke with rosiglitazone compared with other anti-diabetic medicines. When these data were integrated with data from DREAM and ADOPT, a numerical trend was seen, but as rightly noted in the presentation to the Advisory Committee and the press release, the result was not significant. This statement was an accurate reflection of the data GlaxoSmithKline presented to the FDA Advisory Committee. This data was presented to the regulatory authority as it was important information relating to the safety profile of rosiglitazone. As stated previously, the purpose of the press release was to report an accurate, fair and balanced summary of the data GlaxoSmithKline presented to the FDA to investors. This was not a promotional piece and hence this was not a claim. GlaxoSmithKline had not made any promotional claims regarding any benefit on stroke.

Therefore GlaxoSmithKline disputed that there was any breach of the Code. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

'GlaxoSmithKline continues to support Avandia as safe and effective when used appropriately'

This was not a promotional item and hence this was not a claim. Additionally the release was not directed to health professionals or the public. The FDA Advisory Committee hearing specifically discussed the safety of Avandia. It would be very difficult to clearly report GlaxoSmithKline's position on this meeting to a financial (non-medical) audience in other terms. The audience would not necessarily understand the medical term one would use to replace this word. Additionally, the word 'safe' had been qualified by the phrase 'when used appropriately'. GlaxoSmithKline believed it was acceptable to state its position in a press release to the business and financial media. GlaxoSmithKline would not use such a statement in promotional items.

GlaxoSmithKline disagreed that this statement was a breach of the Code. The company reiterated that the press release was not intended for healthcare providers or patients so Takeda's allegation that GlaxoSmithKline had not encouraged the rational use of its products was completely false. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

Important safety Information for Avandia (rosiglitazone maleate)

As stated previously this press release was solely based on events in the US, placed there by the US arm of the company. GlaxoSmithKline was legally obliged to include this information in a US press release and to provide it in layman's language. It was based on the US licence as the press release was regarding data presented to the US regulatory authorities. GlaxoSmithKline completely refuted the allegation that this was directed at or intended for patients.

GlaxoSmithKline also strongly disagreed with Takeda's allegation that '…clearly promoting Avandia to patients in the UK and Europe'. This was not the intention of any press release that was placed on GlaxoSmithKline's corporate website.

GlaxoSmithKline noted Takeda's comment '….it is misleading with respect to the safety of the product'. This suggested that GlaxoSmithKline intentionally misled the FDA Advisory Committee which was an extremely serious allegation that if true would have personal and criminal consequences for GlaxoSmithKline's senior executive who presented that data. GlaxoSmithKline strongly refuted this allegation. GlaxoSmithKline was committed to patient safety and transparency in its data. This press release accurately reflected the presentation given by GlaxoSmithKline at the FDA meeting in a fair and balanced way. GlaxoSmithKline communicated in an appropriate way with health professionals and patients especially with regard to product safety and not through press releases posted on the corporate website clearly intended for investor media that were labelled as such.

GlaxoSmithKline had stated that this press release was issued by the US arm of the company and posted on the corporate website. In response to Takeda's final comments GlaxoSmithKline noted the following:

1 GlaxoSmithKline was a UK headquartered company, thus it was no surprise that the website was UK based. The UK address of the company's registered office was on the bottom of all pages on the corporate website. There was a specific US Pharmaceuticals website as noted by Takeda, however it omitted to mention that there was a UK Pharmaceuticals website also at www.gsk.co.uk; the latter did not contain any of the corporate page links that were seen on www.gsk.com, thus distinguishing it from the corporate pages.
2 Visiting www.gsk.co.uk directed the reader to the UK company website, which referred to the UK Pharmaceuticals Stockley Park office.
3 Navigating from the UK specific site for career opportunities did indeed take the reader to the corporate site. GlaxoSmithKline was a major employer in the UK with worldwide career opportunities and so it was no surprise that the corporate site hosted all of GlaxoSmithKline's recruitment pages.
4 The position of GlaxoSmithKline UK's website was made clear above. If an individual were to 'Google' GlaxoSmithKline they would find the corporate website which reflected GlaxoSmithKline's corporate position. If they wished to find www.gsk.co.uk GlaxoSmithKline expected that this would be typed into the address bar of the browser rather than a search engine. Nevertheless having repeated Takeda's Google search the following was found as the closest match.

United Kingdom - GlaxoSmithKline Worldwide - GlaxoSmithKline
About GlaxoSmithKline summarizes the mission of GlaxoSmithKline and provides users with an overview of the organization and biographies of its Board of Directors and Corporate ...
www.gsk.com/worldwide/uk.htm - 9k

Clicking on the url, took the reader to the same site as www.gsk.co.uk. If a reader was at www.gsk.com there was a box on the front page that invited readers to click to 'Find contact details for GlaxoSmithKline offices around the world'. This link took readers to a listing of countries which was headed by the UK. This too took the reader to the same page as www.gsk.co.uk which contained no press releases.

5 Takeda was correct that the London Stock Exchange (and New York Stock Exchange) prices were given on the front page of its corporate website. GlaxoSmithKline failed to see that this was relevant to the position of GlaxoSmithKline UK, and if anything reinforced its fundamental argument about Takeda's misperception regarding this release and the role of the corporate site.

Takeda questioned the media contacts listed on the press release. They were in fact all corporate media contacts, whose role was to liaise with business and financial media only. This included all global business and financial media.

None of the contacts listed had anything to do with the UK operating company or UK health professionals. All were based at corporate headquarters in the UK.

GlaxoSmithKline noted that Takeda had not referred to the US media contact names also cited on this release.

GlaxoSmithKline was a UK headquartered company which had been exposed to significant publicity regarding the safety of Avandia. This was material to investors given the impact on the share price as detailed above. Events in the US related to this were thus pertinent to investors who should rightly be informed of the company's position regarding the data and its impact.

GlaxoSmithKline found Takeda's position surprising, in that it alleged multiple breaches of the Code for a corporate press release, directed to and labelled as a business release that clearly had business relevant content for one of GlaxoSmithKline's major products. It clearly followed that this was share price relevant information given the events since 21 May when the Nissen and Wolski meta analysis was published. The release referred to regulatory events occurring in the US that were relevant to the US Prescribing Information rather than the European SPC. Given the clarity of the position, GlaxoSmithKline questioned Takeda's motivation for making such an extensive complaint.

In summary GlaxoSmithKline referred to Clause 21.1 which stated, 'Access to **promotional** material directed to a **UK audience** provided on the internet in relation to prescription only medicines should generally be limited to health professionals and appropriate administrative staff' (emphasis added).

Clause 21.2 referred to 'Information or promotional material …. covered by Clause 21.1 …'.

Given the specificity of Clause 21 in this regard, GlaxoSmithKline did not believe that this corporate press release, on GlaxoSmithKline's corporate website, relating to an event in the US could be deemed promotional when it was clearly investor relevant information and was labelled as such on the website page where the link was present. Additionally the release itself was labelled as being from the US office, and all of the individuals named as media contacts were employed in GlaxoSmithKline's corporate office.

GlaxoSmithKline strongly refuted all allegations of breaches of the Code and other wrongdoing as alleged, and respectfully suggested that there was no prima facie case to answer.

PANEL RULING

The Panel noted that much was made about whether the press release was promotional or not and whether the press release was covered by the clauses of the Code. The Panel noted that the supplementary information to Clause 20.2, Information to the public, made it clear that other Clauses of the Code also applied to information to the public.

The Panel noted GlaxoSmithKline's suggestion that there was no prima facie case to answer. This was a matter for the Director to decide prior to referral to the Code of Practice Panel. The Director had decided there was a prima facie case for GlaxoSmithKline to answer and thus the material was before the Panel for consideration.

The Panel examined the press release noting that it had been placed on the corporate website by GlaxoSmithKline US. It had been sent to UK financial media. The press release covered the FDA Advisory Committee which had occurred in the US and related to the US regulatory authorities. The data would obviously be of interest worldwide. The important safety information provided at the end of the press release related to the use of Avandia in the US.

The Panel noted that there had originally been two closely similar versions of the press release on the website. That accessed via 'Avandia News' did not originally feature the heading stating the intended audience. This was remedied by GlaxoSmithKline during inter-company dialogue.

GlaxoSmithKline was a UK headquartered company. It was not unreasonable for UK corporate contact details for the UK media to be included on the press release. The press release was issued in the UK to business/financial journalists, investors and analysts only. The issue would be relevant to such an audience.

The Panel noted Clause 21.2 which stated that

'Information or promotional material about medicines covered by Clause 21.1 above which is placed on the Internet outside the UK will be regarded as coming within the scope of the Code if it was placed there by a UK company or at the instigation or with the authority of such a company and it makes specific reference to the availability or use of the medicine in the UK.'

The Panel considered that information about a prescription only medicine had been placed on the Internet by a UK company or an affiliate or at the instigation or with the authority of such a company. The second part of the clause required specific reference to the availability or use of the medicine in the UK. The Panel noted that the press release at issue referred to Avandia which was available in the UK. It included general information about Avandia but did not specifically refer to its availability or use in the UK. On the contrary the inclusion of important safety information related to the use of the product in the US. The press release related to a particular meeting of the FDA Advisory Committee and was issued as a corporate press release. The Panel did not consider that the press release at issue met both the requirements of Clause 21.2 and thus there was no breach of that clause. This meant that the press release was not within the scope of the Code. The other allegations made by Takeda were as a consequence ruled not to be in breach of the Code including of Clause 2.

During its consideration of this case, the Panel noted that Takeda had referred to the EFPIA Code. The Panel could not make any rulings regarding the EFPIA Code as it had no locus to do so. National associations such as the ABPI were obliged as members of EFPIA to incorporate the requirements of the EFPIA Code into their local codes as far as national law permitted.

Complaint received 20 September 2007

Case completed 11 January 2008