CASE AUTH/2259/8/09

JOHNSON & JOHNSON/DIRECTOR v PFIZER

Promotion of Champix

Johnson & Johnson complained about the promotion of Champix (varenicline) by Pfizer. The items at issue were a leavepiece and an advertisement published in GP. As the complaint involved an alleged breach of undertaking that element was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

The detailed response from Pfizer is given below.

The leavepiece was entitled 'How you and 12 weeks of Champix can aid smoking cessation with your patients'. Johnson & Johnson alleged a breach of the undertaking given in Case AUTH/2203/1/09.

In the leavepiece now at issue, a full page was dedicated to a comparison between Champix and NRT. The page was headed 'Prescribe 12 weeks of Champix for your motivated quitters' and included a bar chart seemingly comparing Champix and NRT at 12 weeks. Below the bar chart were a number of claims relating to the comparison. Johnson & Johnson was concerned about the presentation data from Aubin *et al*.

Johnson & Johnson alleged that although the footnote provided further details about the study, including study design, patient numbers, study duration and primary and secondary endpoints, it was not enough. The Panel's ruling in Case AUTH/2203/1/09 made it clear that any necessary additional information about the study should be included in the body of the advertisement. Providing further information only by way of a footnote was not consistent with the previous Panel ruling.

Johnson & Johnson also alleged that a major issue with Aubin *et al* was that previous treatment might have influenced patient motivation – it was well known that motivation played a role in the success of quit attempts. The importance of previous treatment was particularly relevant in the context of an open-label study where the subjects would have known which treatment they were receiving. It was highly likely that any such bias would favour the new treatment (Champix) as it would be viewed by subjects, and perhaps investigators, as 'novel' and, possibly, an 'advance' in smoking cessation. That Champix was a prescription only medicine and NRT had been available over the counter for many years might also have been significant. An exclusion for patients who had used NRT within the previous 6 months was not rigorous enough to ensure that previous NRT treatment did not bias the result in favour of Champix.

Johnson & Johnson alleged that this potential difference in motivation between the groups was demonstrated by the fact that 2% of patients randomised to NRT dropped out of the study compared with 0.5% randomised to Champix. This was acknowledged by the authors who stated 'A limitation of this study was the open-label design. The differential dropout rate after medication assignment and before the first dose of treatment suggests that some motivational bias may have influenced the results'.

Despite the Panel's ruling that sufficient information relating to the nature of the Aubin data should be included in promotional material, Johnson & Johnson noted that there was no reference to the fact that almost 50% of participants had already received NRT and the potential impact of this upon the results. Therefore, not all relevant information had been presented. Moreover, the footnote on the summary page headed '12 weeks of Champix with quit support helps smokers break their addiction' contained even less information about the study. In particular, there was no mention of its open-label nature.

In summary, Johnson & Johnson alleged that Pfizer's use of a footnote to provide further information about Aubin *et al* was inconsistent with the Panel's ruling which suggested that it should be included as part of the main body of the advertisement. In addition, inadequate information had been provided to explain the failings of the study particularly with regard to previous treatment and ultimately motivation. Finally, Johnson & Johnson was concerned that the leavepiece summary page provided only very limited information about the study and did not clarify that it was open-label.

Johnson & Johnson thus alleged that Pfizer had not complied with the undertaking given in Case AUTH/2203/1/09. In addition, the material was misleading and did not enable the recipient to form their own opinion of the therapeutic value of the medicine.

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The first page at issue in the leavepiece (the inside central page) was headed 'Prescribe 12 weeks of Champix for your motivated quitters [5]*' beneath which was a bar chart which compared the

continuous abstinence rate in the last 4 weeks of treatment of Champix (55.9%) with that of an NRT patch (43.2%) at 12 weeks. The bar chart was headed 'Champix vs. NRT patch at 12 weeks (NiQuitin CQ Clear) (N=746) [5]*'. Three bullet points followed beneath the bar chart including: 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' and 'At 1 year, the quit rate was 26.1% for Champix vs. 20.3% for NRT patch (p=0.056, not significant)'. All the data was referenced to Aubin *et al*. The asterisk by the two claims took readers to a footnote at the bottom of the page, 'Aubin H-J *et al*. An open label, randomised, multi-centre clinical trial of 746 smokers directly compared the recommended treatment courses of Champix for 12 weeks with the NRT patch (NiQuitin CQ Clear) for 10 weeks. The primary endpoint was the continuous abstinence rate (CO [carbon monoxide]-confirmed) at weeks 9-12 for Champix and at weeks 8-11 for NRT. A secondary endpoint was the continuous abstinence rate (CO-confirmed) at weeks 9-52 for Champix and at weeks 8-52 for NRT'.

Less information about Aubin *et al* appeared on the summary page which was headed '12 weeks of Champix with quit support helps smokers break their addiction' and featured 3 bullet points including the claim 'Significantly higher quit rate at 12 weeks versus NRT patch* (NiQuitin CQ Clear), bupropion and placebo[4, 5]'. The comparison with NRT patch was referenced to Aubin *et al* and that with bupropion and placebo was referenced to Nides *et al* (2008). Two footnotes gave limited details about each study; that for Aubin *et al* described its primary and one secondary endpoint, continuous abstinence rate.**

The Panel noted that in the previous case, Case AUTH/2203/1/09, a journal advertisement with the claim 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' was ruled in breach of the Code. The substantiating data was Aubin *et al*, limited details of which appeared as a footnote to a separate claim. The footnote explained that the recommended treatment course for Champix was 12 weeks and for NRT patch (NiQuitin CQ Clear) was 10 weeks. Continuous abstinence rate was CO-confirmed at weeks 9-12 for Champix and at weeks 8-11 for NRT. No further details about Aubin *et al* appeared in the advertisement.

In the present case, Case AUTH/2259/8/09, the Panel noted that there were differences between the claim at issue previously 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' and the two pages in the leavepiece now at issue. The claim at issue previously was not reproduced in the leavepiece although, in the Panel's view the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' was closely similar. The issue was whether sufficient details about Aubin *et al* had been given such that the leavepiece was not caught by the undertaking previously given. The Panel noted that the only details about the study design for Aubin *et al* appeared in footnotes. The footnote on the inside central page mentioned the open-label design, that on the summary page did not. The Panel noted that claims in promotional material should be capable of standing alone as regards the requirements of the Code. Information integral to a reader's understanding of a claim should not be relegated to a footnote, it should appear in the immediate visual field of the claim itself. The open-label nature of the study was a very relevant factor for readers in assessing the claims at issue in both cases. The Panel noted that whilst changes had been made to the material these were insufficient to address the concerns raised by the Panel previously. Whilst it was of course not necessary to detail every aspect of the study, sufficient information should be given such that the reader was aware of the basis of the data. Pertinent information about Aubin *et al* was not an integral part of the main body of the pages at issue in the leavepiece. The footnotes were insufficient in this regard. The leavepiece was thus caught by the undertaking previously given. A breach of the Code was ruled. High standards had not been maintained and the material brought discredit upon and reduced confidence in the pharmaceutical industry; breaches of the Code, including of Clause 2, were ruled.

The Panel noted its comment above about the use of footnotes. Overall, the Panel considered that insufficient information had been provided to enable a reader to form their own opinion of the therapeutic value of the medicine as alleged. A breach of the Code was ruled.

Johnson & Johnson alleged that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' was misleading and all-encompassing. The claim was referenced to Aubin *et al* wherein Champix was compared to the NiQuitin CQ Clear patch (manufactured by GlaxoSmithKline). The NiQuitin CQ Clear patch was a specific formulation which differed from other patches in terms of its release characteristics and pharmacokinetic profile. Johnson & Johnson alleged that the claim implied that all NRT patches were the same and that Champix had proven superiority over all patches. This was not so. There was no clinical efficacy data directly comparing Nicorette patch with any other NRT patch. In addition, Johnson & Johnson was unaware of any direct comparisons between Champix and any nicotine patch other than NiQuitin CQ Clear. Therefore, to imply that Champix was more effective than all NRT patches was misleading and disparaged other NRT patches including Nicorette.

Johnson & Johnson alleged that Pfizer had not taken into account differences between NRT patches and the leavepiece was therefore misleading and the information presented was not accurate, balanced, fair and unambiguous.

The Panel noted that the only references to NiQuitin CQ Clear were in the heading to the bar chart and once in the footnote at the bottom of the page. All other references on the page, including other labelling on the bar chart, were to 'NRT patch'. The Panel did not accept Pfizer's submission that it followed that after the first substantive mention of the comparator treatment all future references to 'NRT patch' would, in effect, mean NiQuitin CQ Clear. That was not necessarily so. The relevant bar of the bar chart was labelled 'NRT patch'. Further, given that no information about the study design appeared in the body of the page, a reader might assume there was more than one arm of the study and thus more than one NRT comparator. The position was not clear.

The Panel noted Johnson & Johnson's submission that there was no direct comparative efficacy data between Nicorette and any other NRT patch and that the NiQuitin CQ Clear patch differed from other patches in terms of its release characteristics and pharmacokinetic profile. Overall, the Panel considered that in the context in which it appeared the claim at issue could not take the benefit of the reference to NiQuitin CQ Clear in the title of the bar chart as submitted by Pfizer. Claims had to be able to stand alone under the Code. The Panel considered that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' was misleading as alleged. A breach of the Code was ruled.

Johnson & Johnson noted that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' related to differences in treatment timing between NiQuitin CQ Clear and Champix. Johnson & Johnson alleged that readers should have been made aware of this. In Aubin *et al*, the primary endpoint was continuous abstinence rates for Champix at weeks 9-12 and for NiQuitin CQ at weeks 8-11. Treatment duration in the Champix group was 12 weeks, compared with 10 weeks for the NRT group. These differences in treatment duration and measurement of the primary endpoint introduced a potential source of bias. Johnson & Johnson alleged that the claim clearly stated 'Champix vs NRT patch at 12 weeks …' which was therefore incorrect. The heading of the graph immediately above the claim also inaccurately stated '12 weeks'. Given this, both the claim and the title of the bar chart were inaccurate and inconsistent with Aubin *et al* and the footnote.

The Panel noted that the treatment periods of both NiQuitin CQ Clear and Champix in Aubin *et al* reflected that recommended in their summaries of product characteristics (SPCs). The Panel noted that the 12 week treatment period for Champix was referred to in the prominent page heading 'Prescribe 12 weeks of Champix for your motivated quitters', again in the title of the bar chart and in the first bullet point. A reference also appeared in the footnote. Comparable information for NiQuitin CQ Clear was not given in the main body of the page. The Panel noted its comments about footnotes above. Whilst the footnote made it clear, *inter alia*, that Aubin *et al* examined NiQuitin CQ Clear for its recommended treatment period of 10 weeks and made clear the differences in the measurement of the primary endpoint the Panel considered that the relegation of this information to a footnote meant that overall the page gave a misleading impression of the treatment duration and measurement of the primary endpoint for NiQuitin CQ. A breach of the Code was ruled.

Beneath the heading 'Champix and the NHS stop smoking service' appeared a highlighted box featuring 3 pie charts headed 'Successful quitters at week 4 follow-up by treatment used (April 2007 – March 2008)'. The pie charts depicted separately the percentage of successful quitters for Champix (63%, n=97,259); NRT (49%, n=474,311) and bupropion (53%, n=22,348). The heading was asterisked to a footnote at the bottom of the page which read 'Based on a statistical report presenting final results from the monitoring of the NHS Stop Smoking Service from the period April 2007 – March 2008. Successfully quit = not smoking at the 4 week follow up (self-reported, not necessarily CO-verified)'.

Johnson & Johnson alleged that the presentation of the pie charts invited a comparison between the various success rates across the three charts. It was an established principle under the Code that apparent differences in graphically presented data were assumed to be statistically significant unless stated otherwise. The presentation of the data in this case implied that Champix was significantly more effective than other treatments. Since no statistical analysis was presented on the pie charts, or within the original NHS data, the statistical significance was not proven. This fact was not clear. Johnson & Johnson alleged that the figure had not been presented in such a way as to give a clear, fair and balanced view of the matter with which it dealt.

It was generally accepted that data presented in promotional material was taken from prospective, randomised clinical trials unless otherwise stated. The NHS data was taken from a retrospective database audit and this had not been made sufficiently clear.

Johnson & Johnson alleged that the presentation of the pie charts was misleading and that insufficient information was provided for the reader to form their own opinion of the therapeutic value of the medicine.

The Panel noted that the data was referenced to statistics on NHS Stop Smoking Services: England, April 2007 – March 2008, a statistical bulletin published by the NHS Information Centre which featured data on people who had received support to quit smoking via a range of NHS Stop Smoking Services. The report stated that varenicline was the

most successful pharmacotherapy used to help people quit in 2007/08 with almost two-thirds of people using it successfully quitting. Of those who set a quit date and used Champix (n=97,259), 63% successfully quit compared with 53% on bupropion (n=22,234) and 49% who were on NRT (n=474,311). Of those who did not receive any type of pharmacotherapy, 55% successfully quit. Among the pharmacotherapies used 66% of people who set a quit date successfully quit using NRT only. The Panel noted the regional, gender and other differences highlighted in the report. The Panel noted, as submitted by Pfizer, that the report was not an interventional trial with statistical analysis but provided data to support clinical trial evidence and was of interest to health professionals. The Panel considered that readers had to be provided with sufficient information about the data such that they could assess the claims made.

The Panel considered that by placing the pie charts immediately adjacent to each other the material invited the reader to directly compare the quit rates and implied that there was an actual difference between the products. This had not been shown as there was no statistical analysis. The statistical analysis on the previous page had shown a difference between Champix and NiQuitin CQ Clear at 12 weeks but not at 1 year. The data related to those who set a quit date and self-reported as having quit at the 4 week follow up. Validation of the quit attempt by CO confirmation did not occur if the intervention was by telephone. Overall 31% of people who set a quit date successfully quit confirmed by CO validation. The information provided about the observational data was wholly inadequate. The footnote was insufficient in that regard. A reader might mistakenly assume that the data was derived from a published clinical study. The comparison was misleading as alleged. Breaches of the Code were ruled.

Johnson & Johnson noted that the presentation of the pie charts excluded the data relating to the percentage of successful quitters where no pharmacotherapy was provided. Had this data been presented, it would have been clear that the success rate for 'no pharmacological treatment' (55%) was seemingly as effective as both NRT and bupropion. This cast serious doubt over the validity of the results as NRT and bupropion were established efficacious treatments for nicotine dependence. This data was not provided and the omission was therefore misleading. Johnson & Johnson alleged that the information presented was incomplete and therefore the recipient would be unable to form their own opinion of the therapeutic value of the medicine.

The Panel noted its comments about the report and data above. The Panel noted Johnson & Johnson's submission that NRT and bupropion were established efficacious treatments for nicotine dependence. The Panel considered it would thus have been helpful to include data on those (55%) who successfully quit without pharmacotherapy. It was not clear whether people who did not receive pharmacotherapy would receive advice from the stop smoking service and whether it was this advice that had motivated smokers to quit. Given that the page was headed 'Champix and the NHS Stop Smoking Service' the Panel considered that the omission of the data was misleading as alleged such that the reader had insufficient information to assess the data presented; a breach of the Code was ruled.

Johnson & Johnson alleged that the headline above the pie charts, 'Champix and the NHS stop smoking service', strongly implied that the NHS endorsed the use of Champix over and above other smoking cessation therapies. This was compounded by the presentation of the data which displayed the pie chart relating to Champix first despite the fact that many more patients were treated with NRT. Johnson & Johnson also noted that underneath the pie charts, 'CHAMPIX' appeared in prominent blue capital letters whereas NRT and bupropion appeared less prominently in grey. Although the reader could be misled into believing that Champix was the NHS Stop Smoking Service medicine of choice, this was clearly not the case as only 14% of patients received it.

In summary, for the reasons outlined above, Johnson & Johnson alleged the page was misleading and implied that the NHS Stop Smoking Service endorsed Champix over and above other pharmacotherapies. This was unsupported by the data and was therefore misleading.

The Panel noted the page heading 'Champix and the NHS Stop Smoking Service'. The Panel further noted that the phrase 'NHS stop smoking service' appeared in a green font, the same shade as the Champix data in the pie chart beneath. However the Panel did not consider that the use of colour, the heading or the page overall directly or indirectly implied NHS endorsement of Champix as alleged. Rather the page purported to reflect the Champix data published in the report. The page was not misleading on this point as alleged. No breach of the Code was ruled.

The advertisement, headed 'New NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10', featured a bar chart which compared the relative impact of 3 stop smoking interventions (no support; individual behavioural support and group behavioural support) combined with no medication, NRT, bupropion or Champix on 4 week quit rates. The heading and bar chart were each asterisked to a footnote which cited the NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10. Adjacent to the bar chart were three bullet points: two highlighted Department of Health (DoH) guidance whilst the third read 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons between treatments across different settings. The 4 week quit rates have not been measured directly but

have been extrapolated from longer term quit rates'. The claim 'Champix – An evidenced-based choice in smoking cessation' ran below the text described above followed by the prescribing information. The product logo appeared in the bottom right hand corner.

Johnson & Johnson alleged that the heading, combined with the overall layout of the advertisement was extremely confusing and misleading. The overall impression was that the advertisement was guidance from the NHS Stop Smoking Service and that the service recommended use of Champix over and above other pharmacotherapies. The impression that the advertisement was NHS guidance was compounded by the statement (which appeared as the third of three bullet points beneath the heading) 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons …'. The word 'this' implied that the advertisement itself was the guidance.

Johnson & Johnson alleged that in addition, the only text-based reference to Champix 'An evidence-based choice in smoking cessation', in association with the heading, clearly implied that the NHS Stop Smoking Services recommended Champix over and above other treatments. This was not true. Indeed, the NHS Service and Monitoring Guidance 2009/10 stated that NRT, Champix and bupropion should all be made available first line.

Johnson & Johnson alleged that the overall impression of the advertisement was ambiguous and therefore misleading.

The Panel noted that the NHS Service and Monitoring Guidance stated that Champix had been proven to be a highly cost-effective treatment resulting in average success rates of 61% at 4 weeks in the first and second quarters of 2008/2009. All motivated quitters should be given the optimum chance of success in any quit attempt and NRT, Champix and bupropion should all be made available in combination with intensive behavioural support as first-line treatments (where clinically appropriate).

The Panel considered that although the heading 'NHS Stop Smoking Services:' appeared in a green font, the same shade as the Champix data in the bar chart, readers would not assume that the advertisement was the official NHS Guidance or that Champix was its medicine of choice as alleged. It was clearly an advertisement for Champix. It featured promotional claims and prescribing information. No breach of the Code was ruled.

Johnson & Johnson noted that the bar chart was referenced to the NHS Stop Smoking Services: Services and monitoring Guidance 2009/10 and was titled 'The relative impact of a variety of evidence-based stop smoking interventions and pharmacotherapies upon 4 week quit rates'. The heading of the bar chart clearly indicated that the data portrayed the 'relative impact' of stop smoking interventions. 'Relative' emphasised the intention to draw a direct comparison between the treatments presented. However, any such comparison would be meaningless as there was no indication as to whether the differences were statistically significant. In addition, there were no patient numbers presented in the bar chart. This meant that the reader could not judge the context of the data. Johnson & Johnson alleged that the bar chart was misleading.

The Panel noted, as stated in a very small footnote beneath the bar chart, that it was adapted from the Cochrane database of systematic reviews. It had been reproduced from the NHS stop smoking services: Services and Monitoring Guidance 2009/10. The bar chart invited the reader to directly compare the 4 week quit rates of each medicine and no medication when used in combination with 3 different evidenced based interventions. Champix had the most favourable outcome with each intervention. Further details about the Cochrane analysis were given in the third bullet point.

The Panel considered that the bar chart implied that in relation to each intervention statistically significantly more smokers quit with Champix than with any other treatment regimen. That was not necessarily so. The statistical significance of the data was unknown. The bar chart was misleading in this regard. Breaches of the Code were ruled.

Johnson & Johnson noted that the third bullet point read 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons between treatments across different settings. The 4 week quit rates have not been measured directly but have been extrapolated from longer term quit rates.' The Cochrane Reviews upon which these data were based appraised studies with a 6 month data point. It was therefore unclear either from the material or the source reference, how the 4 week data were calculated and whether the method used had suitable scientific validity for inclusion within promotional material. Pfizer had failed to explain the basis of this extrapolated data, other than to state that the authors were reputable and credible and hence it believed the data to be valid. Johnson & Johnson alleged that this was insufficient as Pfizer was unable to substantiate the exact methods used to extrapolate the four week data.

Johnson & Johnson alleged that the extrapolation of data to a 4 week comparison without clear explanation or substantiation was misleading. The basis for the 4 week data had not been made sufficiently clear. The advertisement was thus misleading. Additionally the 4 week data was not available and therefore could not be substantiated.

The Panel noted its rulings and comments above. The Panel had concerns about the data. The Panel considered that the third bullet point made it clear

that the 4 week quit rates had been extrapolated from longer term quit rates based on indirect comparisons between treatments across different settings. The Panel did not have a copy of the Cochrane reviews. On the evidence before it the Panel did not consider that it was necessary to provide further information about the calculation of the 4 week quit rates in the advertisement as alleged. The basis of the data was clear. No breach of the Code was ruled on this very narrow point.

The Panel agreed with Pfizer that it was not for the authors of the NHS guidance to substantiate their data. The Code required that companies must be able to substantiate information, claim or comparisons and such data be provided on request from a health professional. The data presented in Pfizer's advertisement had to be capable of substantiation. The authors of the NHS guidance had extrapolated long term data published in the Cochrane reviews to a 4 week time point. No details about the calculation and any assumptions made were published in the NHS guidance document.

The Panel considered the allegation that Pfizer was unable to substantiate the four week data. The Panel noted the supplementary information to the Code listed 'statistical information' as an area where particular care should be taken. This stated, *inter alia*, 'Care must be taken to ensure that there is a sound statistical basis for all information, claims and comparisons in promotional material.' It continued 'Instances have occurred where claims have been based on published papers in which the arithmetic and/or statistical methodology was incorrect. Accordingly, before statistical information is included in promotional material it must have been subjected to statistical appraisal'. The Panel considered that Pfizer's position, that it did not believe it would be expected to ask the authors of the NHS guidance, all of whom were recognised experts in the field of smoking cessation, to substantiate their data was unacceptable. It was Pfizer's responsibility to ensure that it could substantiate all claims and data in its promotional material irrespective of the source of such data. Thus, in the Panel's view, Pfizer should have satisfied itself that the extrapolation of the 4 week quit rates from longer term quit data was capable of substantiation before using such data in promotional material. Pfizer had not provided any data or detail about this calculation and thus the Panel considered that Pfizer had not substantiated the calculation of the 4 week quit rates. A breach of the Code was ruled.

Johnson & Johnson Limited complained about the promotion of Champix (varenicline) by Pfizer Limited. The items at issue were a leavepiece (ref CHA693) available from a stand at a Nursing in Practice event held in April 2009 and an advertisement (ref CHA752a) published in GP, 12 June 2009.

Champix was indicated for smoking cessation.

As the complaint involved an alleged breach of undertaking that element was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

A Champix leavepiece (ref CHA693)

The leavepiece was entitled 'How you and 12 weeks of Champix can aid smoking cessation with your patients'.

1 Alleged breach of undertaking

COMPLAINT

Johnson & Johnson noted that in Case AUTH/2203/1/09 the Panel upheld a complaint regarding the claim 'Champix at 12 weeks provides significantly greater quit success vs. NRT [nicotine replacement therapy] (NiQuitin CQ Clear)' and the use of Aubin *et al* (2008) to support it.

In Case AUTH/2203/1/09 the Panel had stated that: '… whilst an open-label design would not necessarily preclude the use of data derived from Aubin *et al* in promotional material, readers had to be provided with sufficient information about the study to enable them to assess the data. The Panel noted the study authors' conclusions that "motivational influences are likely to exist in a real-world setting and the outcomes of this study show that varenicline is more effective than transdermal nicotine in enhancing quit rates in an open-label setting". The Panel did not consider that the claim at issue was a fair reflection of the study findings in this regard. The main body of the advertisement gave no relevant details about the study design and so the reader would be unaware of the basis of the data'.

Johnson & Johnson stated that the Panel ruled that, when Aubin *et al* was cited in promotional material, it should be accompanied by sufficient information in order that readers could assess the data. The Panel made particular reference to the authors' conclusions that motivational factors were affected by the open-label setting and commented that the main body of the advertisement contained no relevant details regarding the study design. This meant that readers would be unaware of the basis for the data.

Johnson & Johnson noted that in the leavepiece now at issue, a full page was dedicated to a comparison between Champix and NRT. The page was headed 'Prescribe 12 weeks of Champix for your motivated quitters' and included a bar chart seemingly comparing Champix and NRT at 12 weeks. Below the bar chart were a number of claims relating to the comparison. Johnson & Johnson was concerned about the presentation of the Aubin *et al* data.

Johnson & Johnson alleged that although the footnote provided further details about the study, including study design, patient numbers, study

duration and primary and secondary endpoints, this did not go far enough. It was clear from the Panel's ruling in Case AUTH/2203/1/09 that any necessary additional information about the study should be included in the body of the advertisement. Providing further information about the study only by way of a footnote was not consistent with the previous Panel ruling.

Johnson & Johnson also alleged that a major issue with Aubin *et al* was that previous treatment might have influenced patient motivation – it was well known that motivation played a role in the success of quit attempts. The importance of previous treatment would be particularly relevant in the context of an open-label study where the subjects would have known which treatment they were receiving. It was highly likely that any such bias would have favoured the new treatment (Champix) as it would have been viewed by subjects, and perhaps investigators, as 'novel' and, possibly, an 'advance' in smoking cessation. That Champix was a prescription only medicine and NRT had been available over the counter for many years might also have been significant. An exclusion for patients who had used NRT within the previous 6 months was not rigorous enough to ensure that previous NRT treatment did not bias the result in favour of Champix.

Johnson & Johnson alleged that this potential difference in motivation between the groups was demonstrated by the fact that 9 (2%) subjects dropped out of the study when randomised to NRT compared with 2 (0.5%) randomised to Champix. This was acknowledged by the authors who stated 'A limitation of this study was the open-label design. The differential dropout rate after medication assignment and before the first dose of treatment suggests that some motivational bias may have influenced the results'.

In inter-company dialogue Pfizer stated that due to randomisation, it was likely that there were similar numbers of patients who had previously used NRT in both treatment groups. Johnson & Johnson disagreed as only the NRT treatment arm would be negatively biased as a result of previous treatment, and subsequent failure, with NRT.

Despite the Panel's ruling that sufficient information relating to the nature of the Aubin data should be included in promotional material, Johnson & Johnson noted that there was no reference to the fact that almost 50% of all study participants had already received NRT and the potential impact of this upon the results. Therefore, not all relevant information had been presented.

Moreover, the footnote on the summary page headed '12 weeks of Champix with quit support helps smokers break their addiction' contained even less information about the study. In particular, there was no mention of its open-label nature.

In summary, Johnson & Johnson alleged that Pfizer's use of a footnote to provide further information about Aubin *et al* was inconsistent with the Panel's ruling which suggested that it should be included as part of the main body of the advertisement. In addition, inadequate information had been provided to explain the failings of the study in particular around issues of previous treatment and ultimately motivation. Finally, Johnson & Johnson was concerned that the leavepiece summary page provided only very limited information about the study and did not clarify that it was open-label in design.

Johnson & Johnson thus alleged that Pfizer had not complied with the undertaking given in Case AUTH/2203/1/09 in breach of Clause 25 of the Code. In addition, the material was misleading and did not enable the recipient to form their own opinion of the therapeutic value of the medicine in breach of Clause 7.2.

In addition to those clauses cited by Johnson & Johnson the Authority asked Pfizer to respond in relation to the requirements of Clauses 2 and 9.1.

RESPONSE

Pfizer noted that Case AUTH/2203/1/09 concerned the claim 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' in an advertisement. The Panel had stated that: '… whilst an open-label design would not necessarily preclude the use of data derived from Aubin *et al* in promotional material, readers had to be provided with sufficient information about the study to enable them to assess the data'.

In light of this case and its undertaking, Pfizer reviewed all promotional material containing data from Aubin *et al* and immediately withdrew any that was non compliant. During this review Pfizer wanted to ensure that the design of Aubin *et al* was clearly described with sufficient information about the study to enable readers to assess the data. In the leavepiece at issue, the study was described as: 'Aubin H-J *et al*. An open label, randomised, multicentre clinical trial of 746 smokers directly compared the recommended treatment courses of Champix for 12 weeks with the NRT patch (NiQuitin CQ Clear) for 10 weeks. The primary endpoint was the continuous abstinence rate (CO [carbon-monoxide]-confirmed) at weeks 9-12 for Champix and at weeks 8-11 for NRT. A secondary endpoint was the continuous abstinence rate (CO-confirmed) at weeks 9-52 for Champix and at weeks 8-52 for NRT'.

Pfizer submitted that the description made clear that this was an open-label study; the recommended treatment courses for each product – 12 weeks for Champix and 10 for the NRT patch, as per the respective summaries of product characteristics (SPCs); the primary endpoint was assessed at the end of the last 4 weeks of treatment for both products, ie weeks 9-12 for Champix and 8-11 for the NRT patch and the NRT patch used was NiQuitin CQ Clear.

Pfizer submitted that it was standard and acceptable practice to describe the study designs in this format on a page such as this in a leavepiece. Footnotes were not prohibited by the Code and could be used to provide additional information, but only if this information did not alter the interpretation. A misleading headline could not be corrected by a footnote.

Pfizer submitted that the presentation of the study design in this leavepiece was appropriate, not misleading and was not in breach of its undertaking. In this regard it submitted that there had been no breach of Clauses 7.2 or 25. High standards had been maintained (Clause 9.1) and the leavepiece had not brought the industry into disrepute (Clause 2).

With regard to the comments about the fact that almost half of the subjects had previously tried to quit and failed using a transdermal nicotine patch and that this might have favoured Champix, Pfizer submitted that patients were excluded if they had used NRT within the previous 6 months. In addition, treatment by baseline covariate analysis demonstrated that there was no interaction (p>0.10) with prior quit attempt using NRT or transdermal patch, suggesting that this did not influence the efficacy results. In other words, if there was significant motivational bias in this study then those patients who had previously tried NRT should have demonstrated a greater benefit from Champix vs NRT than those patients who had never tried NRT. This was not shown; the benefit of Champix vs NRT was the same regardless of prior NRT use. Pfizer agreed that if there had been a significant interaction with prior NRT use then this should have been presented in the material but as there was no significant interaction this data was not presented.

Pfizer submitted that the leavepiece summary page was a summary of material from the leavepiece itself, it was not necessary to repeat everything again on the summary page, it was made clear in the footnote that the primary endpoint for Champix was at weeks 9-12 and for NRT at weeks 8-11. Pfizer had also reminded the reader that the NRT patch used was NiQuitin CQ Clear. Aubin *et al* was cited at the bottom of the summary page and was described as: 'Aubin H-J *et al*. Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomised, open-label trial. Thorax 2008; 63:717-724'.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the first page at issue in the leavepiece (the inside central page) was headed 'Prescribe 12 weeks of Champix for your motivated quitters 5*' beneath which was a bar chart which compared the continuous abstinence rate in the last 4 weeks of treatment of Champix (55.9%) with that of an NRT patch (43.2%) at 12 weeks. The bar chart was headed 'Champix vs. NRT patch at 12 weeks (NiQuitin CQ Clear) (N=746) 5*'. Three bullet points followed beneath the bar chart including: 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' and 'At 1 year, the quit rate was 26.1% for Champix vs. 20.3% for NRT patch (p=0.056, not significant)'. All the data was referenced to Aubin *et al* (reference 5). The asterisk by the two claims took readers to a footnote at the bottom of the page, 'Aubin H-J *et al*. An open label, randomised, multi-centre clinical trial of 746 smokers directly compared the recommended treatment courses of Champix for 12 weeks with the NRT patch (NiQuitin CQ Clear) for 10 weeks. The primary endpoint was the continuous abstinence rate (CO-confirmed) at weeks 9-12 for Champix and at weeks 8-11 for NRT. A secondary endpoint was the continuous abstinence rate (CO-confirmed) at weeks 9-52 for Champix and at weeks 8-52 for NRT'.

Less information about Aubin *et al* appeared on the summary page which was headed '12 weeks of Champix with quit support helps smokers break their addiction' and featured 3 bullet points including the claim 'Significantly higher quit rate at 12 weeks versus NRT patch* (NiQuitin CQ Clear), bupropion and placebo4, 5**'. The comparison with NRT patch was referenced to Aubin *et al* and that with bupropion and placebo was referenced to Nides *et al* (2008). Two footnotes gave limited details about each study; that for Aubin *et al* described its primary and one secondary endpoint, continuous abstinence rate.

The Panel noted that the previous case, Case AUTH/2203/1/09, concerned a journal advertisement wherein the claim 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' was ruled in breach of Clause 7.2. The substantiating data was Aubin *et al*, limited details of which appeared as a footnote to a separate claim. The footnote explained that the recommended treatment course for Champix was 12 weeks and for NRT patch (NiQuitin CQ Clear) was 10 weeks. Continuous abstinence rate was CO-confirmed at weeks 9-12 for Champix and at weeks 8-11 for NRT. No further details about Aubin *et al* appeared in the advertisement. The relevant part of the Panel ruling in Case AUTH/2203/1/09 is reproduced below.

> 'The Panel noted that Aubin *et al* was an open-label, randomised trial to compare a 12 week standard regimen of Champix with a 10 week standard regimen of NRT for smoking cessation. All patients were motivated to quit and had not used any form of NRT in the previous 6 months. The study authors referred to the intent to treat analysis as a gold standard and explained that they reported the primary analysis population (those who were randomised and took at least one dose of medicine) in the efficacy results as

this was the study's prespecified primary analysis population. The authors noted that this might underestimate the efficacy of Champix relative to NRT because of differential drop out after medication assignment.

The Panel noted each party's submission about the study methodology and limitations. The study authors noted that a limitation of the study was its open-label design and a detailed discussion of the study's limitations appeared in the published paper. The Panel noted the study authors' comment that technical problems made it difficult to create NRT and placebo patches that were indistinguishable in appearance and odour.

The Panel noted that whilst an open-label design would not necessarily preclude the use of data derived from Aubin *et al* in promotional material, readers had to be provided with sufficient information about the study to enable them to assess the data. The Panel noted the study authors' conclusions that 'motivational influences are likely to exist in a real-world setting and the outcomes of this study show that varenicline is more effective than transdermal nicotine in enhancing quit rates **in an open-label setting**' (emphasis added). The Panel did not consider that the claim at issue was a fair reflection of the study findings in this regard. The main body of the advertisement gave no relevant details about the study design and so the reader would be unaware of the basis of the data. The Panel considered the claim 'Champix at 12 weeks provides significant greater quit success vs NRT (NiQuitin CQ Clear)' was misleading in this regard and a breach of Clause 7.2 was ruled.'

Turning to the present case, Case AUTH/2259/8/09, the Panel noted that there were differences between the claim at issue previously 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' and the two pages in the leavepiece now at issue. The claim at issue previously was not reproduced in the leavepiece although, in the Panel's view the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch ($p<0.001$)' was closely similar. The issue was whether sufficient details about Aubin *et al* had been given such that the leavepiece was not caught by the undertaking previously given. The Panel noted that the only details about the study design for Aubin *et al* appeared in footnotes. The footnote on the inside central page mentioned the open-label design, that on the summary page did not. The Panel noted that claims in promotional material should be capable of standing alone as regards the requirements of the Code. Information integral to a reader's understanding of a claim should not be relegated to a footnote, it should appear in the immediate visual field of the claim itself. The open-label nature of the study was a very relevant factor for readers in assessing the claims at issue in both cases. The Panel noted that whilst changes had been made to the material these were insufficient to address the concerns raised by the Panel previously. Whilst it was of course not necessary to detail every aspect of the study, sufficient information should be given such that the reader was aware of the basis of the data. Pertinent information about Aubin *et al* was not an integral part of the main body of the pages at issue in the leavepiece. The footnotes were insufficient in this regard. The leavepiece was thus caught by the undertaking previously given. A breach of Clause 25 was ruled. High standards had not been maintained and the material brought discredit upon and reduced confidence in the pharmaceutical industry; breaches of Clauses 9.1 and 2 were ruled.

The Panel noted its comment above about the use of footnotes. Overall, the Panel considered that insufficient information had been provided to enable a reader to form their own opinion of the therapeutic value of the medicine as alleged. A breach of Clause 7.2 was ruled.

2 Generalisation of data for NiQuitin CQ to all NRT patches

COMPLAINT

Johnson & Johnson alleged that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch ($p<0.001$)' was misleading and all-encompassing. The claim was referenced to Aubin *et al* wherein Champix was compared to the NiQuitin CQ Clear patch (manufactured by GlaxoSmithKline). The NiQuitin CQ Clear patch was a specific formulation which differed from other patches in terms of its release characteristics and pharmacokinetic profile. Johnson & Johnson alleged that the claim implied that all NRT patches were the same and that Champix had proven superiority over all patches. This had not been proven. On the contrary, there was no clinical efficacy data directly comparing Nicorette patch with any other NRT patch. In addition, Johnson & Johnson was unaware of any direct comparisons between Champix and any nicotine patch other than NiQuitin CQ Clear. Therefore, to imply that Champix was more effective than all NRT patches was misleading and disparaged other NRT patches including Nicorette.

Johnson & Johnson stated that it would be unacceptable to make broad generalisations relating to the efficacy of other classes of treatments. For instance, if a study suggested that a novel therapy was more effective than simvastatin in the treatment of hypercholesteraemia, it would not be acceptable to generalise that it was more effective than all other statins. Likewise, such generalisations were not acceptable for NRT where products were available at a variety of strengths, with different dosing periods, release mechanisms, pharmacokinetics profiles and hence potentially efficacy rates. The generalisation of data for

NiQuitin CQ Clear to all NRT patches was repeated throughout the central page including the footnote.

In inter-company dialogue Pfizer had argued that as the title of the bar chart, which was the first substantive mention of the comparator, stated that this treatment was NiQuitin CQ Clear, it was not necessary to refer to it again. Johnson & Johnson alleged that the clarifying statement was not prominent enough to ensure that all readers would, at a glance, know that the patch used was NiQuitin CQ Clear. Indeed, if Pfizer had wanted readers to be in no doubt as to the nature of the patch, then it could have referred to the product by name throughout the leavepiece. Although Pfizer had not explicitly categorised NRT patches as the same, there was a clear implication that the results presented related to all NRT patches.

Johnson & Johnson therefore alleged that Pfizer had failed to take into account differences between NRT patches and the leavepiece was therefore misleading and the information presented was not accurate, balanced, fair and unambiguous. A breach of Clause 7.2 was alleged.

RESPONSE

Pfizer noted that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' was the first bullet point beneath the bar chart. The title of the bar chart clearly stated that the NRT patch used was NiQuitin CQ Clear. This was the first substantive mention of the comparator so it therefore followed that all future references on the same page summarising the same study and the same data referred to the NiQuitin CQ Clear patch. Precisely because Pfizer did not want to mislead the reader into thinking this data applied necessarily to all NRT patches it had been careful to highlight NiQuitin CQ Clear patch at the first substantive mention in the bar chart's title. Pfizer had also stated NiQuitin CQ Clear in the description of the study design. Pfizer had not referred to, or categorised NRT patches to be the same.

As the type of patch was clearly and accurately specified in the title of the bar chart and in the description of the study, Pfizer submitted that the claim was not all-encompassing, misleading, or disparaging or that there had been a breach of Clause 7.2.

PANEL RULING

The Panel noted that the only references to NiQuitin CQ Clear were in the heading to the bar chart and once in the footnote at the bottom of the page. All other references on the page, including other labelling on the bar chart, were to 'NRT patch'. The Panel did not accept Pfizer's submission that it followed that after the first substantive mention of the comparator treatment all future references to 'NRT patch' would, in effect, mean NiQuitin CQ Clear. That was not necessarily so. The relevant bar of the bar chart was labelled 'NRT patch'. Further, given that no information about the study design appeared in the body of the page, a reader might assume there was more than one arm of the study and thus more than one NRT comparator. The position was not clear.

The Panel noted Johnson & Johnson's submission that there was no direct comparative efficacy data between Nicorette and any other NRT patch and that the NiQuitin CQ Clear patch differed from other patches in terms of its release characteristics and pharmacokinetic profile. Overall, the Panel considered that in the context in which it appeared the claim at issue could not take the benefit of the reference to NiQuitin CQ Clear in the title of the bar chart as submitted by Pfizer. Claims had to be able to stand alone under the Code. The Panel considered that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' was misleading as alleged. A breach of Clause 7.2 was ruled.

The Panel noted that in addition Johnson & Johnson had alleged that the claim disparaged other NRT patches including Nicorette but had omitted to cite a clause number, in this instance Clause 8.1, as required under Paragraph 5.2 of the Constitution and Procedure. No ruling was thus made on this point.

3 Difference in treatment times for NiQuitin CQ Clear and Champix

COMPLAINT

Johnson & Johnson noted that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' related to differences in treatment timing between NiQuitin CQ Clear and Champix. Johnson & Johnson alleged that readers should have been made aware of this. In Aubin *et al*, the primary endpoint was continuous abstinence rates for Champix at weeks 9-12 and for NiQuitin CQ at weeks 8-11. Treatment duration in the Champix group was 12 weeks, compared with 10 weeks for the NRT group. These differences in treatment duration and measurement of the primary endpoint introduced a potential source of bias.

Pfizer had clarified that a footnote explained both the duration of treatment and the differences in the measurement of the primary endpoint (continuous abstinence in the last 4 weeks of treatment for both treatment arms – weeks 9-12 for Champix and weeks 8-11 for NRT). However, Johnson & Johnson alleged that the claim clearly stated 'Champix vs NRT patch at 12 weeks …' which was therefore incorrect. The heading of the graph immediately above the claim also inaccurately stated '12 weeks'.

Given this, both the claim and the title of the bar chart were inaccurate and inconsistent with Aubin

et al and the footnote in breach of Clause 7.2.

RESPONSE

Pfizer submitted that Aubin *et al* directly compared the recommended treatment courses for both treatments (as per their SPCs), which were 10 weeks of treatment for NiQuitin CQ Clear and 12 for Champix. This was stated clearly on the page '… recommended treatment courses of Champix for 12 weeks with the NRT patch (NiQuitin CQ Clear) for 10 weeks. The primary endpoint was the continuous abstinence rate (CO-confirmed) at weeks 9-12 for Champix and at weeks 8-11 for NRT'. In addition, the differences when measuring the secondary endpoint, ie 9-52 weeks for Champix vs 8-52 weeks for NRT were also explained.

Pfizer submitted that in addition, a pre-specified sensitivity analysis compared, like for like, 4 week continuous abstinence rates for weeks 9–12 in both treatment groups and weeks 8–11 in both treatment groups. The results showed that the conclusions of the study remained unchanged. In other words there was no evidence that comparing the recommended treatment regimens as per the SPC for each product had introduced bias, whether compared at the end of treatment for each regimen or at the same time point for each regimen.

Pfizer submitted that referring to 'Champix at 12 weeks' was appropriate as this was the recommended treatment regimen in the SPC and the duration of Champix treatment in Aubin *et al*. As the study treatment duration and continuous abstinence rates for both primary and secondary endpoints were clearly stated on the page and clearly referenced to Aubin *et al*, Pfizer submitted that it had given accurate, balanced, fair and objective results which were unambiguous and not misleading. Therefore, Pfizer denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the treatment periods of both NiQuitin CQ Clear and Champix in Aubin *et al* reflected that recommended in their SPCs. The Panel noted that the 12 week treatment period for Champix was referred to in the prominent page heading 'Prescribe 12 weeks of Champix for your motivated quitters', again in the title of the bar chart and in the first bullet point. A reference also appeared in the footnote. Comparable information for NiQuitin CQ Clear was not given in the main body of the page. The Panel noted its comments about footnotes above. Whilst the footnote made it clear, *inter alia*, that Aubin *et al* examined NiQuitin CQ Clear for its recommended treatment period of 10 weeks and made clear the differences in the measurement of the primary endpoint the Panel considered that the relegation of this information to a footnote meant that overall the page gave a misleading impression of the treatment duration and measurement of the primary endpoint for NiQuitin CQ. A breach of Clause 7.2 was ruled.

4 Presentation of the pie charts showing 4 week quit rates and use of audit data

Beneath the heading 'Champix and the NHS stop smoking service' appeared a highlighted box featuring 3 pie charts headed 'Successful quitters at week 4 follow-up by treatment used (April 2007 – March 2008)'. The pie charts depicted separately the percentage of successful quitters for Champix (63%, n=97,259); NRT (49%, n=474,311) and bupropion (53%, n=22,348). The heading was asterisked to a footnote at the bottom of the page which read 'Based on a statistical report presenting final results from the monitoring of the NHS Stop Smoking Service from the period April 2007 – March 2008. Successfully quit = not smoking at the 4 week follow up (self-reported, not necessarily CO-verified)'.

COMPLAINT

Johnson & Johnson alleged that the presentation of the pie charts within a single frame invited a comparison between the various success rates across the three charts.

Johnson & Johnson stated that it was an established principle under the Code that apparent differences in graphically presented data were assumed to be statistically significant unless stated otherwise. The presentation of the data in this case implied that Champix was significantly more effective than other treatments. Since no statistical analysis was presented on the pie charts, or within the original NHS data, the statistical significance was not proven. This fact was not made clear to the reader.

In inter-company dialogue Pfizer had argued that it had simply represented the data from the NHS Stop Smoking Service report in an accurate, balanced, fair and objective manner. Johnson & Johnson disagreed. The fact that no statistics were available in the NHS reference did not make it acceptable to present data implying proven superiority of one treatment over another.

Johnson & Johnson alleged that the figure had not been presented in such a way as to give a clear, fair and balanced view of the matter with which it dealt and alleged a breach of Clauses 7.2 and 7.8.

It was generally accepted that data presented in promotional material was taken from prospective, randomised clinical trials unless otherwise stated. The NHS data was taken from a retrospective database audit and this had not been made sufficiently clear.

Pfizer had argued that the heading of the page, the title of the pie chart and the further information on the page made it very clear as to where the data was from. Johnson & Johnson disagreed. Neither the page heading nor the pie chart title referred to the nature of the data cited. The footnote stated that the charts were 'Based on a statistical report presenting final results from the monitoring of the

NHS Stop Smoking Service from the period April 2007 – March 2008'. However, Johnson & Johnson alleged that this statement was not prominent enough to make this clear to the reader, as the footnote was in a small, pale grey font. The overall impression of the page was such that the reader could easily assume that the data presented was derived from a clinical trial.

Johnson & Johnson alleged that the presentation of the pie charts was misleading and that insufficient information was provided for the reader to form their own opinion of the therapeutic value of the medicine in breach of Clause 7.2.

RESPONSE

Pfizer submitted that these data had been taken from a report from the monitoring of the NHS Stop Smoking Service for the period April 2007 to March 2008. Successful quitters were defined in the report as not smoking at the 4 week follow up based on self reporting and not necessarily CO verified. It was clear that this was not an interventional clinical trial, but an NHS report of real world results over a 12 month period for the 3 smoking cessation treatments. As this was not a clinical trial with an a *priori* hypothesis being tested there was no statistical analysis. Pfizer had presented the data reported by the NHS which was in the public domain, and which was updated on an ongoing basis. Reporting real world data on medicines as they were used in practice was an important addition to reporting efficacy results as found in clinical trials. Pfizer had described the results of Aubin *et al* on the previous page and had referenced the body of clinical trial evidence (Aubin *et al*, Gonzalez *et al* 2006, Nides *et al*, Jorenby *et al* 2008) for Champix. The NHS report provided further supporting data to the clinical trial evidence and was a document that was from a reputable source and was of interest to health professionals who worked in the field of smoking cessation. Pfizer submitted that it had represented the data in an accurate, balanced, fair and objective manner, and therefore denied breaches of Clauses 7.2 and 7.8.

PANEL RULING

The Panel noted that the data was referenced to statistics on NHS Stop Smoking Services: England, April 2007 – March 2008, a statistical bulletin published by the NHS Information Centre which featured data collected on people who had received support to quit smoking via a range of NHS Stop Smoking Services. The report stated that varenicline was the most successful pharmacotherapy used to help people quit in 2007/08 with almost two-thirds of people using it successfully quitting. Of those who set a quit date and used Champix (n=97,259), 63% successfully quit compared with 53% on bupropion (n=22,234) and 49% who were on NRT (n=474,311). Of those who did not receive any type of pharmacotherapy, 55% successfully quit. Among the pharmacotherapies used 66% of people who set a quit date successfully quit using NRT only. The Panel noted the regional, gender and other differences highlighted in the report. The Panel noted, as submitted by Pfizer, that the report was not an interventional trial with statistical analysis but provided data to support clinical trial evidence and was of interest to health professionals. The Panel considered that readers had to be provided with sufficient information about the data such that they could assess the claims made.

The Panel considered that by placing the pie charts immediately adjacent to each other the material invited the reader to directly compare the quit rates and implied that there was an actual difference between the products. This had not been shown as there was no statistical analysis. The statistical analysis on the previous page had shown a difference between Champix and NiQuitin CQ Clear at 12 weeks but not at 1 year. The data related to those who set a quit date and self-reported as having quit at the 4 week follow up. Validation of the quit attempt by CO confirmation did not occur if the intervention was by telephone. Overall 31% of people who set a quit date successfully quit confirmed by CO validation. The information provided about the observational data was wholly inadequate. The footnote was insufficient in that regard. A reader might mistakenly assume that the data was derived from a published clinical study. The comparison was misleading as alleged. Breaches of Clauses 7.2 and 7.8 were ruled.

During its consideration of this point the Panel was extremely concerned about the presentation of data from the bulletin: statistics on NHS stop smoking services April 2007 to March 2008. The data was self reported and not necessarily CO verified. The group sizes differed markedly. That 55% who received no medication successfully quit meant that overall the audit data should be viewed with a degree of circumspection. Companies should be extremely cautious when using such data. In the Panel's view it should not be used directly or indirectly to compare the clinical effectiveness of products or otherwise support clinical claims. There was no allegation on these points before the Panel. The Panel requested that both parties be advised of its views on this point which were also relevant to point 5 below.

5 Absence of relevant data

COMPLAINT

Johnson & Johnson noted that the presentation of the pie charts excluded the data relating to the percentage of successful quitters where no pharmacotherapy was provided. Had this data been presented, it would have been clear that the success rate for 'no pharmacological treatment' (55%) was seemingly as effective as both NRT and bupropion. This cast serious doubt over the validity of the results as it was well established that NRT and bupropion were efficacious treatments for nicotine dependence. This data was not provided and the

omission was therefore misleading.

Pfizer had argued that the data presented represented 'treatment used' and that the data were collected via standard methodology by the NHS Stop Smoking Services as recommended by the DoH. Nevertheless, Johnson & Johnson alleged that the absence of data for 'no pharmacological treatment' (which showed significant cessation rates) meant that the reader did not have sufficient information to draw their own conclusion about the validity of the data.

Johnson & Johnson alleged that the information presented was incomplete and therefore the recipient would be unable to form their own opinion of the therapeutic value of the medicine. Therefore, Johnson & Johnson alleged this was a breach of Clause 7.2.

RESPONSE

Pfizer pointed out that the pie charts were entitled 'Successful quitters at 4 week follow-up **by treatment** used (April 2007 - March 2008)' (emphasis added) thus the data presented was for quitters that took pharmacotherapy. The artwork presented on this page was a faithful representation of treatment used as presented by the NHS Stop Smoking Service report and gave an accurate, balanced, fair and objective view of the data. Pfizer did not agree that Clause 7.2 had been breached.

PANEL RULING

The Panel noted its comments about the report and data in point 4 above. The Panel noted Johnson & Johnson's submission that NRT and bupropion were established efficacious treatments for nicotine dependence. The Panel considered it would thus have been helpful to include data on those (55%) who successfully quit without pharmacotherapy. It was not clear whether people who did not receive pharmacotherapy would receive advice from the stop smoking service and whether it was this advice that had motivated smokers to quit. Given that the page was headed 'Champix and the NHS Stop Smoking Service' the Panel considered that the omission of the data was misleading as alleged such that the reader had insufficient information to assess the data presented; a breach of Clause 7.2 was ruled.

The Panel's views about use of the data in point 4 above also applied here.

6 Implied NHS endorsement

COMPLAINT

Johnson & Johnson alleged that the headline above the pie charts, 'Champix and the NHS stop smoking service', strongly implied that the NHS endorsed the use of Champix over and above other smoking cessation therapies. This was compounded by the presentation of the data which displayed the pie chart relating to Champix first despite the fact that many more patients were treated with NRT. Johnson & Johnson also noted that underneath the pie charts, 'CHAMPIX' appeared in capital letters and in a prominent blue font, whereas NRT and bupropion appeared less prominently in grey. Although the reader could be misled into believing that Champix was the NHS Stop Smoking Service medicine of choice, this was clearly not the case as only 14% of patients received it.

In summary, for the reasons outlined above, Johnson & Johnson alleged the page was misleading and implied that the NHS Stop Smoking Service endorsed Champix over and above other pharmacotherapies. This was unsupported by the data and was therefore misleading in breach of Clause 7.2.

RESPONSE

Pfizer did not agree that the headline implied that Champix was the medicine of choice of the NHS Stop Smoking Services. The headline pointed to the information below, which was the 4 week quit rates for all treatments, as reported by the NHS Stop Smoking Services. As the information detailed for all treatments was of equal size and proportion, Pfizer did not agree that this implied Champix was the medicine of choice. The charts presented not only the 4 week quit rates but also the number of smokers taking each smoking cessation treatment, clearly showing that the largest number (474,311 smokers) used NRT. Pfizer did not agree that a breach of Clause 7.2 had occurred.

PANEL RULING

The Panel noted the page heading 'Champix and the NHS Stop Smoking Service'. The Panel further noted that the phrase 'NHS stop smoking service' appeared in a green font, the same shade as the Champix data in the pie chart beneath. However the Panel did not consider that the use of colour, the heading or the page overall directly or indirectly implied NHS endorsement of Champix as alleged. Rather the page purported to reflect the Champix data published in the report. The page was not misleading on this point as alleged. No breach of Clause 7.2 was ruled.

B Champix journal advertisement (ref CHA752a)

1 Overall impression

COMPLAINT

The advertisement was entitled 'New NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10' referenced to the Department of Health (DoH) website. The text was broken over three lines with the largest font, highlighted in green, reserved for 'NHS Stop Smoking Services.'

Johnson & Johnson alleged that the heading, combined with the overall layout of the advertisement was extremely confusing and misleading. The overall impression was that the advertisement was guidance from the NHS Stop Smoking Service and that the service recommended use of Champix over and above other pharmacotherapies.

Johnson & Johnson alleged that the impression that the advertisement was NHS guidance was compounded by the statement (which appeared as the third of three bullet points beneath the heading) 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons …'. The word 'this' implied that the advertisement itself was the guidance.

Johnson & Johnson alleged that in addition, the only text-based reference to Champix 'An evidence-based choice in smoking cessation', in association with the heading, clearly implied that the NHS Stop Smoking Services recommended Champix over and above other treatments. This was not true. Indeed, the NHS Service and Monitoring Guidance 2009/10 stated that NRT, Champix and bupropion should all be made available first line.

Pfizer had submitted in the inter-company dialogue that the fact that the advertisement had both prescribing information and a Champix logo ensured that it simply served to create awareness of the NHS guidance. Johnson & Johnson disagreed. It was highly likely that many health professionals would be unaware that the inclusion of prescribing information and a product logo indicated that the item was an advertisement. Moreover, the inclusion of the Champix logo could serve to further the overall impression that Champix was the treatment of choice according to the NHS Stop Smoking Services guidance Johnson & Johnson alleged that the overall impression of the advertisement was ambiguous and therefore misleading in breach of Clause 7.2.

RESPONSE

Pfizer submitted that the advertisement was clearly for the new NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10 and was not the guidance itself. Half of the page consisted of prescribing information for Champix, the adverse event reporting box, references, a Champix logo, a Pfizer logo, a date of preparation and a Champix code. This did not look like an NHS document, nor did it have an official NHS logo.

Pfizer refuted that the advertisement misled the reader by suggesting that the service recommended use of Champix over and above other pharmacotherapies. The first bullet point of the advertisement stated 'To optimise success all recommended treatments will need to be offered as a first line intervention.'

Additionally, the claim 'Champix- An evidence-based choice in smoking cessation' was clearly referenced to the clinical trial evidence that supported it and it was an evidence based choice, not the evidence-based choice.

Pfizer did not agree that this was misleading and therefore denied a breach of Clause 7.2.

PANEL RULING

The advertisement headed 'New NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10' featured a bar chart which compared the relative impact of 3 stop smoking interventions (no support; individual behavioural support and group behavioural support) combined with no medication, NRT, bupropion or Champix on 4 week quit rates. The heading and bar chart were each asterisked to a footnote which cited the NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10. Adjacent to the bar chart were three bullet points: two highlighted DoH guidance whilst the third read 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons between treatments across different settings. The 4 week quit rates have not been measured directly but have been extrapolated from longer term quit rates'. The claim 'Champix – An evidenced-based choice in smoking cessation' ran below the text described above followed by the prescribing information. The product logo appeared in the bottom right hand corner.

The Panel noted that the NHS Service and Monitoring Guidance stated that Champix had been proven to be a highly cost-effective treatment resulting in average success rates of 61% at 4 weeks in the first and second quarters of 2008/2009. All motivated quitters should be given the optimum chance of success in any quit attempt and NRT, Champix and bupropion should all be made available in combination with intensive behavioural support as first-line treatments (where clinically appropriate).

The Panel considered that although the heading 'NHS Stop Smoking Services:' appeared in a green font, the same shade as the Champix data in the bar chart, readers would not assume that the advertisement was the official NHS Guidance or that Champix was its medicine of choice as alleged. It was clearly an advertisement for Champix. It featured promotional claims and prescribing information. No breach of Clause 7.2 was ruled.

2 The bar chart showing 4 week quit rates

COMPLAINT

Johnson & Johnson noted that the bar chart was referenced to the NHS Stop Smoking Services: Services and monitoring Guidance 2009/10 and was titled 'The relative impact of a variety of evidence-

based stop smoking interventions and pharmacotherapies upon 4 week quit rates'. The heading of the bar chart clearly indicated that the data portrayed the 'relative impact' of stop smoking interventions. 'Relative' emphasised the intention to draw a direct comparison between the treatments presented. However, any such comparison would be meaningless as there was no indication as to whether the differences were statistically significant. In addition, there were no patient numbers presented in the bar chart. This meant that the reader could not judge the context of the data. Johnson & Johnson alleged that the bar chart was misleading.

Pfizer argued that the title of the bar chart had been reproduced accurately from the NHS Stop Smoking Guidance and that no claim of statistical significance had been made or implied. Johnson & Johnson disagreed. The fact that the title had been faithfully reproduced and that no statistics were available did not make it acceptable to present data which implied superiority of one treatment over another in a promotional item, where superiority had not been demonstrated or referenced. It was an established principle under the Code that where graphically presented data suggested superiority, it was assumed to be statistically significant unless otherwise specified. Johnson & Johnson alleged that the comparative bar chart was misleading and hence in breach of Clauses 7.2, 7.3 and 7.8.

RESPONSE

Pfizer submitted that the bar chart had been reproduced from the NHS Stop Smoking Guidance. The title of the bar chart in the advertisement took the wording directly from the original. In addition, Pfizer had added a description alongside the bar chart which stated that the authors used the Cochrane Database of systematic reviews of smoking cessation treatments and performed indirect comparisons between treatments. It was therefore clear to the reader that this was not an interventional clinical trial which made direct comparisons between treatments. As this was not a clinical trial with an a priori hypothesis being tested there was no statistical analysis. Pfizer had presented the data as reported by the NHS which was in the public domain. Reporting data from Cochrane systematic reviews of evidence was an important addition to reporting efficacy results from single trials. Pfizer had deliberately also referenced a body of clinical trial evidence for Champix (Nides *et al*, Gonzales *et al*, Jorenby *et al* and Aubin *et al*). The NHS report provided further supporting data to the clinical trial evidence, it was from a reputable source and of interest to health professionals who worked in smoking cessation. Pfizer had represented the data in an accurate, balanced, fair and objective manner, therefore, it denied breaches of Clauses 7.2, 7.3 and 7.8.

PANEL RULING

The Panel noted, as stated in a very small footnote beneath the bar chart, that it was adapted from the Cochrane database of systematic reviews. It had been reproduced from the NHS stop smoking services: Services and Monitoring Guidance 2009/10. The bar chart invited the reader to directly compare the 4 week quit rates of each medicine and no medication when used in combination with 3 different evidenced based interventions. Champix had the most favourable outcome with each intervention. Further details about the Cochrane analysis were given in the third bullet point.

The Panel noted that the supplementary information to Clause 7.8 stated that artwork from published studies must be faithfully reproduced except where modification was necessary to comply with the Code. Differences which did not reach statistical significance must not be presented in such a way as to mislead. The Panel considered that the bar chart implied that in relation to each intervention statistically significantly more smokers quit with Champix than with any other treatment regimen. That was not necessarily so. The statistical significance of the data was unknown. The bar chart was misleading in this regard. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

3 Extrapolation of four week data

COMPLAINT

Johnson & Johnson noted that the third bullet point read 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons between treatments across different settings. The 4 week quit rates have not been measured directly but have been extrapolated from longer term quit rates.'

The Cochrane Reviews upon which these data were based appraised studies with a 6 month data point. It was therefore unclear either from the material or the source reference, how the 4 week data were calculated and whether the method used had suitable scientific validity for inclusion within promotional material.

Pfizer had failed to explain the basis of this extrapolated data, other than to state that the authors were reputable and credible and hence it believed the data to be valid. Johnson & Johnson alleged that this was insufficient as Pfizer was unable to substantiate the exact methods used to extrapolate the four week data.

Johnson & Johnson alleged that the extrapolation of data to a 4 week comparison without clear explanation or substantiation was misleading. The basis for the 4 week data had not been made sufficiently clear. Therefore, the advertisement was misleading and in breach of Clause 7.2. In addition, the 4 week data was not available and therefore could not be substantiated in breach of Clause 7.4.

RESPONSE

Pfizer noted that the text in the third bullet point stated that 4 week quit rates were not measured directly, but were extrapolated from longer term quit rates. As stated by Johnson & Johnson, the Cochrane reviews upon which these data were based appraised studies with a 6 month data point. In the same way that short term data from studies could be extrapolated to longer term, with the caveat that long term data had not been directly measured, here the reverse methodology had been used. The Cochrane reviews used longer term data, and the authors of the NHS guidance had extrapolated to the short term (4 weeks). In order not to mislead, Pfizer had made it clear that the 4 week data was calculated from longer term data rather than directly measured. Four week data was cited because this was the time point that was currently directly measured and monitored by NHS Stop Smoking Services across the UK.

Pfizer submitted that this data was substantiated by the published NHS Guidance document and the Cochrane Database of Systematic Reviews. In the same way that a calculation in a published peer reviewed clinical paper could be referenced to the clinical paper, a calculation in published NHS guidance could be referenced to the guidance. Pfizer did not believe that it would be expected to ask the authors of the NHS guidance, all of whom were recognised experts in the field of smoking cessation, to substantiate their data.

Pfizer denied a breach of Clauses 7.2 or 7.4.

PANEL RULING

The Panel noted its rulings and comments above. The Panel had concerns about the data. The Panel considered that the third bullet point made it clear that the 4 week quit rates had been extrapolated from longer term quit rates based on indirect comparisons between treatments across different settings. The Panel did not have a copy of the Cochrane reviews. On the evidence before it the Panel did not consider that it was necessary to provide further information about the calculation of the 4 week quit rates in the advertisement as alleged. The basis of the data was clear. No breach of Clause 7.2 was ruled on this very narrow point.

The Panel agreed with Pfizer that it was not for the authors of the NHS guidance to substantiate their data. The Code required that companies must be able to substantiate information, claim or comparisons (Clause 7.3) and such data be provided on request from a health professional (Clause 7.4).

The data presented in Pfizer's advertisement had to be capable of substantiation. The authors of the NHS guidance had extrapolated long term data published in the Cochrane reviews to a 4 week time point. No details about the calculation and any assumptions made were published in the NHS guidance document.

The Panel considered the allegation that Pfizer was unable to substantiate the four week data. The Panel noted the supplementary information to Clause 7.2 listed 'statistical information' as an area where particular care should be taken. This stated, *inter alia*, 'Care must be taken to ensure that there is a sound statistical basis for all information, claims and comparisons in promotional material.' It continued 'Instances have occurred where claims have been based on published papers in which the arithmetic and/or statistical methodology was incorrect. Accordingly, before statistical information is included in promotional material it must have been subjected to statistical appraisal'. The Panel considered that Pfizer's position, that it did not believe it would be expected to ask the authors of the NHS guidance, all of whom were recognised experts in the field of smoking cessation, to substantiate their data was unacceptable. It was Pfizer's responsibility to ensure that it could substantiate all claims and data in its promotional material irrespective of the source of such data. Thus, in the Panel's view, Pfizer should have satisfied itself that the extrapolation of the 4 week quit rates from longer term quit data was capable of substantiation before using such data in promotional material. Pfizer had not provided any data or detail about this calculation and thus the Panel considered that Pfizer had not substantiated the calculation of the 4 week quit rates. A breach of Clause 7.4 was ruled.

Complaint received **25 August 2009**

Case completed **11 November 2009**