CASE AUTH/2147/7/08

GLAXOSMITHKLINE v SANOFI PASTEUR MSD

Gardasil press release and agency emails

GlaxoSmithKline complained about materials issued by Sanofi Pasteur MSD and activities undertaken on behalf of the company following the Department of Health's (DoH) announcement to use Cervarix (GlaxoSmithKline's human papillomavirus (HPV) vaccine) for the national HPV immunisation programme for the prevention of cervical cancer, instead of Sanofi Pasteur MSD's vaccine, Gardasil. Cervarix and Gardasil were the only two vaccines licensed for the prevention of cervical cancer. At issue were a press release, entitled 'School girls in the UK will not benefit from the World's leading four type human papillomavirus (HPV) vaccine, Gardasil', issued on 18 June following the DoH's announcement about its choice of vaccine, and an email containing press coverage sent by Sanofi Pasteur MSD's public relations (PR) agency.

GlaxoSmithKline alleged that the claim in the press release that Gardasil provided 'unmatched cervical cancer protection' invited a comparison of Gardasil with Cervarix, was all embracing and there was no evidence from head-to-head studies to substantiate it. GlaxoSmithKline's head-to-head study was still ongoing and results were not yet available. The cross-study comparisons cited to support the claim were fundamentally flawed as it was not possible to directly compare the individual results as the populations, methodology and analyses varied between the studies.

In clinical trials, the two vaccines had shown similar, efficacy against cervical pre-cancerous lesions and this was reflected in the Cervarix summary of product characteristics (SPC).

The detailed response from Sanofi Pasteur MSD is given below.

The Panel noted that the press release stated 'We regret that school girls in the UK, unlike most of their peers in Western Europe, the USA, Australia, New Zealand and Canada, will not benefit from the unmatched cervical cancer protection and additional benefits provided by the World's leading HPV vaccine, Gardasil'. The Panel considered that, within the context of the press release, the claim implied that Gardasil had been unequivocally proven to be clinically superior to Cervarix with regard to cervical cancer protection. The SPCs for Gardasil and Cervarix reported high percentage efficacy rates for both products. There was no head-to-head data, however, and so it was not known if any of the differences between the products, based on the figures published in their respective SPCs, were clinically or statistically significant.

The Panel considered that the claim for unmatched cervical cancer protection was misleading, unsubstantiated and exaggerated. Breaches of the Code were ruled.

GlaxoSmithKline made three allegations regarding the claim 'In addition to protection from cervical cancer, Gardasil provides protection from precancerous cervical, vulval and vaginal lesions (an extension to the licence following a recent Commitee for Medicinal Products for Human Use (CHMP) positive opinion) and from genital warts caused by virus types targeted by the vaccine. The four HPV types 6, 11, 16 and 18 together cause the vast majority of cervical cancer and other HPV-related genital disease'.

Firstly GlaxoSmithKline noted that Gardasil was not licensed for the prevention of vaginal pre-cancerous lesions as implied by the claim; a CHMP positive opinion did not equate to a licence extension.

Secondly GlaxoSmithKline submitted that the second sentence of the claim, and indeed the whole press release, was intended to make the reader believe that enhanced cervical cancer protection was offered by choosing a vaccine with four antigens compared with a vaccine with two, when in fact the additional two HPV types (6 and 11) had no impact on cervical cancer protection. The word 'together' perpetuated the misconception. This grouping of HPV types was continued throughout the press release, misleading readers into believing all four types had an impact on cervical cancer.

Thirdly GlaxoSmithKline alleged that the implication that Gardasil could prevent the 'vast majority' of cervical cancer was falsely reassuring, exaggerated the potential benefits of Gardasil in cervical cancer protection, and could affect future uptake of the UK cervical screening programme. HPV 16 and 18 – the two cancer-causing HPV types that Gardasil protected against – did not account for the 'vast majority' of cervical cancer. HPV 16 and 18 caused 70% of cervical cancers, which although substantial did not equate to the vast majority; the common understanding of 'vast majority' would lead people to believe that HPV 16 and 18 caused over 90% of cervical cancers. Sanofi Pasteur MSD had attempted to justify the use of 'vast majority' since it 'related to the diseases, not the vaccine'. However, it was naïve to suggest that the reader would not link this statement with the protection offered by the 'four type (HPV 6, 11, 16, 18) HPV vaccine, Gardasil'. Furthermore, regardless of whether or not the sentence related to the vaccine or the disease, it was inaccurate to say that '6, 11, 16 and 18 together caused the vast majority of cervical cancers…'.

GlaxoSmithKline alleged that the claim, in the context of the rest of the press release, was misleading and exaggerated.

The Panel noted that GlaxoSmithKline was concerned that the claim 'In addition to protection from cervical cancer, Gardasil provides protection from precancerous cervical, vulval and vaginal lesions (an extension to the licence following a recent CHMP positive opinion) …' implied that Gardasil was licensed for the prevention of vaginal pre-cancerous lesions which was not so. Sanofi Pasteur MSD submitted that the matter was satisfactorily dealt with in inter-company dialogue and the archived copy of the press release had been altered. The sentence in the amended copy was the same as the original version except that the text in brackets stated '(the subject of a CHMP positive opinion)'.

In the Panel's view the amended copy of the press release did not substantially change the message; some readers would continue to assume that Gardasil could be used to provide protection from pre-cancerous vaginal lesions and that the product was so authorized. This was not so. Such an implication was inconsistent with the Gardasil SPC and misleading and a breach was ruled. The Panel noted that a press release should not be promotion of a medicine and thus on these narrow grounds the Panel ruled no breach of the Code.

In the Panel's view the second sentence at issue 'The four HPV types 6, 11, 16 and 18 together cause the vast majority of cervical cancer and other HPV-related genital disease' was ambiguous. Some readers might assume that the claim implied that all four HPV types played a role in cervical cancer which was not so. In that regard the claim was misleading and a breach was ruled.

The second sentence stated that the four HPV types together caused the vast majority of cervical cancer and other HPV-related genital disease. In the Panel's view the claim was ambiguous; some readers would assume that the four HPV types caused the vast majority of cervical cancer. GlaxoSmithKline had submitted that HPV 16 and 18 caused 70% of cervical cancers and Sanofi Pasteur MSD submitted it was 75%. In the Panel's view the use of 'vast majority' to describe 70% or 75% was exaggerated as alleged. It was difficult to know exactly what figure constituted a 'vast majority' but in this instance the 30% or 25% of cervical cancers which were not caused by HPV 16/18 was a sizable minority. The Panel ruled a breach of the Code.

GlaxoSmithKline noted that the press release contained a number of statements relating to choice of HPV vaccine by governments/health authorities and health professional preferences, which were inaccurate, misleading and disparaged Cervarix and the DoH's choice of vaccine for the UK immunisation programme. The press release had six footnotes, three of which related to the following claims:

'In all other tenders awarded to date in Western Europe†, health authorities have chosen Gardasil for about 80% of the population covered'. (The footnote† stated 'Regional tenders in Italy, Spain, Sweden; a national tender in Switzerland'.)

GlaxoSmithKline submitted that the word 'chosen' in relation to tenders in this claim was of key importance. In order for there to be a choice, both vaccines had to have been licensed and able to submit a tender application.

Since it received its marketing authorization Cervarix had been awarded nearly two thirds of EU regional and national tenders that had occurred. At the time of the UK tender announcement, Cervarix had been awarded 19 of 29 EU tenders, excluding the UK and Denmark.

Even if one used the countries 'selected' by Sanofi Pasteur MSD and highlighted in the footnote, Cervarix had been awarded the majority; winning 16 out of 23 tenders in Italy, Spain and Sweden. Cervarix was not licensed in Switzerland and so it was inappropriate to use it to support a statement where choice was explicit. Furthermore, GlaxoSmithKline did not agree that it was appropriate to clarify the regulatory status in Switzerland in a footnote to another statement.

Although Sanofi Pasteur MSD had stated that it considered it more accurate not to quote the number of tenders awarded (as some were local or regional and covered small populations) but rather to quantify in terms of the proportion of the population covered, this was at stark odds with the press release which was very much focussed on 'choice'; indeed 'choice' was used four more times.

- **'Two years after its first launch in June 2006, Gardasil is today the HPV vaccine of choice across the world…'.**
- **'…Gardasil will continue to be the HPV vaccine of choice for girls and women worldwide'.**
- **'Where doctors can choose between the two vaccines, more than 9 out of 10 doctors worldwide choose Gardasil'.**
- **'The tender decision made by the UK authorities choosing a two-type (16/18) HPV vaccine for their immunisation campaign means that the girls in this campaign will not benefit from…'.**

GlaxoSmithKline suggested that Sanofi Pasteur MSD selected 'population covered' because the statement 'in all other tenders awarded to date in Western Europe, health authorities have chosen Cervarix', would have been less appealing for the purposes of the press release.

This claim used by Sanofi Pasteur MSD could not be substantiated and was misleading; and although the company claimed to have 'robust evidence' to support it, it had not been provided.

'Gardasil is, or will be, used exclusively for campaigns in the USA, Australia, New Zealand,

Canada and Switzerland‡'. (The footnote‡ stated 'The two-type vaccine has not yet been approved in Canada and Switzerland to the best of our knowledge'.)

GlaxoSmithKline submitted that the claim implied that health service providers in all five countries had actively selected Gardasil over Cervarix, when in fact Cervarix was not actually licensed in three of the countries; following inter-company dialogue, Sanofi Pasteur MSD had stated that it would correct the footnote to include the USA. Nevertheless, to attempt to clarify the regulatory situation, and the true meaning of the statement, by the use of a footnote (positioned eight paragraphs away) was inadequate.

Sanofi-Pasteur MSD had noted that unlike the previous claim which had used the word 'chosen', this claim used '*used*' which did not imply any process of selection. However, a similarly misleading claim occurred earlier in the press release: 'Countries like Australia, New Zealand, *Canada*, France and *Switzerland* have *chosen* Gardasil preferentially or exclusively for their vaccination campaigns' (emphasis added). Again, Canada and Switzerland were cited as countries that had chosen Gardasil, when in fact no choice was available as Cervarix was not licensed in either. GlaxoSmithKline submitted that Sanofi Pasteur MSD's contradictory explanation exposed its clear intention to mislead.

'Where doctors can choose between the two vaccines§, more than 9 out of 10 doctors worldwide choose Gardasil'. (The footnote§ read 'Germany, France and Belgium in Western Europe'.)

Sanofi-Pasteur MSD had stated that although the footnote referred to only three countries, the claim was not confined to Germany, France and Belgium – these were cited as examples in Western Europe, Sanofi Pasteur MSD's territory. This was misleading and exaggerated. Again no evidence had been provided to support individual doctor choice in a global context.

GlaxoSmithKline alleged that the claims were misleading, exaggerated and incapable of substantiation. Furthermore, their use in the context of the press release about the 'UK authorities choosing a two-type (16/18) HPV vaccine', disparaged Cervarix and the DoH choice of vaccine.

The Panel noted that the selection of vaccine by a country/region for use was complicated. The basis of choice could be one of a number of options depending on the regulatory status of the vaccines in the country. Firstly a choice between two licensed products Gardasil and Ceravix, secondly a choice between a licensed product (Gardasil) and an unlicensed product (Ceravix) and thirdly a choice between the only licensed vaccine (Gardasil) or nothing. A fourth factor was also relevant given the differences in indications for the products ie did the country/region only want to vaccinate against cervical cancer or against cervical cancer and genital warts. The Panel did not consider that the press release was sufficiently clear about the options available and the regulatory status of the products at the time the tender decisions were made. The Panel considered it was really important to include very clear information about the factors that might have influenced the tendering decisions round the world. Simple claims were not sufficient given the complexity of the situation.

The three other claims at issue all relied on footnotes to provide clarification. The supplementary information to the Code stated '… that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like'.

In the claim 'In all other tenders awarded to date in Western Europe, health authorities have chosen Gardasil for about 80% of the population covered', Western Europe was asterisked to a footnote 'Regional tenders in Italy, Spain, Sweden; a national tender in Switzerland'. The Panel considered that this was misleading as Italy, Spain, Sweden and Switzerland were a small part of Western Europe. Further, Cervarix was not licensed in Switzerland and so in that country Gardasil was chosen instead of nothing; in the Panel's view the majority of readers would not realise this. The Panel considered that the claim was misleading and in that regard could not be substantiated. Breaches of the Code were ruled.

The claim 'Gardasil is, or will be, used exclusively for campaigns in the USA, Australia, New Zealand, Canada and Switzerland' relied upon the footnote 'The two-type vaccine has not yet been approved in Canada and Switzerland to the best of our knowledge'. The Panel noted its comments above regarding choice and the reader's knowledge of product availability. As above the Panel considered that the claim was misleading and a breach of the Code was ruled.

The claim 'Where doctors can choose between the two vaccines, more than 9 out of 10 doctors worldwide choose Gardasil' relied on the footnote 'Germany, France and Belgium in Western Europe'. The Panel considered that the claim was misleading in its reliance upon a footnote for clarity. The Panel further considered that it was exaggerated to use data from only Germany, France and Belgium in a worldwide claim. Breaches of the Code were ruled. The claim had not been substantiated by the data relating solely to Germany, France and Belgium. Further, as this data was confidential and not to be provided to GlaxoSmithKline it could not be considered by the Panel. A breach of the Code was ruled.

The Panel considered that the claims at issue undermined the DoH's choice of Cervarix and thus disparaged both the product and the DoH. Breaches

of the Code were ruled.

GlaxoSmithKline noted that there was no direction on the Sanofi Pasteur MSD's website or press release itself that it was intended for medical journalists only; it appeared to have been distributed widely to both medical and consumer press. Although company press releases could be distributed to the consumer media when appropriate, particular care must be taken not to promote prescription only medicines to the public and the information presented must be factual and balanced. This was clearly not the case. The purpose of the press release appeared to be to encourage the public to question the choice of vaccine by the DoH and invite them to specifically request Gardasil, which was mentioned 13 times.

In defence of this allegation, Sanofi Pasteur MSD had stated that HPV vaccination was not available outside the national programme. However, Sanofi Pasteur MSD would know that both vaccines were prescribed privately and, although the DoH's Green Book stated that 'vaccination is not routinely recommended for those aged 18 years or over', HPV vaccination could be prescribed on a case-by-case basis to individual women who might benefit.

GlaxoSmithKline alleged the distribution of the press release to consumer media, and therefore the public, was in breach of the Code.

In addition to the press release Sanofi Pasteur MSD distributed, via a PR agency, two emails following the DoH announcement. The first email contained the press release and was sent on 18 June, the day of the DoH announcement; the second contained a summary of the press coverage relating to the tender announcement and was sent the following day. Although the email covered a broad range of media types and publications, GlaxoSmithKline disagreed with Sanofi Pasteur MSD's statement '…the synthesis of the media coverage was not selective'.

Only statements from patient advocacy groups who would be expected to have an interest in protection from genital warts were included: BASHH (British Association for Sexual Health and HIV), Brook (the UK's leading provider of sexual health services and advice for the under 25s) and the Terrence Higgins Trust; the absence of a cervical cancer/cancer advocacy group statement was striking and significant.

Furthermore, the PR agency was careful to note the negative media coverage: 'a number of publications have raised concerns about the Department's decision including The Times, BBC Online, PA News, Reuters, Channel Four, Yorkshire Post, Newcastle Chronicle, Cheshire News'. It was clear that the email was intended to reinforce the messages in the press release.

In addition, of the 21 national and regional articles highlighted in the email, 16 appeared to have been significantly influenced by the Sanofi Pasteur MSD press release, containing direct content/quotes or similar misinformed and misleading messages to those discussed earlier.

In addition to the media, the PR agency distributed the Sanofi Pasteur MSD press release and press coverage in unsolicited emails to health professionals. Due to their surprise at receiving such a press release from Sanofi Pasteur MSD, and their concerns of the impact that this might have on the national immunisation programme, a number of health professionals had contacted GlaxoSmithKline anonymously.

The way in which both emails were used by the PR agency made them promotional and thus subject to the Code. Sanofi Pasteur MSD claimed the distribution was limited to a small group of individuals and organisations who received regular media updates about HPV vaccination. However, this was at odds with GlaxoSmithKline's understanding, and Sanofi Pasteur MSD had not provided any evidence in support of the explicit prior permission which it had received from the health professional recipients. GlaxoSmithKline alleged that the unsolicited distribution of these emails to health professionals breached the Code.

The Panel noted that the press release had been issued to the consumer press. It was not unacceptable to issue press releases about prescription only medicines to the consumer press providing that the information contained therein was factual and balanced. Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine.

The Panel considered that, *inter alia*, describing Gardasil as the World's leading four-type HPV vaccine, with unmatched cervical cancer protection, would encourage patients to ask for the medicine. A breach of the Code was ruled.

With regard to whether the emails were unsolicited, the Panel noted Sanofi Pasteur MSD's submission that a relationship existed between it and the recipients and that they had all received correspondence of a similar nature before. The company had further submitted that the emails were sent to specific individuals because of their role in providing Sanofi Pasteur MSD with advice as well as being experts in handling the media. The Panel was concerned that no explanation had been given in the emails that the PR agency sending the material was acting on behalf of Sanofi Pasteur MSD. Nor did the email state that the audience were those who had a role in providing Sanofi Pasteur MSD with advice. It appeared from Sanofi Pasteur MSD's response that the emails were sent to health professionals who were, in some capacity, acting as consultants to the company. On that basis the Panel considered that the emails were not unsolicited promotional material as alleged. No breach of the Code was ruled.

During its consideration of this matter, the Panel noted with concern Sanofi Pasteur MSD's submission that emails had been sent out by its PR agency without formal copy approval by the company. This was wholly unacceptable; pharmaceutical companies could not delegate their responsibilities under the Code to a third party.

GlaxoSmithKline submitted that Sanofi Pasteur MSD's activities and materials provided evidence of the coordinated campaign, designed to question the robustness of the DoH's decision in its choice of vaccine for the immunisation programme and leave the reader believing that the UK government, unlike most other health authorities, had chosen a less effective vaccine to protect UK girls and women. The widespread distribution of material to the medical and consumer media, health professionals and other organisations would encourage health professionals and the public to question the DoH's vaccine choice and ask for Gardasil, which was mentioned by name 13 times.

GlaxoSmithKline stated that Sanofi Pasteur MSD's campaign had a number of potentially serious consequences. Firstly, the uptake of immunisation was likely to be affected, reducing the number of girls who could benefit from vaccination to prevent cervical cancer. Secondly, for those who had been vaccinated against HPV 16 and 18, the mistaken belief that they would be protected against the 'vast majority' of cervical cancers might lead to a false sense of security and reduce future cervical screening attendance, which was already in decline in younger age groups. This would increase the chances of a pre-cancerous lesion progressing to cervical cancer.

In addition to the clauses cited above GlaxoSmithKline alleged that Sanofi Pasteur MSD had breached the Code in that high standards had not been maintained to the extent that its activities brought discredit upon, and seriously undermined confidence in the pharmaceutical industry and its ability to self-regulate in breach of Clause 2.

The Panel noted that GlaxoSmithKline had requested that Sanofi Pasteur MSD issue a corrective letter. This was not a sanction available to the Panel. It was only available to the Appeal Board.

The Panel noted its rulings of breaches of the Code above. It considered that Sanofi Pasteur MSD had not been sufficiently clear about the situation and thus would cause further confusion in a complicated matter. Taking all the circumstances into account the Panel decided that high standards had not been maintained and a breach of the Code was ruled. On balance the Panel did not consider that the circumstances were in breach of Clause 2 which was used as a sign of particular censure.

GlaxoSmithKline UK Ltd complained about materials issued by Sanofi Pasteur MSD and activities undertaken on behalf of the company following the Department of Health's (DoH) announcement to use Cervarix (GlaxoSmithKline's human papillomavirus (HPV) vaccine) for the national HPV immunisation programme for the prevention of cervical cancer, instead of Sanofi Pasteur MSD's vaccine, Gardasil. Cervarix and Gardasil were the only two vaccines licensed for the prevention of cervical cancer. At issue were a press release, entitled 'School girls in the UK will not benefit from the World's leading four type human papillomavirus (HPV) vaccine, Gardasil', issued on 18 June following the DoH's announcement about its choice of vaccine, and an email containing press coverage sent by Sanofi Pasteur MSD's public relations (PR) agency. Inter-company dialogue had failed to resolve the issues.

By way of background, Sanofi Pasteur MSD submitted that HPV was a ubiquitous virus, with four genotypes (6, 11, 16 and 18) together known to cause approximately 75% of cervical cancers in Europe, 90% of genital warts, at least 50% of cases of high and low-grade cervical pre-cancerous lesions, and 43-62% of cases of vulval and vaginal pre-cancerous lesions. Cervical cancer was usually preceded by identifiable, pre-cancerous stages – CIN (cervical intraepithelial neoplasia). CIN was classified according to the extent of the penetration of abnormal epithelial cells into the cervical mucosa, where CIN 1 was the least severe with abnormal cells occupying the first third of the cervical mucosa and CIN 3 was the most severe with abnormal cells occupying the full thickness of the cervical mucosa. The CIN 3 label denoted severe dysplasia or carcinoma in situ (CIS). When the disease had penetrated the basement membrane of the cervical epithelium and moved into the underlying tissue, the cancer was termed 'invasive'. In practice, histologically it could be difficult to separate CIN 2 and 3; hence they were often considered together.

HPV vaccines stimulated the immune system, providing protection against diseases caused by the targeted HPV types. It was well recognised, for example by the World Health Organization (WHO), that there was no immunological correlate of short or long term protection for any HPV vaccine type. Therefore no correlation existed between immune response, in particular antibody levels, and efficacy against clinical disease due to HPV. Given the long time delay in the development of cervical cancers (up to 10 years or more from initial HPV infection), efficacy against cervical cancer was neither a feasible nor an ethical endpoint in clinical trials. The Gardasil phase 3 trials were designed to show efficacy against CIN 2/3 and CIS with high precision. This surrogate endpoint was recommended by a number of official bodies, including the WHO and the Food and Drug Administration (FDA), as the means to demonstrate vaccine efficacy since these lesions were the obligate and immediate precursors to invasive cancer.

The complaint was considered under the 2006 Code using the 2008 Constitution and Procedure.

Press release

1 'Unmatched cervical cancer protection'

COMPLAINT

The press release stated that Gardasil provided 'unmatched cervical cancer protection'. The claim invited a comparison of Gardasil with Cervarix, when there was no evidence from head-to-head studies to substantiate this all-embracing claim. GlaxoSmithKline's head-to-head study was still ongoing and results were not yet available.

GlaxoSmithKline acknowledged the data provided by Sanofi Pasteur MSD to justify this claim. However, the cross-study comparisons cited were fundamentally flawed as it was not possible to directly compare the individual results as the populations, methodology and analyses varied between the studies.

In clinical trials, the two vaccines had shown similar, excellent efficacy against cervical pre-cancerous lesions and this was reflected in the Cervarix summary of product characteristics (SPC). The primary end point analysis from a large study involving over 18,000 girls and women was tabulated in section 5.1: Cervarix provided 90.4% protection against HPV 16 and/or 18 cervical pre-cancerous lesions. However, this was an area of emerging scientific knowledge and several of the lesions were found to contain multiple HPV types (including non-vaccine types), which was unexpected and it was difficult to determine which HPV type had actually caused the lesion. Therefore, an additional analysis was conducted to determine vaccine efficacy against lesions likely to have been caused by HPV 16 and/or 18 and the SPC stated 'Based on this analysis there were no cases in the vaccine group and 20 cases in the control group (Efficacy 100%; 97.9% CI: 74.2; 100)'. In another study, involving approximately 750 girls and women, Cervarix had demonstrated similar efficacy (100%) which had been sustained for at least 6.4 years to date; this was the longest duration of protection reported for any HPV 16/18 vaccine.

GlaxoSmithKline alleged that the claim breached Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

Sanofi Pasteur MSD submitted that the extensive clinical trials programme for Gardasil had involved more than 30,000 subjects and contributed data that, in 2006, resulted in its fast track approval in the US and rapid approval in Europe. The pivotal phase 3 FUTURE studies were terminated early once it became clear that it was unethical for placebo recipients to remain unprotected when such an efficacious vaccine was available. In light of the high and sustained efficacy demonstrated by Gardasil, the independent Data and Safety Monitoring Board (DSMB) for the FUTURE studies recommended that all women receiving placebo should be offered the benefit of Gardasil. In contrast, Cervarix was licensed in Europe in late 2007 and, despite having been filed in the US in early 2007, the evaluation by the FDA was still on-going after GlaxoSmithKline had responded only very recently to a complete response letter sent by the FDA in December 2007.

Sanofi Pasteur MSD acknowledged that direct comparisons were not possible since populations, methodologies and analyses varied between studies, however it was also true that only Gardasil had robust and complete phase 3 data that was currently unmatched by any other cervical cancer vaccine.

Sanofi Pasteur MSD disagreed with GlaxoSmithKline that clinical trials had shown similar, excellent efficacy against cervical pre-cancerous lesions. GlaxoSmithKline referred to data from a study of 18,000 girls and women. However, to date it had only been able to communicate 15 month interim data from this phase 3 study, which were included in the Ceravix SPC. In the primary analysis, the observed efficacy of Cervarix against HPV 16/18-related CIN 2+ was 90.4% [95% CI: 53.4, 99.3]. Statistically significant efficacy was demonstrated against HPV 16-related CIN 2+ but not against HPV 18-related CIN 2+. Efficacy against HPV 16-related CIN 2+ was 93.3% (95% CI: 47.0, 99.9). Point estimate for efficacy against HPV 18-related CIN 2+ was 83.3% (95% CI: <0.0, 99.9).

In combined clinical trials, Gardasil had demonstrated a consistently high level of protection against high grade cervical cancer precursors that no other vaccine had been able to match. Data from three years of follow up were included in the SPC which showed that in the per protocol population the observed efficacy of Gardasil against HPV 16/18-related CIN 2/3 and CIS was 100% (95% CI: 92.9, 100).

Four year follow-up data was also available and, in the per protocol population, the observed efficacy of Gardasil against HPV 16/18-related CIN 2/3, CIS or worse was 98.2% (95% CI: 93.5, 99.8). Statistically significant efficacy was demonstrated against HPV 16-related CIN 2/3, 97.9% (95% CI: 92.3, 99.8) as well as against HPV 18-related CIN 2/3, 100% (95% CI: 86.6, 100).

Far from being an area of emerging scientific knowledge, as submitted by GlaxoSmithKline, Sanofi Pasteur MSD stated that there was now a wealth of clinical experience with Gardasil with more than 30 million doses distributed worldwide (by the end of June 2008), building on the strong data from large multinational trials. Sanofi Pasteur MSD also noted with interest that in its complaint, and which also formed the main content of a recent GlaxoSmithKline press release, GlaxoSmithKline referred to a phase 2 study which involved approximately 750 girls and women to attempt to

demonstrate a duration of sustained efficacy of at least 6.4 years. This was a small study which was insufficiently powered to demonstrate efficacy against the individual vaccine HPV types. This was in comparison to more than 20,000 women followed in combined studies of Gardasil that yielded the results described above. In addition, the Cervarix SPC stated that 'duration of protection has not fully been established'. In the absence of true head-to-head results, based on clinically meaningful efficacy endpoints, it was surprising that GlaxoSmithKline considered it permissible to claim that its study demonstrated the longest duration of protection reported for any vaccine against HPV 16 and 18. This was in itself misleading since, not only was the study inadequately powered, but it also inferred a comparison between the Cervarix phase 2 data and Gardasil phase 3 data which was not valid.

Considering the above data, Sanofi Pasteur MSD considered that the claim was fair, balanced and factual, readily substantiated and not exaggerated. Sanofi Pasteur MSD considered it was beyond dispute that the protection afforded by Gardasil was indeed unmatched. Consequently it refuted the allegation of breaches of Clauses 7.2, 7.4 and 7.10.

PANEL RULING

The Panel noted that the second paragraph of the press release stated 'We regret that school girls in the UK, unlike most of their peers in Western Europe, the USA, Australia, New Zealand and Canada, will not benefit from the unmatched cervical cancer protection and additional benefits provided by the World's leading HPV vaccine, Gardasil'. The Panel considered that, within the context of the press release, the claim implied that Gardasil had been unequivocally proven to be clinically superior to Cervarix with regard to cervical cancer protection.

The Panel noted that the SPCs for Gardasil and Cervarix reported high percentage efficacy rates for both products. There was no head-to-head data, however, and so it was not known if any of the differences between the products, based on the figures published in their respective SPCs, were clinically or statistically significant.

The Panel considered that the claim for unmatched cervical cancer protection was misleading, unsubstantiated and exaggerated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

2 Claim 'In addition to protection from cervical cancer, Gardasil provides protection from precancerous cervical, vulval and vaginal lesions (an extension to the licence following a recent CHMP positive opinion) and from genital warts caused by virus types targeted by the vaccine. The four HPV types 6, 11, 16 and 18 together cause the vast majority of cervical cancer and other HPV-related genital disease.'

COMPLAINT

GlaxoSmithKline noted that Gardasil was not licensed for the prevention of vaginal pre-cancerous lesions as implied by the claim; a CHMP positive opinion did not equate to a licence extension.

GlaxoSmithKline submitted that the second sentence of the claim, and indeed the whole press release, was intended to make the reader believe that enhanced cervical cancer protection was offered by choosing a vaccine with four antigens compared with a vaccine with two, when in fact the additional two HPV types (6 and 11) had no impact on cervical cancer protection. The word 'together' perpetuated the misconception. This grouping of HPV types was continued throughout the press release, misleading readers into believing all four types had an impact on cervical cancer.

Sanofi Pasteur MSD would know that the role of the specific HPV types in cervical cancer was poorly understood by health professionals and the public and so it was vital that any media messages intended for these audiences made it clear that HPV 6 and 11 in Gardasil did not add to the cervical cancer protection afforded by HPV 16 and 18.

Although Sanofi Pasteur MSD claimed there was no intention to suggest types 6 and 11 caused cervical cancer, and that it had simply referred to them in numerical order, it was the lack of a clear and explicit statement that HPV 6 and 11 caused genital warts and HPV 16 and 18 caused cervical cancer that made the claim misleading by omission. The paragraph could easily have been constructed to be clear and unambiguous by adding an introductory sentence such as 'HPV 16 and 18 cause cervical cancer and HPV 6 and 11 are responsible for genital warts'. This fundamental point was not clarified anywhere, despite the HPV types being repeatedly mentioned throughout.

GlaxoSmithKline alleged that the implication that Gardasil could prevent the 'vast majority' of cervical cancer was falsely reassuring, exaggerated the potential benefits of Gardasil in cervical cancer protection, and could affect future uptake of the UK cervical screening programme.

HPV 16 and 18 – the two cancer-causing HPV types that Gardasil protected against – did not account for the 'vast majority' of cervical cancer. HPV 16 and 18 caused 70% of cervical cancers, which although substantial did not equate to the vast majority; the common understanding of 'vast majority' would lead people to believe that HPV 16 and 18 caused over 90% of cervical cancers.

GlaxoSmithKline noted that Sanofi Pasteur MSD had attempted to justify the use of 'vast majority' since it 'related to the diseases, not the vaccine'. However, it was naïve to suggest that the reader would not link this statement with the protection offered by the 'four type (HPV 6, 11, 16, 18) HPV vaccine, Gardasil'. Furthermore, regardless of

whether or not the sentence related to the vaccine or the disease, it was inaccurate to say that '6, 11, 16 and 18 together caused the vast majority of cervical cancers…'.

GlaxoSmithKline alleged that the claim, in the context of the rest of the press release, was misleading and exaggerated in breach of Clauses 3.2, 7.2 and 7.10.

RESPONSE

Sanofi Pasteur MSD noted that, as agreed during inter-company dialogue, it had clarified the wording in the archive copy of the press release to distinguish that pre-cancerous vaginal lesions were the subject of a positive CHMP opinion and so the company was surprised that the allegation remained in the complaint.

Sanofi Pasteur MSD agreed that a positive CHMP opinion did not equate to a licence extension, but was the step before the licence extension was granted. However, the claim at issue did not state that this was the indication of Gardasil. Furthermore, in the notes to editors below, the precise regulatory status of the indication extension was described. Notwithstanding, inclusion of the fact that Gardasil could protect against pre-cancerous lesions of the vagina was acceptable in accordance with Clause 20.2 (2006 Code). Sanofi Pasteur MSD therefore also refuted this allegation of a breach of Clause 3.2.

With regard to the final sentence of the claim, there was no intention to suggest that HPV types 6 and 11 caused cervical cancer. The sentence was carefully constructed in order to state that the four types together caused the vast majority of HPV-related genital diseases, including cervical cancer which was specifically mentioned as it was the primary target for vaccination. When the four types were referred to together, logically, they were always referred to in numerical order (6, 11, 16 and 18); the order stated nothing about which types caused which diseases.

Sanofi Pasteur MSD submitted that the press release did not imply that Gardasil could prevent the vast majority of cervical cancer. The sentence describing its licensed indications was factual and stood alone. In addition, further detail was provided in the notes to editors. The sentence containing 'vast majority' came afterwards and clearly related to the diseases, not the vaccine.

Sanofi Pasteur MSD considered that the claim at issue was factual, capable of substantiation and did not imply anything about Gardasil, let alone exaggerate its potential benefits.

Sanofi Pasteur MSD noted that GlaxoSmithKline's final point regarding the statement focused on the phrase 'vast majority', alleging that it implied that Gardasil protected against the vast majority of cervical cancer. As stated above, the claim did not imply this. When taken together, however, Sanofi Pasteur MSD considered that in preventing 75% of cervical cancer and over 90% of genital warts, it was reasonable to state that 'The four HPV types 6, 11, 16 and 18 together cause the vast majority of cervical cancer and other HPV-related genital diseases'.

Consequently the company considered that that the claim did not refer to unauthorised indications, was not misleading and did not use superlatives. Sanofi Pasteur MSD therefore denied breaches of Clauses 3.2, 7.2 and 7.10.

PANEL RULING

The Panel noted that GlaxoSmithKline was concerned that the statement 'In addition to protection from cervical cancer, Gardasil provides protection from precancerous cervical, vulval and vaginal lesions (an extension to the licence following a recent CHMP positive opinion) …' implied that Gardasil was licensed for the prevention of vaginal pre-cancerous lesions which was not so. Sanofi Pasteur MSD had submitted that the matter was satisfactorily dealt with in inter-company dialogue and the archived copy of the press release had been altered. The Panel noted that the sentence in the amended copy was the same as the original version except that the text in brackets stated '(the subject of a CHMP positive opinion)'. GlaxoSmithKline had not referred to the inter-company dialogue on this point.

In the Panel's view the amended copy of the press release did not substantially change the message; some readers would continue to assume that Gardasil could be used to provide protection from pre-cancerous vaginal lesions and that the product was so authorized. This was not so. Such an implication was inconsistent with the particulars listed in the Gardasil SPC and misleading; a breach of Clause 7.2 was ruled. The Panel noted that Clause 3 related to the promotion of a medicine. A press release should not be promotional. Thus on these narrow grounds the Panel ruled no breach of Clause 3.2.

In the Panel's view the second sentence at issue 'The four HPV types 6, 11, 16 and 18 together cause the vast majority of cervical cancer and other HPV-related genital disease' was ambiguous. Some readers might assume that the claim implied that all four HPV types played a role in cervical cancer which was not so. In that regard the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that the second sentence stated that the four HPV types together caused the vast majority of cervical cancer and other HPV-related genital disease. In the Panel's view the claim was ambiguous; some readers would assume that the four HPV types caused the vast majority of cervical cancer. GlaxoSmithKline had submitted that HPV 16

and 18 caused 70% of cervical cancers and Sanofi Pasteur MSD submitted it was 75%. In the Panel's view the use of 'vast majority' to describe 70% or 75% was exaggerated as alleged. It was difficult to know exactly what figure constituted a 'vast majority' but in this instance the 30% or 25% of cervical cancers which were not caused by HPV 16/18 was a sizable minority. The Panel ruled a breach of Clause 7.10.

3 Tender awards and health professional preferences

COMPLAINT

GlaxoSmithKline alleged that the press release contained a number of statements relating to choice of HPV vaccine by governments/health authorities and health professional preferences, which were inaccurate, misleading and disparaged Cervarix and the DoH's choice of vaccine for the UK immunisation programme. The press release had six footnotes, three of which related to the following claims:

- **'In all other tenders awarded to date in Western Europe†, health authorities have chosen Gardasil for about 80% of the population covered'**

The footnote† stated 'Regional tenders in Italy, Spain, Sweden; a national tender in Switzerland'.

GlaxoSmithKline submitted that the word 'chosen' in relation to tenders in this claim was of key importance. In order for there to be a choice, both vaccines had to have been licensed and able to submit a tender application.

Since it received its marketing authorization Cervarix had been awarded nearly two thirds of EU regional and national tenders that had occurred. At the time of the UK tender announcement, Cervarix had been awarded 19 of 29 EU tenders, excluding the UK and Denmark.

Even if one used the countries 'selected' by Sanofi Pasteur MSD and highlighted in the footnote, Cervarix had been awarded the majority; winning 16 out of 23 tenders in Italy, Spain and Sweden. Cervarix was not licensed in Switzerland and so it was inappropriate to use it to support a statement where choice was explicit. Furthermore, GlaxoSmithKline did not agree that it was appropriate to clarify the regulatory status in Switzerland in a footnote to another statement.

Although Sanofi Pasteur MSD had stated that it considered it more accurate not to quote the number of tenders awarded (as some were local or regional and covered small populations) but rather to quantify in terms of the proportion of the population covered, this was at stark odds with the press release which was very much focussed on 'choice'; indeed 'choice' was used four more times.

- 'Two years after its first launch in June 2006, Gardasil is today the HPV vaccine of choice across the world…'.
- '…Gardasil will continue to be the HPV vaccine of choice for girls and women worldwide'.
- 'Where doctors can choose between the two vaccines, more than 9 out of 10 doctors worldwide choose Gardasil'.
- 'The tender decision made by the UK authorities choosing a two-type (16/18) HPV vaccine for their immunisation campaign means that the girls in this campaign will not benefit from…'.

GlaxoSmithKline suggested that Sanofi Pasteur MSD selected 'population covered' because the statement 'in all other tenders awarded to date in Western Europe, health authorities have chosen Cervarix', would have been less appealing for the purposes of the press release.

This claim used by Sanofi Pasteur MSD could not be substantiated and was misleading; and although Sanofi Pasteur MSD claimed to have 'robust evidence' to support it, it had not been provided.

- **'Gardasil is, or will be, used exclusively for campaigns in the USA, Australia, New Zealand, Canada and Switzerland‡'**

The footnote‡ stated 'The two-type vaccine has not yet been approved in Canada and Switzerland to the best of our knowledge'.

GlaxoSmithKline submitted that the claim implied that health service providers in all five countries had actively selected Gardasil over Cervarix, when in fact Cervarix was not actually licensed in three of the countries; following inter-company dialogue, Sanofi Pasteur MSD had stated that it would correct the footnote to include the USA. Nevertheless, to attempt to clarify the regulatory situation, and the true meaning of the statement, by the use of a footnote (positioned eight paragraphs away) was inadequate.

Sanofi-Pasteur MSD had noted that unlike the previous claim which had used the word 'chosen', this claim used '*used*' which did not imply any process of selection. However, a similarly misleading claim occurred earlier in the press release: 'Countries like Australia, New Zealand, *Canada*, France and *Switzerland* have *chosen* Gardasil preferentially or exclusively for their vaccination campaigns' (emphasis added). Again, Canada and Switzerland were cited as countries that had chosen Gardasil, when in fact no choice was available as Cervarix was not licensed in either. GlaxoSmithKline submitted that Sanofi Pasteur MSD's contradictory explanation exposed its clear intention to mislead.

- **'Where doctors can choose between the two vaccines§, more than 9 out of 10 doctors worldwide choose Gardasil'**

The footnote§ read 'Germany, France and Belgium in Western Europe'.

Sanofi-Pasteur MSD had stated that although the footnote referred to only three countries, the claim was not confined to Germany, France and Belgium – these were cited as examples in Western Europe, Sanofi Pasteur MSD's territory. This statement was misleading and exaggerated. Again no evidence had been provided to support individual doctor choice in a global context.

GlaxoSmithKline alleged that the claims were misleading, exaggerated and incapable of substantiation in breach of Clauses 7.2, 7.4 and 7.10. Furthermore, their use in the context of the press release about the 'UK authorities choosing a two-type (16/18) HPV vaccine', disparaged Cervarix and the DoH choice of vaccine in breach of Clauses 8.1 and 8.2.

RESPONSE

Sanofi Pasteur MSD noted that, since the tender award was announced, it had had a number of face-to-face meetings with the DoH and no complaint had been made about its activities, in particular relating to its response to the tender award. Had the DoH considered that Sanofi Pasteur MSD had disparaged its choice of vaccine, it was sure the DoH would have informed it.

- **'In all other tenders awarded to date in Western Europe†, health authorities have chosen Gardasil for about 80% of the population covered'.**

† 'Regional tenders in Italy, Spain, Sweden; a national tender in Switzerland'.

Sanofi-Pasteur MSD noted that GlaxoSmithKline had implied that this claim was in the main body of the press release whereas it was actually in the notes to the editors. Sanofi Pasteur MSD disagreed with GlaxoSmithKline's selective and flawed interpretation of the meaning of the word 'chosen' in this context; both vaccines did not have to be licensed and able to submit a tender application for a choice to be possible.

If Cervarix had been precluded from a tendering process because it did not have a marketing authorization, then clearly it could not be part of the selection process; however authorities still had to make a choice. Where there was only one product an authority could choose that product (eg US, Switzerland) or wait for competition (eg UK). Hence, the fact that Cervarix might not have had a marketing authorization when a tender was awarded in a particular region or country was irrelevant to the fact that Gardasil was chosen.

Sanofi Pasteur MSD noted that it was a joint venture between Sanofi Pasteur, the vaccine division of Sanofi-Aventis, and Merck & Co Inc and it was present in 19 Western European countries. A worldwide picture of HPV vaccine use could only be drawn including data from Sanofi Pasteur MSD and its parent company Merck, which marketed Gardasil in other countries. Furthermore, Sanofi Pasteur MSD did not believe it was valid to compare numbers of tenders won (as some were local or regional and covered small populations) but rather to quantify tender awards in terms of the proportion of the population covered. GlaxoSmithKline had supplied figures for EU HPV vaccine tenders as of 18 June 2008, but it was not valid to only consider tenders that had been granted since Cervarix received its marketing authorization. In addition, some of the recent tenders were awarded on a regional basis. For example, Italy had 26 separate tenders and so simply adding up the number of tenders won around the world would be relatively meaningless and give a distorted, misleading impression. Gardasil's world leading position was further underlined by the fact that according to GlaxoSmithKline's own press release of 18 June 2008, the UK was the first major national tender for which it had bid.

Sanofi Pasteur MSD maintained its position that Gardasil was the world's leading HPV vaccine and vaccine of choice for girls and women worldwide. This was not only on the basis of number of doses distributed worldwide (more than 30 million compared with 1 million doses of Cervarix), but also on share of tender markets by population covered; Gardasil had 80% share according to the recommendations per region/country. Furthermore, Gardasil also had 90% share in prescriptions in its home territory (data on this point was provided in confidence and was not to be shared with GlaxoSmithKline), as well as a 90% global market share. The press releases which included details of quarter 1 2008 financial reports from both Merck and GlaxoSmithKline were provided, where Gardasil global sales were $390M and Cervarix global sales were £12M.

Sanofi Pasteur MSD considered that the claim had been robustly substantiated and was not misleading; the company refuted any alleged breaches.

- **'Gardasil is, or will be, used exclusively for campaigns in the USA, Australia, New Zealand, Canada and Switzerland‡.'**

‡ 'The two-type vaccine has not yet been approved in Canada and Switzerland to the best of our knowledge.'

Sanofi-Aventis MSD noted that this claim was not in the main body of the press release; it was a clarifying note to the editors and an unambiguous statement of fact. During inter-company dialogue it was agreed, however, to correct an omission from the footnote, namely that Cervarix was also not approved in the US. The claim itself did not imply that health service providers in all five countries had actively selected Gardasil over Cervarix. Sanofi Pasteur MSD repeated its views regarding the word 'chosen' and whilst not specifically mentioned in this statement, reiterated the principle that regardless of Cervarix not having a licence in 3 of the 5 countries, the authorities in those countries still had to make a choice to use the vaccine or not.

Furthermore, in the above statement, the word 'used' did not imply any process of selection and consequently the company denied breaches of Clauses 7.2 and 8.1.

With regard to GlaxoSmithKline's comments about the claim 'Countries like Australia, New Zealand, Canada, France and Switzerland have chosen Gardasil preferentially or exclusively for their vaccination campaigns or recommendations', Saudi Pasteur MSD explained that Australia, New Zealand and France had chosen Gardasil preferentially and Canada and Switzerland had chosen it exclusively. The company disagreed that the statement was misleading since it stated 'preferentially **or** exclusively' (emphasis added). Furthermore it was clear in the notes to editors that Cervarix was not licensed in Canada or Switzerland.

- **'Where doctors can choose between the two vaccines[§], more than 9 out 10 doctors worldwide choose Gardasil.'**

§ 'Germany, France and Belgium in Western Europe.'

Sanofi Pasteur MSD submitted that this claim was not confined to Germany, France and Belgium – they were cited as examples in Western Europe, Sanofi Pasteur MSD's territory. The data was based on a 90% market share in the company's home market by prescriptions (Sanofi Pasteur MSD supplied data in confidence which was not to be shared with GlaxoSmithKline).

Sanofi Pasteur MSD submitted that all of the above statements were factual, had been substantiated, were not misleading or exaggerated and consequently the company denied any breach of Clauses 7.2, 7.4 and 7.10, 8.1 or 8.2.

PANEL RULING

The Panel considered that the selection of vaccine by a country/region for use was complicated. The basis of choice could be one of a number of options depending on the regulatory status of the vaccines in the country. Firstly a choice between two licensed products Gardasil and Ceravix, secondly a choice between a licensed product (Gardasil) and an unlicensed product (Ceravix) and thirdly a choice between the only licensed vaccine (Gardasil) or nothing. A fourth factor was also relevant given the differences in indications for the products ie did the country/region only want to vaccinate against cervical cancer or against cervical cancer and genital warts. The Panel did not consider that the press release was sufficiently clear about the options available and the regulatory status of the products at the time the tender decisions were made.

The Panel considered it was really important to include very clear information about the factors that might have influenced the tendering decisions round the world. Simple claims were not sufficient given the complexity of the situation.

The Panel noted that the three other claims at issue all relied on footnotes to provide clarification. The supplementary information to Clause 7 stated 'It should be borne in mind that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like'.

In the claim 'In all other tenders awarded to date in Western Europe, health authorities have chosen Gardasil for about 80% of the population covered', Western Europe was asterisked to a footnote 'Regional tenders in Italy, Spain, Sweden; a national tender in Switzerland'. The Panel considered that this was misleading as Italy, Spain, Sweden and Switzerland were a small part of Western Europe. Further, Cervarix was not licensed in Switzerland and so in that country Gardasil was chosen instead of nothing; in the Panel's view the majority of readers would not realise this. The Panel considered that the claim was misleading and in that regard could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled. In making its ruling the Panel did not consider the data which had been provided in confidence and which could not be given to GlaxoSmithKline. The claim 'Gardasil is, or will be, used exclusively for campaigns in the USA, Australia, New Zealand, Canada and Switzerland' relied upon the footnote 'The two-type vaccine has not yet been approved in Canada and Switzerland to the best of our knowledge'. The Panel noted its comments above regarding choice and the reader's knowledge of product availability. As above the Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that the claim 'Where doctors can choose between the two vaccines, more than 9 out of 10 doctors worldwide choose Gardasil' relied on the footnote 'Germany, France and Belgium in Western Europe'. The Panel considered that the claim was misleading in its reliance upon a footnote for clarity. The Panel further considered that it was exaggerated to use data from only Germany, France and Belgium in a worldwide claim. Breaches of Clauses 7.2 and 7.10 were ruled. The claim had not been substantiated by the data relating solely to Germany, France and Belgium. Further, as this data was confidential and not to be provided to GlaxoSmithKline it could not be considered by the Panel. A breach of Clause 7.4 was also ruled.

With regard to the alleged breaches of Clauses 8.1 and 8.2, the Panel considered that the claims at issue undermined the DOH's choice of Cervarix and thus disparaged both the product and the DOH. Breaches of Clauses 8.1 and 8.2 were ruled.

4 Distribution of materials

COMPLAINT

GlaxoSmithKline noted that the press release was

distributed to the media through the usual channels and also added to Sanofi Pasteur MSD's website. However, there was no direction on the website or press release itself that the press release was intended for medical journalists only; it appeared to have been distributed widely to both medical and consumer press. Although company press releases could be distributed to the consumer media when appropriate, particular care must be taken not to promote prescription only medicines to the public and the information presented must be factual and balanced. This was clearly not the case with this concerted campaign. The purpose of the press release appeared to be to encourage the public to question the choice of vaccine by the DoH and invite them to specifically request Gardasil, which was mentioned 13 times.

In defence of this allegation, Sanofi Pasteur MSD had stated that HPV vaccination was not available outside the national programme. However, Sanofi Pasteur MSD would know that both vaccines were prescribed privately and, although the DoH's Green Book stated that 'vaccination is not routinely recommended for those aged 18 years or over', HPV vaccination could be prescribed on a case-by-case basis to individual women who might benefit.

GlaxoSmithKline alleged the distribution of the press release to consumer media, and therefore the public, was a breach of Clause 20.2.

GlaxoSmithKline noted that in addition to the press release Sanofi Pasteur MSD distributed, via a PR agency, two emails following the DoH announcement. The first email contained the press release and was sent on 18 June, the day of the DoH announcement; the second contained a summary of the press coverage relating to the tender announcement and was sent the following day. Although the email covered a broad range of media types and publications, GlaxoSmithKline disagreed with Sanofi Pasteur MSD's statement '…the synthesis of the media coverage was not selective'.

Only statements from patient advocacy groups who would be expected to have an interest in protection from genital warts were included: BASHH (British Association for Sexual Health and HIV), Brook (the UK's leading provider of sexual health services and advice for the under 25s) and the Terrence Higgins Trust; the absence of a cervical cancer/cancer advocacy group statement was striking and significant.

Furthermore, the PR agency was careful to note the negative media coverage: 'a number of publications have raised concerns about the Department's decision including The Times, BBC Online, PA News, Reuters, Channel Four, Yorkshire Post, Newcastle Chronicle, Cheshire News'. It was clear that the email was intended to reinforce the messages in the press release.

In addition, of the 21 national and regional articles highlighted in the email, 16 appeared to have been significantly influenced by the Sanofi Pasteur MSD press release, containing direct content/quotes or similar misinformed and misleading messages to those discussed earlier.

In addition to the media, the PR agency distributed the Sanofi Pasteur MSD press release and press coverage in unsolicited emails to health professionals. Due to their surprise at receiving such a press release from Sanofi Pasteur MSD, and their concerns of the impact that this might have on the national immunisation programme, a number of health professionals had contacted GlaxoSmithKline anonymously.

The way in which both emails were used by the PR agency made them promotional and thus subject to the Code. Sanofi Pasteur MSD claimed the distribution was limited to a small group of individuals and organisations who received regular media updates about HPV vaccination. However, this was at odds with GlaxoSmithKline's understanding, and Sanofi Pasteur MSD had not provided any evidence in support of the explicit prior permission which it had received from the health professional recipients. GlaxoSmithKline alleged that the unsolicited distribution of these emails to health professionals breached Clause 9.9.

RESPONSE

Sanofi Pasteur MSD noted that GlaxoSmithKline was concerned about the content of the press coverage email, although a specific breach of the Code had not been alleged. GlaxoSmithKline was concerned that the press coverage was selective and that only statements from patient advocacy groups which would be expected to have an interest in protection from genital warts were included. Sanofi Pasteur MSD was surprised that GlaxoSmithKline had stated that the complete absence of a cervical cancer/cancer advocacy statement was striking and significant. To the contrary, Sanofi Pasteur MSD found it striking and significant that GlaxoSmithKline had not mentioned that the fourth hyperlink on the page (the second hyperlink in the Newswires section) was a press release from Jo's Trust, the UK's leading cervical cancer charity (the item was also included in the press clippings that GlaxoSmithKline had supplied to the Authority). Furthermore this was an entirely positive press release relating to the DoH's choice of vaccine.

To further substantiate that the content of the emails was not selective or promotional, the PR agency had told Sanofi Pasteur MSD that between 17 June 2008 and the beginning of July Google news alerts (using the search terms 'HPV vaccine' and 'tender announcement') were used in addition to Factiva (an alert service to which the agency subscribed) and in house scanning of all the national daily newspapers and weekly/monthly medical publications. In addition, the agency had an

ongoing Google alert set up for 'HPV' and 'Gardasil'.

All articles forwarded in the email were unbiased in that the PR agency was not selective over which coverage was sent. All tender-related coverage to that date from a broad range of media types was forwarded regardless of which product it mentioned, including articles that were positive for GlaxoSmithKline.

Sanofi Pasteur MSD noted that GlaxoSmithKline was also concerned that the emailing of the press release, which GlaxoSmithKline alleged to be misleading, had influenced the national and regional articles that were included in the email. Sanofi Pasteur MSD had already responded to the allegations regarding the content of the press release above and so refuted the allegation that misinformed and misleading messages were picked up by the press coverage. The company therefore denied the allegation of a breach of Clause 20.2.

Sanofi Pasteur MSD noted that GlaxoSmithKline was concerned about the distribution by the agency of the Sanofi Pasteur MSD press statement and press coverage by email, alleging that the emails had been sent unsolicited to health professionals. Sanofi Pasteur MSD denied this allegation and thus a breach of Clause 9.9.

The emails were not unsolicited. A relationship existed and previous correspondence of a similar nature had taken place with all those who received the emails. The recipients of the emails had a legitimate interest in receiving such information so they were well placed to offer Sanofi Pasteur MSD advice when required and also to remain adequately informed so that they might handle media enquiries in a responsible manner. As part of the ongoing dialogue no one had ever complained or asked to stop receiving information. In the context of the DoH announcement, it was therefore in keeping with previous practice with this group to provide them with both a copy of the company's statement and a synthesis of media coverage.

This was further supported by a letter and slides from an advisory board where it was made clear that Sanofi Pasteur MSD intended to provide email updates of licence application news and data communications (with copies of abstracts/papers/media coverage of interest). Those involved at an early stage therefore had the opportunity face to face in these meetings to opt out. The emails were found to be of relevance – demonstrated by recipients' responses when they were called upon to give comment to the media at short notice.

Sanofi Pasteur MSD therefore refuted the allegations that the sending of these emails breached Clause 9.9.

With regard to the emails from its PR agency, Sanofi Pasteur MSD knew that the agency intended to send these types of emails and did not object since they were deemed to be a legitimate part of the ongoing dialogue that had taken place since working with the recipients. The emails were not formally copy approved by Sanofi Pasteur MSD. The agency knew about, received regular training on, and was committed to complying with, the Code and reviewed the emails as part of its own approval process.

Sanofi Pasteur MSD disagreed with the allegation that the purpose of the press statement was to encourage the public to question the choice of vaccine by the DoH and to invite them to specifically request Gardasil. The company thus denied a breach of Clause 20.2. The press statement was fair, balanced, factual and well substantiated. The brand name was used for clarity since the generic name was long and unwieldy and might have confused readers.

A recent editorial in the BMJ further highlighted the controversial nature of the decision, stating that 'The decision to select the bivalent vaccine implies that the Department of Health is willing to accept foregone health benefits (and additional cost savings) from averting cases of genital warts for the reduced financial outlay, which may be allocated to other priority investments in health'. This was a hugely topical area for both health professionals and consumers.

Given the above, it was beyond dispute that the issue was clearly a significant public health issue and very relevant for a consumer audience as well as health professionals. In fact a government minister had recently stated that the national immunisation campaign was one of the biggest public health campaigns in recent history.

The press release was distributed to the media via the usual channels, following releases by both the DoH and GlaxoSmithKline on 18 June 2008. The company website contained an archive of previous releases to which this was also added. This was in the section of the website that was clearly marked as being for journalists, both on the homepage and on the page containing the release itself. Nonetheless, it was entirely appropriate for the press release to be accessible to consumer journalists.

Clause 20.2 allowed non-promotional information about prescription only medicines to be provided to the public including via press announcements. The press statement was factual, fair, balanced and would not encourage the public to specifically request Gardasil. In fact the opposite was true since the press statement actually reinforced the fact that girls in the national immunisation programme would not be able to receive Gardasil and consequently Sanofi Pasteur MSD believed that people would actually be deterred from asking for Gardasil. Furthermore, the DoH's Green Book stated that the HPV vaccine was not routinely recommended for those outside of the national

programme. There was no mention in the press release that the vaccine could be prescribed on a case-by-case basis.

PANEL RULING

The Panel noted that the press release had been issued to the consumer press. It was not unacceptable to issue press releases about prescription only medicines to the consumer press providing that the information contained therein was factual and balanced. Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine.

The Panel considered that, *inter alia*, describing Gardasil as the World's leading four-type HPV vaccine, with unmatched cervical cancer protection, would encourage patients to ask for the medicine. It was irrelevant that they might not be able to get it on the NHS. A breach of Clause 20.2 was ruled.

With regard to the allegations of breaches of Clauses 9.9 and 9.10, the Panel noted Sanofi Pasteur MSD's submission that such allegations had not been discussed in inter-company dialogue. A letter to Sanofi Pasteur MSD, however, was headed 'Unsolicited emails to health professionals, patient organisations and charities'. The Panel considered that, in that regard, the issue of whether the emails were sent unsolicited had been raised. There was no mention in the inter-company correspondence, however, of whether the material needed to include a declaration of sponsorship (Clause 9.10) and so this aspect of the complaint was not considered.

With regard to whether the emails were unsolicited, the Panel noted Sanofi Pasteur MSD's submission that a relationship existed between it and the recipients and that they had all received correspondence of a similar nature before. The company had further submitted that the emails were sent to specific individuals because of their role in providing Sanofi Pasteur MSD with advice as well as being experts in handling the media. The Panel was concerned that no explanation had been given in the emails that the PR agency sending the material was acting on behalf of Sanofi Pasteur MSD. Nor did the email state that the audience were those who had a role in providing Sanofi Pasteur MSD with advice. It appeared from Sanofi Pasteur MSD's response that the emails were sent to health professionals who were, in some capacity, acting as consultants to the company. On that basis the Panel considered that the emails were not unsolicited promotional material as alleged. No breach of Clause 9.9 was ruled.

During its consideration of this matter, the Panel noted with concern Sanofi Pasteur MSD's submission that emails had been sent out by its PR agency without formal copy approval by the company. This was wholly unacceptable; pharmaceutical companies could not delegate their responsibilities under the Code to a third party.

5 High standards and alleged breach of Clause 2 of the Code

COMPLAINT

GlaxoSmithKline submitted that Sanofi Pasteur MSD's activities and materials provided evidence of the coordinated campaign, designed to question the robustness of the DoH's decision in its choice of vaccine for the immunisation programme and leave the reader believing that the UK government, unlike most other health authorities, had chosen a less effective vaccine to protect UK girls and women. The widespread distribution of material to the medical and consumer media, health professionals and other organisations would encourage health professionals and the public to question the DoH's vaccine choice and ask for Gardasil, which was mentioned by name 13 times.

Sanofi Pasteur MSD's campaign had a number of potentially serious consequences. Firstly, the uptake of immunisation was likely to be affected, reducing the number of girls who could benefit from vaccination to prevent cervical cancer. Secondly, for those who had been vaccinated against HPV 16 and 18, the mistaken belief that they would be protected against the 'vast majority' of cervical cancers might lead to a false sense of security and reduce future cervical screening attendance, which was already in decline in younger age groups. This would increase the chances of a pre-cancerous lesion progressing to cervical cancer.

In addition to the clauses cited above GlaxoSmithKline alleged that Sanofi Pasteur MSD had breached Clause 9.1 in that high standards had not been maintained to the extent that its activities brought discredit upon, and seriously undermined confidence in the pharmaceutical industry and its ability to self-regulate in breach of Clause 2.

Given the widespread distribution of these misleading, inaccurate and damaging materials to media organisations, health professionals and patient groups, GlaxoSmithKline requested that a corrective letter, with the Authority's and GlaxoSmithKline's prior agreement, be issued to all parties on the original press release and email distribution lists. In addition, the letter should be sent to all media that had published inaccurate information taken from the press release in order to address the inaccuracies and minimise the damage caused to the national immunisation programme.

RESPONSE

Sanofi Pasteur MSD believed that it and its PR agency had acted responsibly and appropriately in

light of the DoH's decision to select Cervarix for the national immunisation programme. Sanofi Pasteur MSD strongly refuted all allegations of breaches of the Code. Sanofi Pasteur MSD was a responsible company, dedicated to vaccines and public health, and believed that it had maintained high standards throughout and consequently denied breaching Clause 9.1. Furthermore it disagreed with the allegation that its activities had brought discredit upon and seriously undermined confidence in the pharmaceutical industry and its ability to self-regulate. Sanofi Pasteur MSD thus refuted the alleged breach of Clause 2.

Sanofi Pasteur MSD did not believe that any of its activities or content of materials had been misleading, inaccurate or damaging. To the contrary it believed that its materials and activities had conformed to the highest standards. During the inter-company dialogue, it agreed to correct the omission of the US from a footnote and also to clarify the wording in the archive copy of the press release to distinguish that pre-cancerous vaginal lesions were the subject of a positive CHMP opinion. It did not agree with GlaxoSmithKline's request to issue a corrective statement for widespread distribution.

PANEL RULING

The Panel noted that GlaxoSmithKline had requested that Sanofi Pasteur MSD issue a corrective letter. This was not a sanction available to the Panel. It was only available to the Appeal Board following a ruling by the Appeal Board (Paragraph 10.6 of the Constitution and Procedure) or when it was considering a report (Paragraph 11.3).

The Panel noted its rulings of breaches of the Code above. It considered that Sanofi Pasteur MSD had not been sufficiently clear about the situation and thus would cause further confusion in a complicated matter. Taking all the circumstances into account the Panel decided that high standards had not been maintained and a breach of Clause 9.1 was ruled.

On balance the Panel did not consider that the circumstances were in breach of Clause 2 which was used as a sign of particular censure.

Complaint received **22 July 2008**

Case completed **22 September 2008**