

# DOCTOR v SANOFI PASTEUR MSD

## Gardasil journal advertisement

A doctor complained about a double page journal advertisement for Gardasil (Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)) issued by Sanofi Pasteur MSD. Gardasil was licensed, *inter alia*, for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to human papillomavirus (HPV) types 6, 11, 16 and 18.

The complainant alleged that the claim 'Now there's Gardasil a vaccine that can prevent cervical cancer' was still to be proven. Clinical trials had shown that the vaccine was successful in removing transient HPV 16 and 18 infections and might prevent pre-stages to cervical cancer, but no evidence had been seen of final prevention of cervical cancer.

The Panel considered that as Gardasil was licensed, *inter alia*, for the prevention of cervical carcinoma the claim 'Now there's Gardasil a vaccine that can prevent cervical cancer' was not misleading nor incapable of substantiation as alleged. No breach of the Code was ruled.

The complainant alleged that the claim 'Benefit from 4 types – before and beyond cervical cancer' was misleading and false. What was known was that HPV types 6 and 11 could cause genital warts but never cervical cancer. Types 16 and 18 together with several other HPV oncogene types could cause cervical cancer, but only if the virus had transformed and started to produce oncogene proteins (E6/E7).

The Panel noted that the claim 'Benefit from 4 types - before and beyond cervical cancer' appeared in a relatively small typeface beneath the bold, prominent claim considered above: 'Now there's Gardasil a vaccine that can prevent cervical cancer' on the first page of the double page spread. The facing second page of the advertisement was headed 'The first vaccine that can prevent cervical cancer' beneath which 2 bullet points discussed the licensed indication of Gardasil and the HPV types 6, 11, 16 and 18. The Panel considered that the claim 'Benefit from 4 types - before and beyond cervical cancer' was ambiguous. Some might consider that the four types referred to HPV types 6, 11, 16 and 18. Given the prominence of the preceding claim 'Now there's Gardasil a vaccine that can prevent cervical cancer' and its reference to cervical cancer some readers might assume that the claim at issue implied that HPV types 6, 11, 16 and 18 each had a role in cervical cancer. It was only by reading the less prominent text in the bullet points on the

facing page that the causative effects of the four HPV types became clear. Others might consider that '4' referred to the four licensed indications. On balance, the Panel considered that in the context in which it appeared it was not entirely clear what the claim 'Benefit from 4 types - before and beyond cervical cancer' meant and in this regard it was ambiguous, misleading and incapable of substantiation. Breaches of the Code were ruled.

On appeal by Sanofi Pasteur MSD, the Appeal Board had some concerns that in the claim at issue 'before ... cervical cancer' related to time ie high-grade cervical dysplasia whereas 'beyond cervical cancer' related to anatomy ie vulval lesions or external genital warts. However the Appeal Board considered it unlikely that readers would assume that 'beyond' referred to a time after which a woman had developed cervical cancer given that the very prominent claim which preceded the claim at issue clearly referred to the prevention of cervical cancer.

The Appeal Board did not consider that the claim implied that HPV types 6, 11, 16 and 18 all caused cervical cancer as alleged.

Although noting its concern above, the Appeal Board considered that, in the context in which it appeared, the claim was not ambiguous or misleading and could be substantiated. No breach of the Code was ruled.

The complainant alleged that the claim 'Gardasil can also ... reduce incidence of vaginal pre-cancers caused by human papillomavirus types 6, 11, 16 or 18' was misleading. It was known that HPV types 6 and 11 could cause genital warts but never cervical cancer. HPV types 6 and 11 could not support the production of oncogene E6 and E7 proteins. Types 16 and 18 together with several other HPV oncogene types could produce oncogene E6 and E7 proteins, the cause of cervical cancer.

The Panel considered that as Gardasil was licensed to prevent high grade vulvar dysplastic lesions (VIN 2/3) the claim 'Beyond the cervix Gardasil can also prevent vulval pre-cancers and genital warts and reduce the incidence of vaginal pre-cancers caused by human papillomavirus types 6, 11, 16 or 18' was not misleading. The phrase 'Beyond the cervix ...' made it clear that the claim related to conditions other than cervical cancer. There was no implication that HPV types 6 and 11 caused cervical cancer as inferred by the complainant. No breach was ruled.

The complainant alleged that the claim 'To protect

young women, children and adolescents' was a hanging comparison. The Panel considered that the claim clearly related to Gardasil's licensed indication and no breach of the Code was ruled.

A doctor complained about a double page journal advertisement (ref 10/06 09214c) for Gardasil (Human Papillomavirus Vaccine [Types 6, 11, 16, 18]. (Recombinant, adsorbed)) issued by Sanofi Pasteur MSD Ltd. Gardasil was licensed for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to HPV types 6, 11, 16 and 18.

## COMPLAINT

The complainant asserted that the claim 'Now there's Gardasil a vaccine that can prevent cervical cancer' was still to be proven. Clinical trials had shown that the vaccine was successful in removing transient human papillomavirus (HPV) 16 and 18 infections and might prevent pre-stages to cervical cancer, but no evidence had been seen of final prevention of cervical cancer. The vaccine might even make it very difficult for the current screening method to detect underlying pre-stages of cervical cancer.

The complainant alleged that the claim 'Benefit from 4 types – before and beyond cervical cancer' was directly misleading and false. What was known was that HPV types 6 and 11 could cause genital warts but never cervical cancer. Types 16 and 18 together with several other HPV oncogene types could cause cervical cancer, but only if the virus had transformed and started to produce oncogene proteins (E6/E7).

The complainant alleged that the claim 'Gardasil can also ... reduce incidence of vaginal pre-cancers caused by human papillomavirus types 6, 11, 16 or 18' was another directly misleading statement. What was known was once again that HPV types 6 and 11 could cause genital warts but never cervical cancer. HPV types 6 and 11 could not support the production of oncogene E6 and E7 proteins. Types 16 and 18 together with several other HPV oncogene types could produce oncogene E6 and E7 proteins, the cause of cervical cancer.

The complainant alleged that the claim 'To protect young women, children and adolescents' was a hanging comparison in breach of the Code.

When writing to Sanofi Pasteur MSD, the Authority asked it to respond in relation to Clause 7.2 and 7.4 of the Code.

## RESPONSE

Although Sanofi Pasteur MSD recognised that it did not guarantee compliance with the Code, the advertisements referred to were pre-vetted by the Medicines and Healthcare products Regulatory

Agency (MHRA).

Sanofi Pasteur MSD noted that Gardasil was indicated, *inter alia*, to prevent cervical cancer causally related to HPV types targeted by the vaccine (section 4.1 of the summary of product characteristics (SPC)). The claim 'Now there's Gardasil a vaccine that can prevent cervical cancer' therefore reflected the indication - Gardasil could prevent cervical cancer.

Sanofi Pasteur MSD did not consider that the claim 'Benefit from four types – before and beyond cervical cancer' was either misleading or false. It was clear from the SPC that in addition to the prevention of cervical cancer Gardasil was also indicated for the prevention of cervical dysplasia (pre-cancerous lesions that developed before cervical cancer itself), as well as diseases that occurred beyond the cervix (ie vulval intra-epithelial neoplasia, genital warts), all causally related to HPV types targeted by the vaccine. These details were expanded upon in the body of the advertisement. Furthermore Sanofi Pasteur MSD was unsure why the complainant distinguished between types 6 and 11 versus types 16 and 18 since the claim was not just about cervical cancer.

Again, Sanofi Pasteur MSD did not believe that the claim 'Gardasil can also ... reduce the incidence of vaginal pre-cancers caused by human papillomavirus types 6, 11, 16 or 18' was either misleading or false. The company was also unsure why the complainant referred to cervical cancer since this claim was not about cervical cancer. The reference to the four HPV types simply reflected section 5.1 of the SPC (subsection titled 'Efficacy in subjects naïve to the relevant vaccine HPV type(s)') where results for CIN 2/3 or adenocarcinoma in situ (AIS) were related to types 16 or 18 whereas all other results were related to types 6, 11, 16 or 18.

The claim 'To protect young women, children and adolescents' was not a hanging comparison since no comparison was made. In the context of an advertisement for a quadrivalent HPV vaccine, which described the diseases against which the vaccine was effective, it was self-evident what the protection was against. In addition, it reflected the population for which Gardasil was indicated.

Sanofi Pasteur MSD submitted that all of the claims at issue were accurate, balanced, fair, objective and not misleading; all of the claims could be substantiated by the SPC. The company denied any breaches of either Clause 7.2 or 7.4 of the Code.

## PANEL RULING

The Panel noted that Gardasil was licensed for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to HPV types 6, 11, 16 and 18. Section 5.1 of the SPC,

Pharmacodynamic properties, discussed data on the immune response to Gardasil which showed that overall, 99.9%, 99.8%, 99.8% and 99.6% of individuals who received Gardasil became anti-HPV6, anti-HPV11, anti-HPV16 and anti-HPV18 seropositive, respectively, by one month post dose three across all age groups tested. The Panel noted the complainant's submission about treatment of transient HPV infections and their causal link to prevention of pre-stages to cervical cancer but considered that given the product's licensed indication the claim 'Now there's Gardasil a vaccine that can prevent cervical cancer' was not misleading nor incapable of substantiation as alleged. No breach of Clauses 7.2 and 7.4 was ruled.

The claim 'Benefit from 4 types - before and beyond cervical cancer' appeared in a relatively small typeface beneath the bold, prominent claim considered above, 'Now there's Gardasil a vaccine that can prevent cervical cancer' on the first page of the double page spread. The facing second page of the advertisement was headed 'The first vaccine that can prevent cervical cancer' beneath which 2 bullet points discussed the licensed indication of Gardasil and the HPV types 6, 11, 16 and 18. The Panel considered that the claim 'Benefit from 4 types - before and beyond cervical cancer' was ambiguous. Some might consider that the four types referred to HPV types 6, 11, 16 and 18. Given the prominence of the preceding claim 'Now there's Gardasil a vaccine that can prevent cervical cancer' and its reference to cervical cancer some readers might assume that the claim at issue implied that HPV types 6, 11, 16 and 18 each had a role in cervical cancer. It was only by reading the less prominent text in the bullet points on the facing page that the causative effects of the four HPV types became clear. Others might consider that '4' referred to the four licensed indications. On balance, the Panel considered that in the context in which it appeared it was not entirely clear what the claim 'Benefit from 4 types - before and beyond cervical cancer' meant and in this regard it was ambiguous, misleading and incapable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled. This ruling was appealed.

The Panel considered that as Gardasil was licensed to prevent high grade vulvar dysplastic lesions (VIN 2/3) the claim 'Beyond the cervix Gardasil can also prevent vulval pre-cancers and genital warts and reduce the incidence of vaginal pre-cancers caused by human papillomavirus types 6, 11, 16 or 18' was not misleading as alleged. The phrase 'Beyond the cervix ...' made it clear that the claim related to conditions other than cervical cancer. There was no implication that HPV types 6 and 11 caused cervical cancer as inferred by the complainant. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel did not consider the claim 'To protect young women, children and adolescents' was a hanging comparison as alleged. It clearly related to Gardasil's licensed indication. No breach of Clause 7.2 was ruled.

## APPEAL BY SANOFI PASTEUR MSD

Sanofi Pasteur MSD noted that Gardasil was indicated not just for the prevention of cervical cancer, but also for the prevention of high-grade cervical dysplasia (CIN 2/3) (pre-cancerous lesions that developed before cervical cancer itself), as well as diseases that occurred beyond the cervix (ie high-grade vulvar dysplastic lesions (VIN 2/3) and external, genital warts) all causally related to HPV types targeted by the vaccine (6, 11, 16 and 18). These details were expanded upon in the body of the advertisement.

Sanofi Pasteur MSD submitted that the fact that Gardasil provided protection against four HPV types was clear from the generic name which was displayed in a large font beneath the most prominent mention of the brand name in the top right hand corner of the advertisement. Sanofi Pasteur MSD had never seen the indications for any medicine referred to as 'types'. Therefore four types could only refer to the four virus types covered by the vaccine. So, was the positioning of the claim misleading by implying that the four types might be causal in the development of cervical cancer? Sanofi Pasteur MSD did not believe this to be the case. Despite being in the 'bubble' with the claim about cervical cancer, the reference to four types was immediately qualified after the hyphen - namely that the benefits accrued from the vaccine protecting against four types that occurred before (cervical dysplasia) and beyond (other HPV-related diseases) cervical cancer. Indeed, in its ruling on the third component of the complaint, referring to the body text on the right hand side of the advertisement, the Panel stated that the phrase 'Beyond the cervix ...' made it clear that the claim related to conditions other than cervical cancer. This claim did not misleadingly imply that HPV types 6, 11, 16 and 18 were all implicated in the aetiology of cervical cancer. In summary, the claim 'Benefit from 4 types - before and beyond cervical cancer' was neither ambiguous nor misleading and was therefore not in breach of Clause 7.2.

Sanofi Pasteur MSD submitted that regardless of the interpretation of the claim, both the fact that there were benefits from targeting four virus types with Gardasil and the fact that Gardasil had four indications was supported by the SPC. In addition, the fact that the benefits accrued from the vaccine protecting against four types occurred before (cervical dysplasia) and beyond (other HPV-related diseases) cervical cancer was also supported by the SPC. Therefore the claim in question could be substantiated and was not in breach of Clause 7.4.

## COMMENTS FROM THE COMPLAINANT

The complainant was astonished and surprised that the response and appeal only referred to the SPC; no publication had been submitted to support the claim at issue.

For information the complainant provided an email

from a professor who he had asked for help and support in this case. The professor had searched the whole medical worldwide database (ENTREZ PUBMED) for any reports about the relationship between HPV6, HPV6b or HPV11 and vulvar dysplastic lesions or high-grade vulvar dysplastic lesions and was unable to find anything. The most important evidence for the causal role between HPV and cancer progression was the binding and degrading by the HPV E6 full-length protein and the p53 tumour suppressor protein. In Hiller *et al* (2006), 'in contrast, the E6 proteins of HPV6 and 11 and HPV44, 54, and 61, regarded as possible carcinogenic or low-risk HPV types, respectively, did not degrade p53'. In Hudelist *et al* (2004), further HPV typing in cervical biopsies of 78 women showed that HPV6 and 11 were restricted to **benign cellular changes**, CIN I and II, whereas HPV16 and 18 were observed predominantly in CIN III/CIS (p=0.01). No clear distribution pattern was observed for HPV31, 33, 52b and 58. Expression of HPV E6 and E7 transcripts was uniformly correlated with the different physical state of HPV DNA.

The complainant alleged that there was no scientific support to justify the claims that HPV types 6 and 11 had anything to do with cervical cancer. The complainant noted that 'histology CIN I' was now nearly accepted to have nothing to do with cervical cancer.

## APPEAL BOARD RULING

The Appeal Board had some concerns that in the claim 'Benefit from 4 types - before and beyond cervical cancer', 'before ... cervical cancer' related to time ie high-grade cervical dysplasia whereas 'beyond cervical cancer' related to anatomy ie vulval lesions or external genital warts. However the Appeal Board considered it unlikely that readers would assume that 'beyond' referred to a time after which a woman had developed cervical cancer given that the very prominent claim which preceded the claim at issue clearly referred to the prevention of cervical cancer.

The Appeal Board did not consider that the claim implied that HPV types 6, 11, 16 and 18 all caused cervical cancer as alleged.

Although noting its concern above, the Appeal Board considered that, in the context in which it appeared, the claim was not ambiguous or misleading and could be substantiated. No breach of Clauses 7.2 and 7.4 was ruled. The appeal was successful.

Complaint received      8 December 2006

Case completed          22 February 2007