

**National Assembly for Wales
Health and social Services Committee
Review of Cancer Services for the People of Wales**

Name of respondent: <i>Dr Nicholas Kitchin</i>
Are you responding on behalf of an organisation? <i>Yes, as its Medical Director</i>
If so please give the name <i>Sanofi Pasteur MSD</i>
Address: <i>Mallards Reach, Bridge Avenue, Maidenhead, Berkshire, SL6 1QP</i>
Telephone number: <i>01628 785291</i>
Would you be willing to give oral evidence to the Committee? <i>Yes</i>
If the evidence you give below is your personal view, rather than that of an organisation, please state whether or not you are willing for your evidence to be published by putting a X in the appropriate box below:
I am content for my evidence to be published
I am not content for my evidence to be published

1	How can information technology be used more effectively to track and facilitate the patient's journey?
Response	Not applicable
2)	How effectively is research and good practice being integrated with service delivery? What can be done and by whom to improve this?
Response	Not applicable
3	What are your views on the complexity of commissioning services? Is the process hampered by the involvement of the local health boards, cancer networks and Health Commission Wales? How could it be simplified?
Response	Not applicable

4	What evidence is there of the value of screening and immunisation?
Response	<p>Background</p> <p>Cervical cancer is the twelfth most common cause of cancer deaths in women in the UK, accounting for approximately 2% of all female cancers. Despite the success of the National Cervical Screening Programme, there were still 3,181 new cases of cervical cancer and 1,529 related deaths in the UK in 2002. In Wales, during the period 1993-2002, there were on average 181 registrations and 82 deaths per year.</p> <p>Human Papillomavirus has been identified as the primary cause of cervical cancer and has been detected in over 99% of cases worldwide. Studies have shown that the majority (approximately 70% or more, depending on region) of cervical cancer cases are related to two types of Human Papillomavirus (16 and 18). Other Human Papillomavirus-related cancers include vulval and vaginal cancers.</p> <p>Two vaccines designed to protect against Human Papillomavirus have been submitted for licensure in Europe, including the United Kingdom. One of these vaccines, Gardasil[®] which will be marketed by Sanofi Pasteur MSD, targets four Human Papillomavirus types (6, 11, 16 and 18) and is designed to prevent the sequelae of Human Papillomavirus infection with the types targeted by the vaccine.</p> <p>Gardasil contains non-infectious virus-like particles (VLPs) of each of the four Human Papillomavirus types (6, 11, 16 and 18) contained in the vaccine. The VLPs contain no viral DNA and cannot infect cells, reproduce or cause disease. However, they do stimulate the body's immune system to develop antibodies that prevent Human Papillomavirus infection, and the subsequent pre-cancerous and cancerous changes that can result. A course of Gardasil comprises three 0.5mL intramuscular injections administered over a six month period.</p>

Although Gardasil is currently being reviewed for licensure in Europe, it has already been licensed in the United States (where it has been recommended for universal vaccination), as a vaccine indicated in girls and women 9-26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, and 18:

- Cervical cancer
- Genital warts (condyloma acuminata)

and the following precancerous or dysplastic lesions:

- Cervical adenocarcinoma in situ (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1

Clinical effectiveness

The aim of the Gardasil clinical development programme was to define the impact of the vaccine on the risk for development of (1) Human Papillomavirus type 16 or Human Papillomavirus type 18 related invasive cervical cancer, (2) cervical intraepithelial neoplasia (CIN) caused by the vaccine types, (3) external genital lesions caused by the Human Papillomavirus vaccine types, (4) vulvar and vaginal cancer.

The efficacy of Gardasil was assessed in four placebo-controlled, double-blind, randomised phase II and III clinical studies. The first phase II study evaluated the Human Papillomavirus type 16 component of Gardasil (N=2391) and the second evaluated all four components of Gardasil (N=551). The Phase III studies evaluated Gardasil in 5,442 (FUTURE I) and 12,157 (FUTURE II) subjects. Together, these four studies evaluated 20,541 women 16 to 26 years of age at enrolment. The median duration of follow-up was 4.0, 3.0, 2.4, and 2.0 years for

these four studies respectively. Subjects were enrolled from 5 continents and 22 countries.

Choice of primary efficacy endpoint

Following guidance from the World Health Organisation and the Committee for Medicinal Products for Human Use (CHMP), Gardasil studies examined efficacy against moderate to severe pre-cancerous changes (cervical intraepithelial neoplasia [CIN] 2/3) as their endpoint.

The rationale for selecting CIN 2/3 was that they:

- Are the first step in the development of cervical cancer
- Are closely associated in pathophysiological sequence to the development of cervical cancer
- Are at high risk of developing into cervical cancer
- Represent a clinically important syndrome requiring treatment
- If treated, are shown to result in a reduction in the risk of cervical cancer developing

Other efficacy endpoints evaluated in the clinical studies included any grade of Cervical Intraepithelial Neoplasia (CIN), Adenocarcinoma in Situ (AIS), Vulvar Intraepithelial Neoplasia (VIN) Grade 2/3, Vaginal Intraepithelial Neoplasia (VaIN) Grade 2/3, external genital warts, and persistent Human Papillomavirus infection.

Summary of results of key Gardasil studies

In those women that received all doses of vaccine and were not infected with Human Papillomavirus vaccine types before they completed the course of vaccination, Gardasil was shown to be highly effective in preventing cervical intraepithelial neoplasia (CIN) 1-3, adenocarcinoma in situ (AIS), cervical, vulval and vaginal cancers, and external genital lesions including genital warts, vulval intraepithelial neoplasia (VIN) 1-3 and vaginal intraepithelial neoplasia (VaIN) 1-3, related to Human Papillomavirus types 6, 11, 16 and 18. Gardasil was 100% effective in preventing CIN 2/3 related to Human Papillomavirus types 16 and 18. Follow-up data exists up to five years after enrolment to one study.

The immune response in adolescents is as least as good as that in young adult women.

Clinical trials have indicated that in women with a recent Human Papillomavirus infection, administration of Gardasil may reduce the risk that the infection will progress to CIN 1 or worse. In women who were infected with one of the vaccine types at study entry, the same level of protection has also been demonstrated against the Human Papillomavirus types in the vaccine to which they were naïve. As well as eliciting an immune response to types 6, 11, 16 and 18, vaccination with Gardasil has been demonstrated to elicit antibodies that cross-react with Human Papillomavirus types 31, 42, 52 and 58.

Overall, Gardasil is well tolerated and has a good safety profile. The number of side effects other than at the injection site reported in clinical trials was comparable between vaccine and placebo groups and the majority were of mild to moderate severity.

Expected impact of vaccination

A vaccine that protects against Human Papillomavirus types known to be associated with a significant proportion of the indicated conditions is expected to reduce the incidence of these diseases. Consistent with these expectations, the clinical trial findings show that in a population setting, Gardasil is likely to be highly effective in reducing the incidence of cervical cancer and other clinical diseases related to Human Papillomavirus types 6, 11, 16, and 18, while offering long-term protection and a good tolerability profile.

Universal vaccination of girls and young women, prior to significant exposure to Human Papillomavirus, could be achieved through a schools based programme with potential 'catch up' of older cohorts. A health economic evaluation has demonstrated that Gardasil, if given through a schools based programme, in addition to current UK

	screening programmes, is cost-effective.
5	What are the barriers to the NHS in Wales keeping abreast of, and responding to, developing technologies and therapies? How might these barriers be overcome?
Response	Not applicable
6	How can the NHS and the voluntary sector work together more effectively to deliver services?
Response	Not applicable
7	How can the collection and use of data on where the terminally ill spend their last weeks or months be improved better to inform service provision for those people?
Response	Not applicable
8	There are a number of issues around prescribing and the cost of drugs:
8(i)	What should be done and by whom to reduce continued prescribing of inappropriate drugs?
Response	Not applicable
8(ii)	Should people who are prepared to pay privately for drugs not available to them on the NHS, be able to do so without having to become private patients and having to pay for all their treatment?
Response	Not applicable
8(iii)	Do doctors, pharmacists and other health professionals have adequate access to <i>independent</i> advice and guidance on the prescribing of drugs?
Response	Not applicable
9	Are services centred on the patient, with service users consulted? If not what are the reasons for this and how patient involvement

	be improved?
Response	Not applicable

Thank you for responding. If possible please e-mail your response to jane.westlake@wales.gsi.gov.uk . Alternatively post it to Jane Westlake, Clerk to the Health and Social Services Committee, Room B4.07, National Assembly for Wales, Cardiff Bay Cardiff, CF99 1NA. **The closing date for responses is Monday 24 July 2006**