



The Honorable Margaret A. Hamburg, M.D., Commissioner
U. S. Food and Drug Administration (FDA)
10903 New Hampshire Ave.
Silver Spring MD 20993-0002

October 19, 2010

Subject: Request that the FDA rescind its approval for Gardasil™ as a vaccine to prevent cervical cancer or to prevent genotype-specific human papillomavirus (HPV) infection due to use of an inappropriate primary endpoint and unreliable HPV genotyping methods for efficacy evaluation

Dear Dr. Hamburg:

S.A.N.E. Vax, Inc. is a non-profit organization established to promote safe, affordable, necessary and effective vaccines and vaccination practices. In response to inquiries from families of girls around the world suffering mysterious illnesses and death after HPV vaccination, our team began researching the mechanisms of action of HPV vaccines in general and Gardasil™ in particular.

This research revealed the fact that in November 2001 the VRBPAC committee allowed the vaccine manufacturer, Merck & Co., Inc., to use:

CIN 2/3, AIS, or cervical cancer; i.e. CIN 2/3 or worse by histology- with virology to determine the associated HPV type- as the primary endpoint in the evaluation of a vaccine to prevent cervical cancer. [1]

Using this primary endpoint for statistical calculation in the clinical trials invalidates the claimed efficacy of Gardasil™ as a vaccine to prevent cervical cancer. The reason is as follows:

It is well known in the natural history of cervical cancer development only a small fraction of the CIN 2 lesions will progress to CIN 3 lesions; and only a small fraction of CIN 3 lesions will progress to cervical cancer. Therefore, there are many more CIN 2 lesions than CIN3 lesions and cervical cancers combined in any female population, including the subjects enrolled in the Gardasil™ clinical trials. As a result, the overwhelming majority of the “CIN 2/3 or worse” cases used for evaluation of efficacy, and listed in the VRBPAC Background Document on Gardasil™ HPV Quadrivalent Vaccine presented at the May 18, 2006 VRBPAC Meeting [1] must have been CIN 2 lesions.

A scientific report published by the National Cancer Institute (NCI) concludes:

CIN 2 is not a true biologic entity but an equivocal diagnosis of pre-cancer, representing an admixture of HPV infection and pre-cancer. The existence of CIN 2 biopsy results as a clinical entity may be the consequence of the inaccuracies of colposcopy and colposcopically directed biopsy, which could result in less-than-perfect representation of the underlying disease state. That CIN 2 is the least reproducible of all histopathologic diagnoses may in part reflect sampling error; i.e., the biopsy procedure could make a CIN 1 or HPV infection appear worse by sampling the lesion area diagonally and, thereby, make the lesion

appear thicker and could make a CIN 3 lesion appear less severe by only partially sampling the precancerous lesion. ^[2]

Two additional NCI reports further confirmed that approximately 40% of undiagnosed CIN 2 will regress over two years ^[3] and that even the CIN 3 lesions are heterogeneous. ^[4]

Based on the above NCI findings, the data presented in the VRBPAC Background Document on Gardasil™ HPV Quadrivalent Vaccine only supports the claim that Gardasil™ can prevent “*an equivocal diagnosis of pre-cancer, representing an admixture of HPV infection and pre-cancer*” –about half of which are self-reversing to normal - not cervical cancer which is a malignant lesion at a point of no return to normalcy.

Furthermore, based on a recent NCI document, the only reliable HPV genotyping method is a “*PCR system with short target sequences.*”^[5] However, such a reliable HPV genotyping method was never used to ‘*determine the associated HPV type*’ in the clinical trials for evaluation of the efficacy of Gardasil™ to prevent type-specific HPV infections. Obviously, any data collected using unreliable methods cannot be used to reliably evaluate the efficacy of any drugs or vaccines.

The FDA has approved a vaccine which is being marketed as a cancer vaccine, when in fact it has only been proven to prevent ‘*not a true biologic entity,*’ in the words of the NCI, the inventor of the current HPV vaccine technology and the co-developer of Gardasil™.

The situation is exacerbated because the FDA and the NCI have not attempted to encourage development of a reliable HPV genotyping method for post-license monitoring of the effects of Gardasil™ vaccination on the epidemiology of HPV infections in the American population. One of the two FDA-approved HPV tests generates two to four times more positive results than the other. ^[6] The doctors do not know which test to use for patient management, which may lead to more unnecessary harmful colposcopic biopsies on women at a great cost to society. ^[7]

In view of the fact the FDA is a science-based, science-driven regulatory agency whose stated mission is to ‘promote and protect the health of the public,’ S.A.N.E. Vax, Inc. respectfully requests a temporary suspension of the sales and marketing of Gardasil™ as a cervical cancer preventive, until such time as the efficacy of the vaccine is properly re-evaluated using the true endpoint for cervical cancer prevention, and a reliable HPV genotyping method for detection of type-specific HPV infections.

I am looking forward to receiving your response to this reasonable request on behalf of medical consumers around the world.

Yours respectfully,

Norma Erickson, President
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Signed on behalf of the Board of Directors, S.A.N.E. Vax, Inc.
Leslie Carol Botha, Vice President of Public Relations
Janny Stokvis, Vice President of Research
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References

- 1.VRBPAC Background Document: Gardasil™ HPV Quadrivalent Vaccine. May 18, 2006 VRBPAC Meeting www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.pdf
- 2.Castle PE, Stoler MH, Solomon D, Schiffman M. The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report. *Am J Clin Pathol.* 2007;127:805-815.
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- 4.Schiffman M, Rodríguez AC. Heterogeneity in CIN3 diagnosis. *Lancet Oncol.* 2008;9:404-406. A comment on the article - McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, Skegg DC. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol.* 2008;9:425-434.
- 5.National Cancer Institute. HPV Genotyping. Solicitation Number: NCI-100143-MM. August 2, 2010. https://www.fbo.gov/index?s=opportunity&mode=form&id=da396b97ad6eb7ec4f7d511f85d9e325&ab=core&_cview=0
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- 7.Stout NK, Goldhaber-Fiebert JD, Ortendahl JD, Goldie SJ. Trade-offs in cervical cancer prevention: balancing benefits and risks. *Arch Intern Med.* 2008; 168: 1881-1889.

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