October 19, 2010

Jack Stapleton, M.D., Chair
Vaccines and Related Biological Products Advisory Committee
University of Iowa Hospital Clinic
200 Hawkins Drive
Iowa City, Iowa 52242

SUBJECT: Valid endpoint and reliable HPV genotyping for expanded use proposal of Gardasil™ vaccine

Dear Dr. Stapleton:

S.A.N.E. Vax, Inc. is a non-profit organization established to promote safe, affordable, necessary and effective vaccines and vaccination practices. We have been informed by the news media that the Vaccines and Related Biological Products Advisory Committee will meet on Nov. 17 to discuss the effectiveness of Gardasil™ vaccination of males and females to prevent anal dysplasia and anal cancer, in fact to initiate a regulatory process which may lead to FDA expanded use approval allowing Gardasil™ to be marketed as a cancer vaccine to the general American population, including both men and women.

Although detailed information has not been provided, the vaccine manufacturer seems to propose using '*anal dysplasia and anal cancer*' as a single primary endpoint for evaluating the effectiveness of this virus vaccine.

The SaneVax team believes this primary endpoint is inappropriate for the following reasons:

1. Anal dysplasia, also known as anal intraepithelial neoplasia (AIN),[1] is a term representing collectively various grades of precancerous changes, also referred to as epithelial dysplasia, grades I, II and III. There is considerable inter-observer variation in the reporting of this condition even by experienced histopathologists.[1] If anal dysplasia is used as an endpoint for evaluation in the clinical trials, the grades of dysplasia must be stratified in the vaccinated group and in the placebo group so that the percentage of a particular grade of anal dysplasia can be compared between the vaccinated and the placebo-receiving subjects for efficacy calculation. The vaccine manufacturer must present data to show the percentage of spontaneous regression of each grade of anal dysplasia in the trial human population so that the self-reversing lesions in a low grade of dysplasia will not introduce bias in the calculation of the effectiveness of the vaccine.

2. A number of risk factors have been implicated in the development of anal dysplasia, with the most significant being anal HPV infection, receptive anal intercourse, HIV infection, and lower CD4+ levels. The subjects enrolled into the clinical trial

programs for the evaluation of the efficacy of Gardasil™ to prevent anal dysplasia must have similar risk factors. Only when all risk factors have been equalized, a reduced rate of anal dysplasia observed in the vaccinated group, if any, compared to the placebo-receiving group, can be attributed to the effects of Gardasil vaccination. It is well known that different HPV genotypes pose different levels of cancer risk. Reliable HPV genotyping is essential in stratification of risk factors to anal dysplasia among enrolled trial subjects. Since PCR/short target DNA sequencing is the only reliable method for HPV detection and genotyping, [2] all pre-vaccination and post-vaccination HPV infections in these trial subjects must be ruled out by PCR or confirmed by short target sequencing genotyping. It is obvious that trial subjects infected by different genotypes of HPV will have different risks in developing anal dysplasia independent of the effects of Gardasil™ vaccination.

3. The vaccine manufacturer must demonstrate the effectiveness of Gardasil™ in preventing each grade of anal dysplasia. The criteria of diagnosis for each grade of anal dysplasia must be clearly defined and the diagnosis must be consistently reproducible among at least three board-certified pathologists.

4. It is well known that anal dysplasia is largely a pathology found in patients who have a history of practicing receptive anal intercourse.[3] The clinical trial data derived from study subjects practicing anal sex should not be extrapolated to populations which do not practice anal sex. If the vaccine manufacturer claims that Gardasil™ is also effective in preventing anal dysplasia in the populations which do not practice anal sex and intends to market Gardasil™ to the latter group, then trial subjects who do not practice anal sex must be recruited for the clinical studies, independent of those studies in which the trial subjects are practitioners of anal sex.

5. If the vaccine manufacturer intends to claim that Gardasil™ can prevent the development of anal cancer, then anal cancer must be used as the primary endpoint to determine the efficacy of the vaccine. Precancerous changes, such as anal dysplasia grade I, grade II or grade III, should not be used as a surrogate endpoint for anal cancer in the clinical trials.

6. If the vaccine manufacturer intends to claim that Gardasil™ can prevent anal infection by vaccine-relevant HPV genotypes, then a reliable method, namely a PCR system with short target DNA sequencing[2] must be used to detect HPV DNA in the anal specimens and for HPV genotyping.

Our research also revealed that an inappropriate primary endpoint was used in the evaluation of Gardasil™ to prevent cervical cancer, and that no reliable HPV genotyping methods were used to validate the efficacy of Gardasil™ to prevent genotype-specific HPV infections in women. A letter to the FDA commissioner, requesting that the FDA rescind approval of Gardasil™ as a vaccine for prevention of cervical cancer, is enclosed herewith for your reference.

In the interest of promoting and protecting the public health, S.A.N.E. Vax, Inc. respectfully requests that expanded use for Gardasil™ as an anal cancer preventive vaccine be delayed, until such time as the efficacy of the vaccine is properly evaluated using the true endpoint for anal 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.
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Janny Stokvis, Vice President of Research
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References

1. Carter PS, Sheffield JP, Shepherd N, Melcher DH, Jenkins D, Ewings P, Talbot I, Northover JM. Interobserver variation in the reporting of the histopathological grading of anal intraepithelial neoplasia. J Clin Pathol. 1994;47:1032-1034.
2. National Cancer Institute. HPV Genotyping. Solicitation Number: NCI-100143-MM. August 2, 2010. https://www.fbo.gov/index?s=opportunity&mode=form&id=da396b97ad6eb7ec4f7d511f85d9e325&tab=core&_cview=0
3. Moscicki AB, Hills NK, Shiboski S, Darragh TM, Jay N, Powell K, Hanson E, Miller SB, Farhat S, Palefsky J. Risk factors for abnormal anal cytology in young heterosexual women. Cancer Epidemiol Biomarkers Prev. 1999;8:173-178.

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