November 2, 2010

The Honorable Margaret Hamburg, M.D., Commissioner, FDA
The Honorable Harold E. Varmus, M.D., Director, NCI

Subject: Request recommending a reliable human papillomavirus (HPV) genotyping test to support the national virology-based cervical cancer prevention program for patient care

Dear Dr. Hamburg and Dr. Varmus:

A recently published letter to the editor of 'Obstetrics and Gynecology,' authored by two senior officials from the National Cancer Institute (NCI), has confirmed it is on the NCI's agenda to replace the traditional Papanicolaou (Pap) cytology with a virology-based program to prevent cervical cancer in the United States.[1]

As we all know, regular Pap cytological screening has successfully reduced the U.S. cervical cancer prevalence rate to one of the lowest in the world in the past 60 years. Now, cervical cancer in the U.S. is primarily a disease among women who have not received regular Pap screenings, or whose Pap tests have not been properly performed.

The proposed virology-based program by the NCI consists of prophylactic vaccination of adolescents against carcinogenic HPV infections and HPV testing followed by colposcopic biopsies.[2]

The SaneVax team is very concerned about instituting a virology approach for cervical cancer prevention because the current HPV vaccines have not been proven to be effective in preventing cervical cancer among the highly heterogeneous female populations in the U.S., as elaborated in our previous letter addressed to the FDA commissioner on October 19, 2010.

Based on a recent NCI document [3], the currently FDA approved HPV tests on the market may not be reliable in generating HPV genotyping information for patient care. The results of two FDA-approved HPV tests often contradict each other. The NCI officials now "agreed that the increased detection of HPV by Hologic Cervista in the data submitted to the FDA is a concern that must be addressed in the mandated postmarketing studies." [1]

The SaneVax team finds this disclosure highly disturbing. If the data submitted to the FDA in support of a Class III medical device premarket approval application (PMA) raised a concern about its safety and efficacy, why did the governmental regulatory agency approve the device to be marketed to the general consumers without resolving the concern at the reviewing stage?

Knowing there was a concern that must be addressed and relying on mandated postmarketing studies to address the concern should not be the right way for the FDA to approve a PMA diagnostic device. Common sense tells us that the damage to the public will be extensive if the FDA waits for a known safety or efficacy issue of a drug or a medical device to become obvious during postmarketing monitoring before addressing the issue.

Since the Cervista™ HPV HR test was approved by the FDA "to screen patients with atypical squamous cells of undetermined significance (ASC-US) cervical cytology results to determine the need for referral to colposcopy," a positive test result is used by gynecologists as a triage tool to channel women into harmful 4-quadrant cervical biopsies. More false positive HPV test results will lead to more unnecessary biopsies on women at a greater cost to society.

Our research further revealed that the Cervista™ HPV HR test kit was approved in March 2009 without conducting an FDA advisory committee public meeting. Approval of a Class III medical device without an open session advisory meeting is highly unusual.

As a result of this non-transparent approval process, the public does not know what the positive predictive value *(ppv)* is for the Cervista™ HPV test for CIN3 detection.[4]

Since the NCI has now disclosed this concern, we are respectfully requesting the FDA to conduct an advisory committee public meeting to review the original data submitted for the PMA application of Cervista™ to determine if the device was properly reviewed and approved for marketing.

Since the senior NCI official in charge of the HPV project also works with the FDA, the vaccine manufacturer, and the HPV test device manufacturer[1] in developing the virology-based cervical cancer prevention program, and acknowledges the fact that "increased detection of HPV by Hologic Cervista in the data submitted to the FDA is a concern," SaneVax believes both the FDA and NCI have a responsibility to address the concern over why one FDA-approved HPV test generates two to four times more positive results than the other.[5]

Since reliable HPV genotyping is a valuable tool for pre-vaccination and post-vaccination monitoring of type-specific HPV infections, S.A.N.E. Vax, Inc. hereby requests permission to attend any future advisory committee public meetings for

HPV test applications to convey the desire of the consumers to the committee members for consideration.

A copy of this letter is being sent to Shanika Craig, the designated federal official of the microbiology devices panel, as a formal request for notification whenever meetings are scheduled to discuss HPV PMA applications.

Thank you,

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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
Rosemary Mathis, Vice President, Victim Support
Freda Birrell, Secretary
Linda Thompson, Treasurer

References

1. Schiffman M, Wentzensen N. From human papillomavirus to cervical **c**ancer**.** In Reply to a Letter to the Editor. Obstet Gynecol 2010;116:1221-2.
2. Schiffman M, Wentzensen N. From human papillomavirus to cervical cancer. Obstet Gynecol 2010;116:177-85.
3. 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

4. Stoler MH, Castle PE, Solomon D, Schiffman M. The expanded use of HPV testing in gynecologic practice per ASCCP-guided management requires the use of well-validated assays. Am J Clin Pathol 2007;127:1-3.
5. Kinney W, Stoler MH, Castle PE. Special commentary: patient safety and the next generation of HPV DNA tests. Am J Clin Path 2010;134:193-9.

cc.

Microbiology Devices Panel:

Shanika Craig, Designated Federal Official