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The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U. S. Food and Drug Administration (FDA)
5600 Fishers Lane
Rockville MD 20857 Tel. (301) 827-2410

Via Federal Express delivery #8634 8347 4154

Subject: FDA's withdrawal of approval for expanded use of human papillomavirus (HPV) DNA assay will reduce needless cervical biopsies on American women

Dear Dr. von Eschenbach:

This letter requests that the FDA withdraw the March 31, 2003 approval for the expanded use granted to the Digene Corporation's Hybrid Capture® (HC2) High-Risk Human Papillomavirus (HPV) DNA Test Kit because its expanded use lacks safety and effectiveness when applied to the U.S. population. Against the evidence presented by its own scientists [1], the FDA approved this virology assay "to determine the need for referral to colposcopy" [2], which has led to a large number of unnecessary cervical biopsies on American women in the past five years.

A recent publication by several scientists from the Department of Health Policy and Management, Harvard School of Public Health, has confirmed the observations of the practicing pathologists in this country that more than 95% of referrals to colposcopy for diagnostic workup for cervical precancer and cancer, when following the guidelines directed by this FDA-approved HPV test, are false positive and/or probably excessive in that the procedures are in fact performed on healthy women or women who have mostly reversible non-cancerous lesions [3]. The authors of this published report found that screening with combined cytologic and HPV testing, as approved for use by the FDA in the March 31, 2003 order, regardless of patient age, leads to the highest number of excessive colposcopic referrals. These unnecessary biopsies are psychologically and physically traumatic to the women at a great cost to the society.

Prior to 2003, the Digene High Risk HPV DNA test (the Hybrid Capture II test), a nucleic acid hybridization in vitro diagnostic device, was used for the detection of 13 high-risk types of human papillomavirus (HPV) in cervical specimens, namely a virology test, as stated in the opening remark by Michael L. Wilson, M.D., Chair of the FDA Microbiology Devices Advisory

Panel Meeting held on March 8, 2002. The latter meeting was held to deliberate on a premarket approval (PMA) supplement for the device's modified indication for use "as a general population screening test in conjunction with the Papanicolaou (PaP) smear for women age 30 and older, as an aid to determining the **absence** of high-grade cervical disease or cancer." [1]
<The undersigned high-lighted the bold-faced word "absence".>

The FDA's Sr. Review Scientist, Thomas E. Simms, analyzed the data submitted by the sponsor, based on the proposed indication for use and criteria for screening tests. Simms presented data from the studies in support of the following major FDA concerns [1]:

(1) The eight studies relied on by the sponsor were not originally designed to evaluate Digene's proposed indication for use and establish performance characteristics.
(2) FDA's concerns with the sponsor's data are that not all the studies included the full claimed age range.
(3) The study populations were not consistent with the U.S. population.
(4) One study was a longitudinal study that the sponsor converted to a cross-sectional study for data analysis purposes.
(5) Patient follow up was not consistent with U.S. practice.
(6) Study populations were not stratified for low-risk women.
(7) Unapproved HPV DNA collection devices were used at three sites; the sites demonstrated differences in cytology readings, and one study was conducted with a less sensitive version of the Hybrid Capture II device.

At the same meeting, Marina Kondratovich, Ph.D. mathematical statistician, Office of Surveillance and Biometrics, CDRH of the FDA, stated that the sponsor's estimated increase in sensitivity was affected by verification bias, that "the sponsor's PMA submission overestimated the increase in sensitivity and decrease in false negatives." "The China and Baltimore studies did not demonstrate statistically significant increases in sensitivity when the combination of Pap and HPV tests was used. In addition, the sponsor did not address other biases, such as spectrum bias from differential prevalence and device bias", stated the FDA mathematical statistician. [1]

Based on the data presented by the FDA scientists, a panel consultant, Kenneth I. Noller, M.D. raised a serious question: "An HPV test (*cancer-screening*) will only increase anxiety and translate into increased colposcopy exams. One would have to do many colposcopies to pick up one case of disease-where does one set the bar?"

One panel member, Kathleen G. Beavis, M.D. predicted "Implementing widespread HPV screening could lead to increased colposcopies."

Another panel consultant, George G. Birdsong, M.D. agreed that "if HPV screening were widely implemented, colposcopies would increase."

A panel consultant, Donald A. Berry, Ph.D. pointed out that the sponsor's criteria of decreasing false negative rate more than 25% and not decreasing specificity (true negative rate) by more than 10% to measure the benefit of adding high-risk HPV testing to the normal Pap smear were not acceptable. Sensitivity and specificity are not the only or most relevant characteristics to address.

Panel member, Laura A. Koutsky, Ph.D. agreed that "positive and negative predictive values vary for different populations, depending on prevalence (*of cancer*)".

Dr. Beavis, a panel member, reminded the panel that "the test detects HPV, not the presence of cancer".

L. Barth Reller, M.D. said that the data are insufficient to provide guidance on clinical practice.

According to the Summary Minutes of the Microbiology Devices Panel Meeting Open Session dated March 8, 2002, the panel voted 6-2 to approve the device *(modified indication for use)* with the following four conditions:

1. The sponsor should provide specific recommendations for how to use the test in clinical management (including how to interpret results near the cutoff).
2. The sponsor must demonstrate that the recommendations will have a positive impact on clinical outcomes. These conditions could be satisfied by evidence based on data derived from longitudinal studies.
3. The sponsor must develop educational materials to accompany the tests both for laboratory users and clinicians.
4. Postmarketing surveillance must be conducted to assess the impact of the device performance on clinical outcomes.

However, without a demonstrated positive (beneficial) impact on clinical outcomes, on March 31, 2003, the FDA CDRH issued a PMA order (P890064/S009) for Digene Hybrid Capture 2 (HC2) High-Risk HPV DNA Test with modified indications for use as follows [2].

1. To screen patients with ASCUS (atypical squamous cells of undetermined significance) Pap smear results to determine the need for referral to colposcopy. The results of this test are not intended to prevent women from proceeding to colposcopy.

2. In women 30 years and older the HC2 High-Risk HPV DNA Test can be used with Pap to adjunctively screen to assess the presence or absence of high-risk HPV types. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

The CDRH approved the expanded use of the Digene HC2 HPV test over so many serious safety and effectiveness concerns raised by the FDA's own scientists and panel members if such a device largely developed on populations with a high disease prevalence were to be used as a screening test in a population with low disease prevalence in the United States of America.

A side-by-side comparison of the language contained in the FDA Summary Minutes of the Microbiology Devices Panel Meeting Open Session dated March 8, 2002 and the language contained in the March 31, 2003 approval order reveals that the FDA in fact approved an indicated use of the HC2 test that the sponsor did not request for and presented no data to support. Specifically, the sponsor asked for permission to use the HPV test to "determining the absence of high-grade cervical disease or cancer" (*when the HPV test result is negative*). Instead, the FDA approved the use of the HPV test "to determine the need for referral to colposcopy" (*when the HPV test result is positive*). The events are reiterated as follows.

At the Open Session Panel Meeting of March 8, 2002, Dr. Wilson, Chair of the Panel clearly stated that the Panel's charge was to deliberate on a premarket approval (PMA) supplement that "The device's modified indications are for use as a general population screening test in conjunction with the Papanicolaou (Pap) smear for women age 30 and older, as an aid to determining the **absence** of high-grade cervical disease or cancer [1]." Based on the proposed modified indications for use, the panel discussion was focused on the probability of linking a negative HPV test to the absence of high-grade cervical disease or cancer. At this Open Session Panel Meeting, neither the sponsor nor the FDA CDRH manager disclosed to the Panel members and consultants that the sponsor also intended to market the device as an aid to "**determine the need for referral to colposcopy**", a important phrase in the FDA approval order which allowed Digene Corporation to promote its HC2 HPV assay as the only FDA-approved tool of triage in referring women to an invasive diagnostic procedure.

The language used in the FDA approval order of March 31, 2003 that "the results of this test are not intended to prevent women from proceeding to colposcopy" is also misleading because it does not indicate clearly what to do when the result is negative, and what to do when the result is positive. The statement can be construed to imply an FDA endorsement that the acceptable norm for diagnostic work up on patients with an ASCUS cytology is colposcopy, and that the colposcopic procedure should not be stopped because of a negative HPV test result. It also implies that positive results of this test may be used to determine the need for referring women to colposcopy, an indication for use that the FDA did not spell out clearly in its approval order, but has been used to formulate the guideline for triage of clinical management, leading to an increase in unnecessary colposcopies.

The public records show that the market value of Digene Corporation, a single test manufacturer of the HPV assay kit, increased more than 5 times from $283 million to $1.6 billion [4, 5] since the FDA approved the expanded use of its HPV HC2 test in 2003. As shown by the Free White Papers on SEC Filings and XBRL, Form:DEF 14A, 2001 & 2004 [6], the Compensation Committee of Digene Corporation justified to its shareholders the hefty bonus paid to its chief executive officer each year "for his efforts in assembling a highly qualified executive management team for Digene and Digene's progress with FDA and other regulatory activities, in entering into agreements with strategic partners and in increasing public awareness of Digene's HPV tests".

Now, more than five (5) years have elapsed since the FDA's approval order of March 31, 2003 was issued. Independent postmarketing surveillance has demonstrated an adverse clinical impact of the Digene HC2 device performance on women living in the United States when the HPV test is used according to this FDA approval order. More than 95% of the women referred to colposcopic biopsies based on the FDA-approved HC2 test for triage have underdone an unnecessary traumatic invasive procedure at a great cost to the society. The documents available in the public domain appear to indicate that Digene Corporation by-passed the scrutiny of the FDA Advisory Panel at the open session meeting to secure an approved expanded use for its device to profit itself at the expense of the women patients and the society. May we ask: who were the Digene Corporation's strategic partners in the FDA?

Thank you for your immediate attention to this matter.

Yours respectfully,

Sin Hang Lee, M.D., F.R.C.P.(C), F.C.A.P.
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References (copies enclosed)

1. FDA Summary Minutes of the Microbiology Device Panel Meeting. Open Session. March 8, 2002. http://www.fda.gov/ohrms/dockets/ac/02/minutes/3846m2.pdf

2. FDA Approves Expanded Use of HPV Test. P03-26. March 31, 2003. http://www.fda.gov/bbs/topics/NEWS/2003/NEW00890.html

3. 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.
4. Company news; F.T.C. challenges Cytyc's purchase of Digene (at $283 million). The New York Times, June 25, 2002.
5. Stocks News Europe-Qiagen rises on molecular diagnostics hopes. In 2007, Qiagen had taken over Digene for $1.6 billion. Yahoo Finance. European Market News. October 6, 2007.
6. How is Digene's Chief Executive Officer Compensated? Page 9 of 10. Digene Corp. Form:DEF 14A Filing Date:9/26/2001 and 9/23/2004 Executive Compensation and other information (a, b).

cc. U.S. Representatives Jim Himes (elect), Henry Waxman, Rosa DeLauro, John Dingell and Bart Stupak