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Patient, Consumer, and Public Health Coalition
c/o Anna Mazzucco, Ph.D.
National Research Center for Women & Families
1001 Connecticut Avenue NW, Suite 1100
Washington, DC 20036

Re: Microbiology Medical Devices Panel on Cobas HPV Test Premarket Approval Application

Dear Patient, Consumer, and Public Health Coalition, et al:

FDA Commissioner Margaret Hamburg, M.D., referred your April 14, 2014 letter to me for reply. Thank you for sharing your concerns with us, we value input from patients, advocacy groups and health professionals and share your focus on public health. In fact, a panel of experts discussed many of your concerns during the open public advisory panel meeting last month.

Under section 513(a) of the Federal Food, Drug & Cosmetic Act (the FD&C Act), FDA determines whether PMA applications provide a reasonable assurance of safety and effectiveness by weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use, among other relevant factors.[1] We have carefully weighed the risks and benefits associated with the new intended use and, based on the information, including all data available, we have determined that the cobas HPV Test is safe and effective for the intended use as submitted and found in the Summary of Safety and Effectiveness Data which should be available on our website next week. We would like to address your concerns directly so that you have an understanding of how FDA came to this conclusion. We have organized our response according to the major title sections in your letter, for which we have kept the wording and bold type, and have a detailed discussion on the points you made.

No U.S. guidelines currently sanction HPV testing as a first-line screening test for cancer

In your letter, you express grave concern that the cobas HPV Test replaces a safe and effective, well-established screening tool and regimen that has prevented cervical cancer

[1] Guidance for Industry and Food and Drug Administration Staff: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf

successfully in the U.S. with a new tool and regimen that has not been proven to work in a large U.S. population, and is not supported by any evidence-based U.S. guidelines. FDA's approval of the cobas HPV Test represents the FDA's determination that the device is safe and effective for its stated intended use, allowing the test to be marketed and made available to doctors for the purpose of enabling an additional approach to patient management. FDA does not to establish "U.S. guidelines" for clinical use or reimbursement of cervical cancer screening. Those decisions properly rest with recommending bodies, such as professional societies or the U.S. Preventive Services Task Force and payers, such as CMS.

This distinction was implicit in the statement from two professional societies that provide such testing guidelines—the Society of Gynecologic Oncology (also known as SGO) and the American Society of Colposcopy and Cervical Pathology (also known as ASCCP)—at the March 12 open public meeting. According to that statement:

> All in all, this group felt that primary HPV screening is a potentially very important scientific and clinical advancement of cervical cancer screening since it holds the promise of improved, or at least equal, performance to cytology-based strategies. As with all new advances, there are many questions and concerns that are raised. If primary HPV screening is approved, this group recognizes the immediate importance of providing sound clinical guidance as well as another opportunity to properly educate health care providers who participate in this type of screening. In the end, this guidance panel is supportive of primary HPV testing.

Based on the level of evidence necessary to determine that a medical device is safe and effective, most, if not all, newly approved medical devices have no U.S. clinical guidelines that sanction or recommend their use at the time of approval.

The new indication for Roche Molecular System's (RMS) HPV test is supported by data from a large clinical study (the ATHENA Study) demonstrating the safety and effectiveness of the device. The ATHENA Study included more than 40,000 women and is the largest prospective U.S. clinical study to evaluate performance of an HPV test ever conducted for the purpose of FDA approval. The ATHENA Study is also one of the largest, if not the largest, study conducted to gain approval for any medical device.

Data from this study showed that for patients 25 years and up:

a) HPV primary screening is better than the Pap test alone in all three measures of performance.

b) HPV primary screening is better than "current practice[2]" that is, it has the same percent of

[2] "Current practice" in this letter is defined as ASC-US triage with HPV for women age 25-29 and co-testing with HPV and cytology per current guidelines[3] using Option 2 for women 30 years of age and older.

women being referred to colposcopy, but has an improved positive predictive value and similar negative predictive value.

Algorithm	Percent referred to colposcopy	Percent of patients with cervical disease (≥CIN3) among patients referred to colposcopy (PPV)	Percent of patients with cervical disease (≥CIN3) among patients not referred to colposcopy (1-NPV)
HPV Primary Screening	4.6%	12.3%	0.42%
Pap test alone	9.9%	6.5%	0.59%
Current practice	4.7%	11.0%	0.48%

FDA appreciates that there is a potential concern about prenatal-related co-morbidities. Therefore, at the Advisory Committee meeting, FDA asked members to discuss the benefits and the risk associated with the age range for the proposed new indication. Several panel members expressed concerns about the possibility of overtreatment in the 25 to 29 years of age group and the possible impact it may have on their future reproductive health, noting that the data on the impact of treatment on preterm labor remain inconclusive. Given that there is a significant prevalence of ≥CIN3 in this age range (patients 25-29 years of age have the highest prevalence of cervical disease: 1.53% for patients 25-29 years old versus 0.86% for patients 30 years or older), that the proposed screening algorithm limited direct follow up by colposcopy to those that were HPV genotype 16/18 positive and that over-screening could be mitigated with proper screening intervals, the Committee members agreed that the benefits outweigh the risks.

Under the proposed algorithm; i) only HPV genotype 16/18 positive women are referred to colposcopy; ii) and patients with 12 Other HR HPV positive results would be followed-up with cytology (Pap (smear)test); for this latter category, only if the cytology is abnormal will these patients then be referred to colposcopy. Sending HPV 16 and/or 18 positive women directly to colposcopy regardless of their Pap test result is already acceptable current practice in women 30 years of age and older when "co-testing" by HPV and cytology per current consensus screening guidelines[3]. The risks of developing ≥CIN3 for these HPV positive patients together with cytology results are the following: 32.0% for HPV16/18 positive and >ASC-US; 13.7% for HPV16/18 positive and ASC-US; and 9.9% for HPV16/18 positive with normal cytology (NILM results). The risk for all three levels of abnormal cytology is high and therefore it makes sense that all HPV16/18 positive patients (*regardless of their cytology*) be referred to colposcopy. In the ATHENA study, for women age 25- 29, 7% had HPV16/18 positive results. The risk of ≥CIN3 (cervical disease) for these women was 12.7% thus justifying their direct referral to colposcopy.

Significant design problems with the pivotal clinical trial

The FDA disagrees with the assertion that the ATHENA study is a flawed clinical trial.

[3] Saslow D, Solomon D, Lawson H, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. Am J Clin Pathol 2012;137:516-542.

RMS began their study before the 2012 guidelines were adopted, and it is appropriate that the cytology alone comparator was consistent with clinical practice at the time. Also, FDA considers cytology alone (2006 Guideline algorithm[4]) to be an appropriate comparator, as it is more familiar to clinicians and has better sensitivity than the 2012 Guideline cytology alone algorithm (immediate colposcopy only for women with ≥LSIL cytology). Fortunately, the primary screening indication was also compared to co-testing with HPV and cytology per current guidelines[1] using Option 2 for women 30 years of age and older and ASC-US triage with HPV for women age 25-29, which can be considered "current practice" as a currently recommended screening algorithm. Both comparisons can be found in the Advisory Committee briefing pack, which was given ahead of the meeting to the Committee members and is available on the Internet[5]. Both comparators (cytology alone and "current practice") were considered for the benefit-risk analysis for the cobas HPV Test primary screening claim.

Since the study to support approval was cross-sectional (that is a one-time test with three-year follow-up) the company will not be able to make any claims with respect to the safety and effectiveness of the repeated use of this test, nor did the FDA evaluated the test in that context. It is typical for recommending bodies to set clinical practice parameters, including recommending interval of testing based on the best available evidence. The FDA noted during the panel meeting that as population dynamics evolve, future intended use populations e.g., after 15-20 years of using the 2012 guideline and an increase in the percent of women vaccinated for HPV, may be different from the current population, a fact that will also affect the current testing modalities. As a result, the label for the product contains limitations with an explanation of this fact.

In your letter you claim there is a problem with the study in regard to the participant age. Our assessment is that the study population was representative of the existing U.S. population and follows a well-recognized, scientific approach.

Minimal gains in detection

Per 10,000 women ≥25, the cobas HPV Test primary screening indication would be expected to detect 61 cases of ≥CIN3 compared to 41 cases with the Pap test alone and 52 cases with current practice. Thus an improvement in detection of 9 to 20 cases per 10,000 women. For women age 25-29 the cobas HPV Test primary screening indication detected 110 cases of ≥CIN3 compared to 66 cases by Pap test alone and the same number of cases, 66, with current practice. This represents an improved detection of 44 cases per 10,000 women—which FDA believes is significant.

[4] Wright T, Massad LS, Dunton C, et al. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. American Journal of Obstetrics and Gynecology. 2007; 197(4):346-55.
[5] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/ucm388531.htm

Clinically important information thrown away

The Bethesda System for Classifying Cervical/Vaginal Diagnoses from cytology tests includes non-cancer related diagnostic categories such as, the ability to detect microscopically, certain organisms and abnormal endometrial cells. The cobas HPV Test is not designed to screen for these additional diagnostic categories. Based on their clinical experience, the Committee discussed the potential impact on patients if this additional diagnostic information would be lost. They generally agreed that patients would not be adversely impacted by loss of these cytology categories since other better testing methods now exist for these conditions that clinicians are using rather than relying on cytology.

In conclusion, based on the totality of the data, the benefit and risk analysis, and the discussion from the panel meeting, the FDA review team unanimously concluded that the cobas HPV Test is safe and effective for an indication of primary HPV screening based on the algorithm described in the labeling.

We appreciate you bringing your concerns to our attention so that we could consider them during our decision-making. Your input is valuable and helps us better perform our mission of protecting and promoting public health.

Sincerely yours,

Alberto Gutierrez -S

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