



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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DEC 14 2007

Food and Drug Administration
2098 Galther Road
Rockville MD 20850

Re: Reclassification Order
Docket No. 2007P-0210
Petition for Reclassification: Human Papillomavirus (HPV) DNA Nested
Polymerase Chain Reaction (PCR) Detection Device (K063649)

Dear Mr. Lee,

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your petition for reclassification of the Human Papillomavirus (HPV) DNA Nested Polymerase Chain Reaction (PCR) Detection Device (HPV DNA Nest PCR Test) that is intended for the following uses:

- (1) To screen patients with ASCUS (atypical squamous cells of undetermined significance) Pap smear results and to provide materials suitable for human papillomavirus (HPV) genotyping by direct automated DNA sequencing 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 HPV DNA Nest PCR Test in conjunction with genotyping by direct automated DNA sequencing 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.

You requested that the device be reclassified from class III to class II. After reviewing the information you submitted, FDA has concluded that it must deny your petition for reclassification for the reasons discussed below. Accordingly, by order in the form of this letter, FDA is denying your petition; your device remains in class III and is subject to premarket approval requirements.

Statutory Background

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360c(f)(1)), devices that were not introduced or delivered for introduction into interstate commerce for commercial distribution prior to May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976 (the amendments)), generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. A postamendments device remains in class III unless and until: (1) the device is classified as class I or II under section 513(f)(2) of the Act (21 U.S.C. 360c(f)(2)); (2) the device is reclassified into class I or II under section 513(f)(3) of

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the Act (21 U.S.C. 360c(f)(3)); or (3) FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the Act (21 U.S.C. 360c(i)), to a legally marketed predicate class I or class II device. The agency determines whether new devices are substantially equivalent to legally marketed predicate devices by means of premarket notification procedures in section 510(k) of the Act (21 U.S.C. 360(k)) and Part 807 of the FDA regulations (21 C.F.R. Part 807).

Devices that have been classified by section 513(f)(1) into class III require premarket approval (PMA) in accordance with section 515 of the Act. See section 515(a)(2) (21 U.S.C. 360e(a)(2)) (requiring PMA for devices classified into class III by section 513(f)); see also section 513(a)(1)(C) (21 U.S.C. 360c(a)(1)(C)) (defining a class III device as one that "is to be subject, in accordance with section 515, to premarket approval to provide reasonable assurance of its safety and effectiveness").

Because the HPV DNA Nest PCR Test is a postamendments device, it is automatically classified as class III under section 513(f)(1). It will therefore remain in class III until it is reclassified into class I or II or is found to be substantially equivalent to a legally marketed predicate class I or class II device.

Legal Framework for Reclassification

Under section 513(f)(3) of the Act (21 U.S.C. 360c(f)(3)), the manufacturer of a device automatically classified as class III under section 513(f)(1) may petition the Secretary for issuance of an order reclassifying the device into class I or class II. Section 513(a)(1) of the Act defines and establishes each of the three device classifications. Your petition requested reclassification of the HPV DNA Nest PCR Test from class III into class II. It is your burden, as the petitioner, to prove that the device meets the requirements for the proposed reclassification. See, e.g., General Med. Co. v. FDA, 770 F.2d 214, 219 (D.C. Cir. 1985).

Under section 513(a)(1)(B) of the Act, a class II device is one "which cannot be classified as a class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance."

A class III device, by contrast, is a device: that cannot be classified as class II because insufficient information exists to determine that special controls would provide reasonable assurance of its safety and effectiveness; that cannot be classified as class I because "insufficient information exists to determine that the application of general controls [is] sufficient to provide reasonable assurance of safety and effectiveness of the device"; and that "(I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or (II) presents a potential unreasonable risk of illness or injury." Section 513(a)(1)(C) (21 U.S.C. 360c(a)(1)(C)). A class III device is subject to premarket approval, in accordance with section 515, to provide reasonable assurance of its safety and effectiveness. Id.

Your Submissions to FDA Regarding the HPV DNA Nest PCR Test

You submitted a 510(k) filing for the HPV DNA Nest PCR Test (K063649) on December 7, 2006, seeking a determination of substantial equivalence. This 510(k) submission identified as your predicate device Digene's Hybrid Capture 2(hc2) High-Risk HPV DNA Test, a class III device that itself has an approved PMA (PMA # P890064). On its face, then, this premarket notification submission did not provide a basis for removal of the HiFi HPV DNA Nest PCR Test from automatic classification as a class III device in accordance with section 513(f)(1), or from a subsequent requirement of premarket approval under section 515(a).¹ A contention that a device is "substantially equivalent" to an approved class III device can not lead either to the classification of the new device as a class II device or to it otherwise being permitted to reach the market without premarket approval. For this reason, FDA did not review the data contained in your 510(k) submission at that time and rejected K063649 by letter dated January 9, 2007. This letter informed you that your device was classified into class III and would be subject to the requirement of PMA under section 515(a)(2) unless reclassified.

On January 18, 2007, you submitted a Request for Evaluation of Automatic Class III Designation under section 513(f)(2) of the Act. On February 22, CDRH advised you to withdraw the 513(f)(2) submission and submit a petition under section 513(f). You withdrew your 513(f)(2) petition and submitted a reclassification petition, dated March 7, 2007, under section 513(f). This petition was date-stamped as received on May 22. FDA has now completed its review of this petition.

In conducting its review, FDA analyzed both the petition for reclassification under section 513(f) and the prior premarket notification submission for the same device, K063649. Although you did not resubmit K063649 with the petition, FDA believes that you intended to incorporate K063649 by reference, by repeatedly directing FDA to information in K063649. See, e.g., pp. 15-16 ("[as] described in the K063649," "[a]s

¹ Section 515(a) of the Act requires premarket approval for any class III device that either "is a class III device because of section 513(f)" or is subject to a regulation promulgated under section 515(b)(2). Under section 515(b), there must be a particular rulemaking procedure before a PMA can be required for the following class III devices: a class III device which "(A) was introduced or delivered for introduction into interstate commerce for commercial distribution before the date of enactment of this section [May 28, 1976]; or (B) is (i) of a type so introduced or delivered, and (ii) is substantially equivalent to another device within that type." While certain postamendments class III devices are therefore not subject to premarket approval until after a section 515(b) rulemaking has been conducted, your HPV DNA Nest PCR Test is not such a device. The predicate cited for your device was not one of the limited set of class III devices identified by section 515(b)(1). Rather, the Digene hc2 Test is itself a postamendments device initially classified into class III under section 513(f), and as such, immediately subject to the requirement for premarket approval under section 515(a)(2). (As already noted, the Digene hc2 Test in fact has an approved PMA.)

stipulated in the K063649").² It is FDA's intention, in reviewing K063649 alongside the petition, to accord you a thorough examination of the relevant data and analyses that you submitted in the petition, either directly or through incorporation by reference. The information in these two submissions is substantially the same, though K063649 is at times more detailed.

FDA Decision on Reclassification Petition

As already noted, the HPV DNA Nest PCR Test was automatically classified into class III under section 513(f)(1) of the Act. It is your burden, as the petitioner for reclassification, to prove that your device meets the requirements for classification into class II.³

Your device can only be downclassified to class II if there is sufficient information to establish special controls that, when combined with general controls, will provide reasonable assurance of the safety and effectiveness of the device, in accordance with section 513(a)(1)(B) of the Act (21 U.S.C. 360c(a)(1)(B)). According to FDA regulations, a reclassification petition must include a "full statement of the reasons, together with supporting data satisfying the requirements of § 860.7, why the device should not be classified into its present classification and how the proposed classification will provide reasonable assurance of the safety and effectiveness of the device." 21 C.F.R. 860.123(a)(6). The "supporting data satisfying the requirements of § 860.7" referred to is "adequate, valid scientific evidence." 21 C.F.R. 860.7(g)(1).

After careful consideration of the relevant information, FDA has determined that you have not demonstrated that there exists adequate valid scientific evidence establishing that special controls, when combined with the general controls under the Act, are sufficient to provide reasonable assurance of safety and effectiveness of the HPV DNA Nest PCR Test. Specifically, FDA has determined that: (1) the supporting data you submitted are inadequate; (2) the special controls you propose do not provide reasonable assurance of the safety and effectiveness of the device; and (3) there is insufficient information to establish adequate special controls for this device at this time.

² Unless otherwise noted, page references are references to the petition for reclassification.

³ You did not seek reclassification of the HPV DNA Nest PCR Test into class I and therefore class I is not an issue here. See General Med. Co., 770 F.2d at 218. As explained infra note 4, however, your device could not be classified as class I even if your petition had requested such a classification.

a. The Device is Intended for a Use which is of Substantial Importance in Preventing Impairment of Human Health and also Presents a Potential Unreasonable Risk of Illness or Injury

As part of your argument in favor of downclassification, you contend that the HPV DNA Nest PCR Test device is not intended for a use which is of substantial importance in preventing impairment of human health. As support, you state that your device is intended only as "an adjunctive assay," to be used in conjunction with Pap testing; it is not intended to "generate a stand-alone diagnosis of human disease" (pp. 16, 18). You further state that your device does not present a potential unreasonable risk of illness or injury because "appropriate special controls in addition to general control requirements" will provide reasonable assurance of safety and effectiveness (p. 18).

FDA disagrees with both of these contentions.⁴ First, FDA has determined based on your intended use statement that your device is purported or represented to be for a

⁴ Your petition requests reclassification of your device into class II. What governs classification as a class II device is whether there exists sufficient information to establish special controls that, when combined with general controls under the Act, will provide reasonable assurance of the safety and effectiveness of the device. See section 513(a)(1)(B) (21 U.S.C. 360c(a)(1)(B)). In addition to supplying information on proposed special controls, however, your petition attempts to support reclassification into class II by arguing that your device does not meet the definition of a class III device under section 513(a)(1)(C) (21 U.S.C. 360c(a)(1)(C)), although it has already been classified as a class III device by operation of statute under section 513(f)(1). Specifically, you argue at length that the device is not intended for a use of substantial importance in preventing impairment of human health, and more briefly contend that it is not intended to be life-supporting or life-sustaining and does not present a potential unreasonable risk of illness or injury, at least when subject to special controls. Compare section 513(a)(1)(C)(ii) (21 U.S.C. 360c(a)(1)(C)(ii)) with 513(a)(1)(B) (21 U.S.C. 360c(a)(1)(B)) with 513(a)(1)(C)(ii) (21 U.S.C. 360c(a)(1)(C)(ii)).

If special controls could be established that would provide a reasonable assurance of the safety and effectiveness of your device, it could be classified into class II even if it had one or more of the characteristics of a class III device specified in section 513(a)(1)(C)(ii). As explained in this letter, FDA denies your request for reclassification into class II because you have not demonstrated that such special controls can be established. In addressing the arguments raised by your petition, FDA has also rejected your contentions that your device is not of substantial importance in preventing impairment of human health and does not present potential unreasonable risk of illness or injury. In so doing, FDA rebuts an argument that would otherwise theoretically have remained, although you did not raise it, that your device should be reclassified as a class I device under section 513(a)(1)(A)(ii) of the Act, 21 U.S.C. 360c(a)(1)(A)(ii), despite the insufficiency of information to establish special controls that will provide a reasonable assurance of safety and effectiveness, or to determine that general controls will suffice to provide such assurance. See section 513(a)(1)(A)(ii) (21 U.S.C. 360c(a)(1)(A)(ii)).

use which is of substantial importance in preventing impairment of human health. Second, FDA has concluded that your device presents a potential unreasonable risk of illness or injury because its rate of false negative results is not known. Insofar as you allege that "appropriate special controls" will be adopted that will negate all potential unreasonable risk of illness or injury, FDA has determined that the special controls proposed in your petition are inadequate and that there is insufficient information at this time to establish adequate special controls for this device, as detailed below in sections (c) and (d).

According to your statement of intended use (p. 16), your device is intended for the following uses:

(1) To screen patients with ASCUS (atypical squamous cells of undetermined significance) Pap smear results and to provide materials suitable for human papillomavirus (HPV) genotyping by direct automated DNA sequencing 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 HPV DNA Nest PCR Test in conjunction with genotyping by direct automated DNA sequencing 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.

Both of these stated intended uses relate to identifying HPV infection status in order to assess a woman's risk of developing cervical cancer where some risk is already suggested, either because of: identified laboratory findings based on present cytology, i.e. abnormal Pap test results (first stated intended use); or statistical risk based on age and possibly other factors (second stated intended use). FDA recognizes that your device is not intended as a stand-alone diagnostic assay. Nonetheless, your device is intended to inform the determination of risk and guide patient management decisions that can themselves lead to more definitive diagnosis and treatment of cervical cancer.

1. Intended for a Use Which is of Substantial Importance in Preventing Impairment of Human Health

Your first stated intended use is to screen patients with ASCUS Pap results and provide materials suitable for HPV genotyping in order to determine the need for referral to colposcopy, a procedure to magnify the cervix and permit visual inspection for any abnormal and potentially cancerous areas. Often, if any abnormality is observed through colposcopy, the tissue in question is biopsied to assess whether it is precancerous or cancerous. Whereas referral to colposcopy helps ensure early detection and treatment of cervical cancer, non-referral may postpone detection and thereby increase the risk of mortality and morbidity from cervical cancer.

In your petition (p. 18), you contend that Pap testing is the primary tool for detection of "atypical cells which may be cancerous or indicative of a potential early development of cancer." You concede that this use is of substantial importance in preventing impairment of human health (p. 18), yet nonetheless contend that your device does not have a use of substantial importance in preventing such impairment. An ASCUS Pap result, however, means that the findings based on Pap testing were neither definitively normal nor definitively signs of precancer or cancer: ASCUS, as you recognize in your petition (p. 16), means "Atypical Squamous Cells of Undetermined Significance," (emphasis added).⁵ When the Pap testing alone provides only this indeterminate information, your device is intended to help physicians make a potentially significant decision: whether to immediately refer patients to colposcopy, which can in turn lead to biopsy and intervention, or to advise patients to wait and be screened again later. Because it is intended to influence this decision, particularly where information from Pap testing is equivocal, the HPV DNA Nest PCR Test is intended for a use of substantial importance in preventing impairment of human health.⁶

Your second stated intended use is also of substantial importance in preventing impairment of human health. This intended use is to adjunctively screen (with Pap), and in conjunction with genotyping, women 30 years and older⁷ for the presence or absence of high-risk HPV types; this information, in turn, "may be used to guide patient management" when considered alongside the physician's assessment of cytology history, other risk factors, and professional guidelines. Your device is thus intended to be used to help assess whether a patient has "high risk" HPV -- meaning HPV strains associated with high risk for cervical cancer -- and to inform decisions on screening frequency and scope. The "professional guidelines" that your intended use statement expressly indicates should be consulted confirm that your test is intended to inform whether, how often, and to what extent a patient should be screened for cervical abnormalities and possible malignancies. According to professional guidelines codified recently into a single consensus guidance,⁸ a woman 30 years or older with a negative Pap test result and a

⁵ See also Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002;287:2116.

⁶ FDA acknowledges the disclaimer in the final sentence of this first stated intended use: that the results of the HPV DNA Nest PCR Test are "not intended to prevent women from proceeding to colposcopy." Your test is nevertheless intended to help inform this decision, with negative results suggesting (albeit not mandating) non-referral to colposcopy.

⁷ Cervical cancer is more prevalent in women 30 years and older than in younger women.

⁸ The 2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests were published in the American Journal of Obstetrics and Gynecology (2006 Consensus Guidelines), 197(4): 346-355 (October 2007), and are available on-line at <http://www.asccp.org/consensus/cytological.shtml>.

positive high-risk⁹ HPV DNA test result would undergo another Pap and high-risk HPV test at one year. If this same woman instead had a negative high-risk HPV DNA test result, she would not undergo any additional screening for another three years.¹⁰ Because your device is intended to influence such patient management decisions, it is intended for a use which is of substantial importance in preventing impairment of human health.

ii. Presents a Potential Unreasonable Risk of Illness or Injury

FDA has also determined that your device presents a potential unreasonable risk of illness or injury. A false negative test result from your device may lead to delays in timely diagnosis and treatment, allowing an undetected condition to worsen and potentially increasing morbidity and mortality from cervical cancer.¹¹ That is, a decision not to refer a patient to colposcopy or not to suggest annual or more frequent screening based in part on a falsely negative HPV DNA test result may present a serious potential risk to human health. Despite the potential harms from false negative results, you have neither established the risk of false negative test results for your device nor shown that this risk is reasonable. Because of this evidentiary failing, FDA concludes that your device poses a potential unreasonable risk of illness or injury. See, e.g., H.R. Rep. No. 853, 94th Congress, 2d. Sess., at 36 (1976) ("The fact that a device is being marketed without sufficient testing is an adequate basis for the Secretary's conclusion that the device presents a potential unreasonable risk to health.").

⁹ Although the 2006 Consensus Guidelines repeatedly use the term "HPV testing" and not "high-risk HPV DNA testing" the guidelines explicitly state in the text that: "Testing for low-risk (nononcogenic) HPV types has no role in the evaluation of women with abnormal cervical cytological results. Therefore, whenever 'HPV testing' is referred to in the guidelines, it applies only to testing for high risk (oncogenic) HPV types." Id.

¹⁰ Id. at 352.

¹¹ While you acknowledge the following limitation of your device -- that a negative result does not guarantee that there is no HPV DNA in the clinical specimen tested (p. 43) -- you propose a test result interpretation of "negative for HPV DNA" if the sample does not show HPV amplification but does show evidence of human genomic amplification (p. 40). As for confirmation, you state throughout your petition that only positive results should be confirmed, not negative results. You repeatedly state that positive results of the HPV DNA Nest PCR Test should proceed to genotyping for confirmation (pp. 17, 29, 44), and in your supporting study you sent only positive results for subsequent genotyping (p. 51). The unavoidable inference from these statements and supporting data is that only positive results "provide materials suitable" for HPV specific genotyping; negative results do not. Only specimens that test positive for HPV DNA by your device can themselves be confirmed through genotyping; specimens that test negative cannot be so confirmed.

b. Supporting Data Inadequate

FDA has carefully analyzed your study descriptions and supporting data.¹² FDA has determined that the scientific evidence you submitted in support of reclassification is deficient for reliably establishing performance characteristics of your device. The supporting evidence thus does not meet the requirements of 21 C.F.R. 860.7 and 860.123(a)(6). It is not adequate, valid scientific evidence showing how the proposed reclassification will provide reasonable assurance of the safety and effectiveness of the device.¹³

Deficiencies that FDA identified in your data and study descriptions include:

(1) You failed to perform any crossreactivity or interfering substances studies to show that your test results will not be affected by: (a) substances potentially present in cervical cytology specimens (such as contraceptives, personal hygiene products, etc.); and/or (b) microorganisms other than the HPV strains targeted by your assay, such as microorganisms that are normally found in the genital tract and any HPV genotypes that are not specifically targeted by your test. (Precisely which HPV strains targeted by your test is unclear from your test description, as noted below in (4).)

(2) Regarding "Sensitivity in detection of purified HPV DNA" (pp. 44-45): You did not adequately establish the limit of detection (the lowest number of copies of targeted HPV DNA that can be detected by your assay) because you (a) did not use appropriate specimen types (they were diluted in buffer and so did not adequately mimic

¹² The reclassification petition and the earlier 510(k) submission for the HPV DNA Nest PCR Test device both refer to the same studies, so FDA examined the fuller descriptions in the 510(k) in order to have a more complete understanding of what data exists on the performance of the device.

¹³ In addition to the studies described in your petition, you attached to the petition copies of 94 source documents that you contend generally support your request for reclassification of the HPV DNA Nest PCR Test. The majority of the literature you cited is general literature on HPV and cervical cancer (e.g., petitioner's references 55 and 66). Only a single article was provided that contains data generated by the your device (petitioner's reference 13), and it describes what appears to be the same studies provided in the petition -- the studies that FDA has evaluated and deemed inadequate, as explained in this letter. Of the papers that utilize HPV detection methods similar to your device [PCR amplification of HPV DNA with both MYO9/11 and GP5/6 primers (e.g., petitioner's references 45 and 50)], none describe the clinical sensitivity and specificity of these methods in the relevant intended use populations. The documents in your Appendix therefore do not provide sufficient valid scientific evidence that would support the reclassification of your device.

real clinical specimens), (b) did not test a statistically significant number of replicates, and (c) did not include every high-risk HPV genotype targeted by the assay.

(3) Regarding "Sensitivity in detection of HPV DNA in clinical samples, compared to FDA-approved device" (pp. 46-51): You have not submitted information on the age distribution and cervical pathologic conditions of the study subjects, and apparently you did not collect it. See p. 46 ("Age distribution of the patients and the cervical pathologic conditions were not the subjects of this study.") You have therefore not demonstrated that your study specimens represent the intended use population for your device, nor have you demonstrated whether they were positive or negative for cervical precancer or cancer. Without knowing whether the subjects are positive or negative for cervical precancer or cancer, FDA cannot assess clinical sensitivity, meaning the proportion of individuals who have precancer/cancer who test positive on the HPV DNA Test.

FDA likewise cannot assess the rate of false negative test results, meaning the proportion of individuals who have precancer/cancer who test negative on the HPV DNA test. This evidentiary failure is particularly troubling to FDA because, as explained above, one of the greatest risks posed by this device is the risk of delivering false negative test results, as these results may lead to delays in timely diagnosis and treatment of cervical cancer. Because of these evidentiary deficiencies, FDA cannot conclude that there is a reasonable assurance of the safety and effectiveness of the device for its intended use.

(4) Regarding "Specificity in detection of HPV DNA in clinical samples" (pp. 51-54): These samples are not identified but are presumably the same samples from the "clinical sensitivity" study above. The same deficiencies identified above therefore apply. Without knowing whether the study subjects are positive or negative for cervical precancer or cancer, FDA cannot assess clinical specificity of the device, meaning the proportion of individuals who do not have precancer/cancer who test negative on the HPV DNA device. FDA therefore cannot conclude that there is a reasonable assurance of the safety and effectiveness of the device for its intended use.

Another reason this "specificity" study is inadequate is that FDA cannot determine the precise degree to which your device detects non-carcinogenic or low risk HPV in addition to high risk HPV. Nor, if your device does indeed detect low risk HPV, can FDA determine to what extent this broad detection is intentional (as a blanket HPV screen) or unintentional (as a result of crossreactivity).

(5) Both of your stated intended uses indicate that your device is to be used in conjunction with "HPV genotyping by direct automated DNA sequencing," and some of your proposed special controls (warnings and sales conditions) incorporate and rely on such genotyping. FDA has not to date approved any HPV genotyping test for diagnostic use, however. Nor have you submitted any evidence to establish that there exists a clinically validated, safe and effective diagnostic HPV genotyping test -- meaning an

HPV genotyping test validated for diagnostic use in relation to cervical cancer, as your intended use statement requires.

(6) Regarding "Reproducibility of HPV Nest PCR Test in clinical specimen testing" (p. 52): This study failed to account adequately for multiple operators, laboratories, days, and reagent lots as applicable. You have therefore failed to establish, with reasonable assurance, that the device will perform consistently (i.e. not produce erroneous results) over time from operator to operator and laboratory to laboratory, in a clinical setting -- as the device is intended to be used.

(7) Regarding "Stability of HPV Nest PCR Test Reagent" (p. 53): Studies are insufficiently described. It appears that stability was not established in a clinically valid manner, for example by using clinical specimens (or simulated clinical specimens such as cell lines diluted in cytology collection media), or with analyte levels that challenge the medical decision point(s) of the assay. Failure to demonstrate stability may lead to inappropriate storage and handling recommendations for the device. The use of non-stable reagents may lead to device failure and subsequently the reporting of false negative or false positive test results.

c. Proposed Special Controls Inadequate

Your proposed special controls are likewise inadequate as they do not provide a reasonable assurance of the safety and effectiveness of the device.

The inadequacies identified by FDA include the following:

(1) Proposed Special Control: The device is for professional use.

FDA agrees that this device should be for professional use. As a special control, however, this proposal is inadequate. You have failed to explain how designating the device "for professional use" will allay the many safety and effectiveness concerns related to your device. If the test is inaccurate, for example, that inaccuracy will not be remedied by limiting it to professional use.

(2) Proposed Special Control: Warnings. The proposed warnings include:

- o Not for use by women with normal Pap smear under age 30;
- o Not intended to substitute for Pap smear;
- o There is insufficient evidence to show that a single normal Pap smear result with concurrent negative HPV Nest PCR Test confers low risk similar to consecutive annual, technically adequate normal Pap results;
- o The use of the device has not been evaluated for the management of women with prior cytological or histological abnormalities, hysterectomy, who are postmenopausal, or who have other risk factors (e.g., HIV +, immunocompromised, DES exposure, history of STD);

- o The device is designed to augment existing methods for the detection of cervical disease and for following persistent HPV infections;
- o Device results should not be used as the sole basis for clinical assessment and treatment of patients;
- o Positive results should be confirmed by genotyping with DNA sequencing, or be considered inconclusive if no genotyping results can be obtained by DNA sequencing.

While FDA believes many of these warnings may be appropriate, they are not adequate to provide a reasonable assurance of the safety and effectiveness of the HPV Nest PCR Test. Of these proposed warnings, FDA finds the final warning especially problematic. This warning states that positive results should be confirmed by genotyping with DNA sequencing; otherwise, they should be considered inconclusive. This reliance on genotyping for confirmation echoes an element of the device's intended use: the device is intended to "provide materials suitable" for HPV specific genotyping, and to be used in conjunction with such genotyping. Your reliance on genotyping is problematic because you have failed to demonstrate that a clinically validated, safe and effective diagnostic HPV genotyping test exists (whether or not approved by FDA). Absent this showing, the final warning cannot be an adequate special control; there is no information or data showing that it would provide a reasonable assurance of safety and effectiveness.

(3) Proposed Special Control: The sales conditions of the device will stipulate that the users of the device will validate all positive nested PCR products by an HPV genotyping method that has been properly validated.

As explained above, you have not shown that a safe and effective, clinically validated diagnostic HPV genotyping method exists. This sales condition therefore cannot be an adequate special control; there is no information or data showing that it would provide a reasonable assurance of device safety and effectiveness.

(4) Proposed Special Control: "[T]he petitioner will maintain a division of HPV DNA genotyping by direct automated DNA sequencing to provide needed clinical assistance to those laboratories that are using this device. The experience of the users with the device and the problems encountered will be recorded on file. Periodic reports will be made to the FDA if required to assure the safety and effectiveness of the device." (pp. 17-18)

You have articulated an intent to "maintain a division of HPV DNA genotyping" without providing sufficient explanation as to what this division will do, whether and to what extent it will exercise control over participating laboratories, how you will determine which problems to report to FDA, and how you intend to correct and prevent problems. It is not clear, for example, whether this proposed special control indicates that you intend to conduct HPV genotyping yourself. Moreover, as already noted, you have submitted no substantive information to establish the safety and effectiveness of any HPV genotyping for diagnostic use. You have neither explained nor demonstrated how

this special control will provide a reasonable assurance of the safety and effectiveness of the device.

d. Insufficient Information to Establish Special Controls at This Time

You have failed to demonstrate through adequate, valid scientific evidence that the device will perform effectively in the clinical setting, with actual patients -- as it is intended to be used. As explained above in FDA's analysis of your "sensitivity" and "specificity" studies, you have demonstrated neither the clinical sensitivity (proportion of individuals who have precancer/cancer who test positive on the HPV DNA Test) nor the clinical specificity (the proportion of individuals who do not have precancer/cancer who test negative on the HPV DNA Test) of your device. You have thereby failed to demonstrate the clinical effectiveness of your device.

This showing of clinical effectiveness is a prerequisite to providing reasonable assurance of the effectiveness of the device for its intended use. As set forth in FDA regulations, a reasonable assurance that a device is effective means that "it can be determined, based upon valid scientific evidence, that in a significant target portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results." 21 C.F.R. 860.7(e)(1) (emphases added). Here, because it cannot be determined from existing information that the device will provide clinically significant results in a significant portion of the target population, there is not a reasonable assurance that the device is effective for its intended use. There is therefore insufficient information at this time about your device to downclassify it to class II.

There are many reasons why a device of your type, an HPV molecular diagnostic test (HPV DNA test), may not be clinically effective (with patients) even if it were shown to be effective in the laboratory (with specimens). Even if the device could effectively detect HPV in an isolated specimen sample, it may not provide "clinically significant results . . . in a significant target portion of the target population." Among the reasons for this disconnect are:

(a) Sampling Method: If the test works from a very small volume of the original cervical sample, it may not sample an adequate number of cervical cells to consistently pick up infected cells. As a result, the specimen taken from the patient may test negative for HPV DNA but the patient may nonetheless be infected with HPV. The relationship between sample volume and clinical performance is not well established, is likely to vary from test to test, and may substantially undermine device effectiveness.

(b) Combination of HPV Genotypes Targeted: Approximately 15 HPV genotypes are considered carcinogenic or high risk for cancer, but relative risk levels for each genotype vary by demographics and the most effective combination of genotypes for cervical cancer screening is currently under debate.

The specific combination of genotypes targeted by a test can profoundly impact its clinical effectiveness.

(c) Probe Design: Probe design is a critical process for HPV DNA testing because of the large number of closely related HPV genotypes. Complex probe cocktails may crossreact and/or compete with one another. There is currently no standardized clinical panel of representative HPV samples available against which specific probe combinations can be evaluated for clinical effectiveness. Accordingly, it is difficult if not impossible at this time for FDA to conclude, absent well-developed clinical data, that a chosen probe design for a device of this type is reasonably safe and effective.

This list is not intended to be exhaustive. It merely exemplifies the many factors involved that affect clinical performance and potentially undermine clinical effectiveness of a device of this type. Given these many factors, it is impossible for FDA at this time to impute clinical effectiveness of the HPV DNA Nest PCR Test from the studies that you submitted, even if these studies were otherwise scientifically sound -- which they are not for the reasons delineated above, pp. 9-11. There is thus insufficient information to establish special controls that would provide a reasonable assurance that the device is clinically effective for its intended use, as required under 21 C.F.R. 860.7(e)(1). There is, in short, insufficient information supporting reclassification of the device at this time.

Conclusion

For the reasons set forth above, FDA is hereby denying your petition for reclassification of the HPV DNA Nest PCR Test. The device shall therefore be retained in class III and is subject to premarket approval requirements.

If you have any questions concerning the denial of the petition, please contact Sally Hojvat at 2098 Gaither Road, Rockville, MD 20850.

Regards,



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