HiFi DNA Tech, LLC
160 Hawley Lane
Trumbull, CT 06611

Fax 203 385-3832

October 19, 2007

Division of Dockets Management
Office of Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockeville, Maryland 20852

In triplicate

Via Federal Express delivery 8634 8347 4051

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

Dear Sir/Madam:

In the above referenced reclassification petition, the petitioner urges the FDA to down-classify all PCR-based HPV DNA tests as class II devices so that small innovative companies can use the less burdensome 510k applications to introduce their new molecular technologies into the market on a competitive basis based on the scientific merits of their devices.

According to a news report, the FDA has accepted two Roche diagnostics HPV tests for review [1]. The report stated: "The Linear Array HPV Genotyping Test is designed to identify which of the 13 high-risk HPV genotypes are present in a sample." Although it is not stated in the report, it is assumed that this is a PCR-based test and depends on DNA probe hybridization for genotyping.

In connection with reviewing the data of analytical sensitivity and specificity of a genotyping test for HPV, this letter brings to your attention the following pieces of scientific information:

1) When a PCR product of the HPV L1 gene with hypervariable DNA sequence is targeted for developing a multiplex genotyping method, the DNA probe designed for one HPV may react with other HPV types due to cross-hybridization despite the presence of mismatches in each pair [2]. Therefore, the methodology designed for specific genotyping must be validated by DNA sequencing, the generally accepted gold standard method for viral genotyping.

2) Pathologists' cytologic interpretations of high-grade squamous intraepithelial lesions (HISL) or cervical intraepithelial neoplasia (CIN2 or CIN3) are well known to be poorly reproducible [3]. Therefore, if a cytologic classification of HISL, CIN2 or CIN3 is used as a means to validate a PCR-based HPV DNA assay in any way, the validating method must be pre-validated to show that the cytologic diagnostic result on each case has been confirmed by cervical biopsy as reviewed by at least two independent board-certified pathologists not connected with the original cytologic diagnosis.

2007P-0210 LET1

3) Since PCR assays depending on single amplification have been shown to be insensitive for the detection of HPV DNA in cervical specimens [4], the analytical sensitivity of a PCR HPV assay must be validated by a nested PCR which is known to be at least 30% more sensitive than a single PCR amplification in detection of HPV DNA in clinical specimens.

In view of the fact that the Roche HPV genotyping test application is not published for public comments on the FDA Dockets Management website, this letter is submitted under the instant Reclassification Petition for public record. The Petitioner requests that the FDA review the analytical sensitivity and specificity data of all applications with the same set of criteria for scientific accuracy.

Thank you for your attention. No new information is being introduced.

Sincerely,

Sin Hang Lee, M.D.
President, HiFi DNA Tech, LLC

Tel. 203 876-4258 (direct line to medical office)
Fax 203 385-3832

Encl.

References

1) http://www.news-medical.net/print_article.asp?id=22425

2) Schmitt M, Bravo IG, Snijders PJ, Gissmann L, Pawlita M, Waterboer T. Bead-based multiplex genotyping of human papillomaviruses. J Clin Microbiol. 2006, 44:504-12.

3) Renshaw AA, Davey DD, Birdsong GG, Walsh M, Styer PE, Mody DR, Colgan TJ; College of American Pathologists Comparison Program in Cervicovaginal Cytology. Precision in gynecologic cytologic interpretation: a study from the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. Arch Pathol Lab Med. 2003;127:1413-20.

4) Schiffman M, Wheeler CM, Dasgupta A, Solomon D, Castle PE; The ALTS Group. A comparison of a prototype PCR assay and hybrid capture 2 for detection of carcinogenic human papillomavirus DNA in women with equivocal or mildly abnormal Papanicolaou smears. Am J Clin Pathol 2005, 124:722-32.