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Office of In Vitro Diagnostic Device Evaluation and Safety

OIVD

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Letter to Ventana Medical Systems, Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

VIA FEDERAL EXPRESS

March 18, 2004

Mr. Christopher Gleeson
President and Chief Executive Officer
Ventana Medical Systems, Inc.
3865 North Business Center Drive
Tucson, Arizona 85705

Re: INFORM® Human Papillomavirus (HPV) In-Situ Hybridization (ISH) probes and related articles

Dear Mr. Gleeson:

The Office of In Vitro Diagnostic Devices (OIVD) has reviewed information relevant to the regulatory status under the Federal Food, Drug, and Cosmetic Act (the act) of the INFORM® Human Papillomavirus (HPV) In-Situ Hybridization (ISH) probes and related reagents and instruments, constituting an automated diagnostic test system. You describe these products as analyte specific reagents (ASRs), which under 21 CFR 864.4020 are class I and exempt from the premarket notification requirement of section 510(k) of the act (21 U.S.C. § 360(k)). OIVD has determined that it is unnecessary to decide whether this assertion is correct. Even if the products were to qualify as ASRs under the regulation, they would lose their class I, 510(k)-exempt status by operation of other provisions of the act and

of FDA regulations.

Under section 510(l) of the act (21 U.S.C. § 360(l)), a device that is within a type of device that has been classified into class I is not exempt from the premarket notification requirement of section 510 (k) of the act if it is "intended for a use which is of substantial importance in preventing impairment of human health" or if it "presents a potential unreasonable risk of illness or injury." Under 21 CFR 864.9, which applies to ASRs, "The exemption from the requirement of premarket notification for a generic type of class I or II device is only to the extent that the device has existing or reasonably foreseeable characteristics of commercially distributed devices within that generic type." According to these provisions, whether an ASR is exempt from premarket notification depends on its intended use or potential risk and on the technological or other characteristics relative to other ASRs.

The INFORM® HPV ISH probes are intended for use in identifying types of HPV associated with cervical cancer. Package inserts for the probes indicate that HPV infection results in approximately 14,000 new cases of cervical cancer and 5,000 deaths annually. It is one of the most common cancers in women worldwide. The risk of disease progression from dysplasia to cervical cancer is dependent on the HPV type present within the epithelial cells. [C] omplementation of conventional morphologic slide evaluation with identification of the virus by sensitive techniques such as slide-based in situ hybridization (ISH) may support further clinical decisions. The in situ system offers several advantages over other methods that involve the obligatory destruction of the target squamous cell, including direct correlation with the cytologic findings, ability to test archival specimens, a very high sensitivity and specificity which is especially important when dealing with an oncogenic and sexually transmitted virus, and the ability to differentiate those cases of ASCUS associated with high risk of SIL from those that are due to benign conditions.

Your press release issued May 13, 2003, announced:

> a new assay and software protocol are now available for use with Ventana's INFORM® Human Papillomavirus (HPV) analyte specific reagent probes which have been designed to detect HPV in samples prepared using the SurePath™ test pack from TriPath Imaging, Inc. This means that laboratories processing liquid based cytology may now use Ventana's BenchMark™ Automated Slide Staining System to analyze samples obtained via Cytyc's ThinPrep™ and/or TriPath's SurePath™ liquid based prep tests. Ventana's INFORM® HPV analyte specific reagent probe is the only automated, slide-based HPV

assay to provide viral detection in the presence of morphologic change. This contributes to the pathologist's interpretation and in the reporting of abnormal cervical cytology -- an integral part of patient care. Research has clearly proven that HPV is the major contributor to cervical cancer. Studies also suggest that HPV may play a role in cancers of the anus, vulva, vagina, and penis, and some cancers of the orpharynx (the middle part of the throat that includes the soft palate, the base of the tongue, and the tonsils). Ventana's automated solutions provide standardized and reproducible test results thereby allowing physicians to help patients expedite decisions that will improve the patient's quality of life.

OIVD believes that the intended use of the products, to identify types of HPV associated with cervical cancer, is of substantial importance in preventing impairment of human health. Regardless of the generic type of device to which the probes belong, they are not exempt from the premarket review requirement of section 510(k) of the act. Consequently, they cannot be commercially distributed without an appropriate premarket determination from FDA. According to our records, you have not received premarket approval or clearance for the INFORM® HPV system or the HPV probes.

We recommend that Ventana submit a premarket approval application (PMA) for the system. Similar systems intended for use in identifying and typing HPV infection to stratify women at risk for cervical cancer have been assigned to class III, requiring submission and approval of PMAs. We recommend, further, that Ventana submit premarket notifications for the probes and reagents. If any probe or reagent is found not substantially equivalent, Ventana can seek denovo classification under section 513(f) of the act (21 U.S.C. § 360c(f)). The device classification of any such probe or reagent would depend on the outcome of FDA's premarket review.

We are committed to working with you as we strive to protect the public health without unnecessarily imposing regulatory burdens on the marketing of products of potential clinical importance. If you have questions, or would like to discuss premarket submission plans for the products, please contact me at 301-594-3084.

Sincerely yours,

/S/

Steven I. Gutman, M.D., M.B.A.
Director

Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Updated March 23, 2004
