SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Optical Detection System (ODS)
Device Trade Name:	LUMA™ Cervical Imaging System
Applicant Name and Address:	MediSpectra, Inc. 45 Hartwell Avenue Lexington, MA 02421 USA
Date of Panel Recommendation:	May 17, 2005
Premarket Application (PMA) Number:	P040028
Date of Notice of Approval to Applicant:	March 16, 2006

II. INDICATION FOR USE

The LUMA™ Cervical Imaging System is indicated for use as an adjunct to colposcopy for the identification of high-grade disease (CIN 2,3+) in women referred to colposcopy with a Pap test result of atypical squamous cells (ASC), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion or cancer (HSIL+).

III. CONTRAINDICATIONS

There are no contraindications for use of the Luma™ Cervical Imaging System.

IV. WARNINGS AND PRECAUTIONS

The WARNINGS and PRECAUTIONS can be found in the Luma™ Cervical Imaging System labeling.

V. DEVICE DESCRIPTION AND BACKGROUND

Device Description

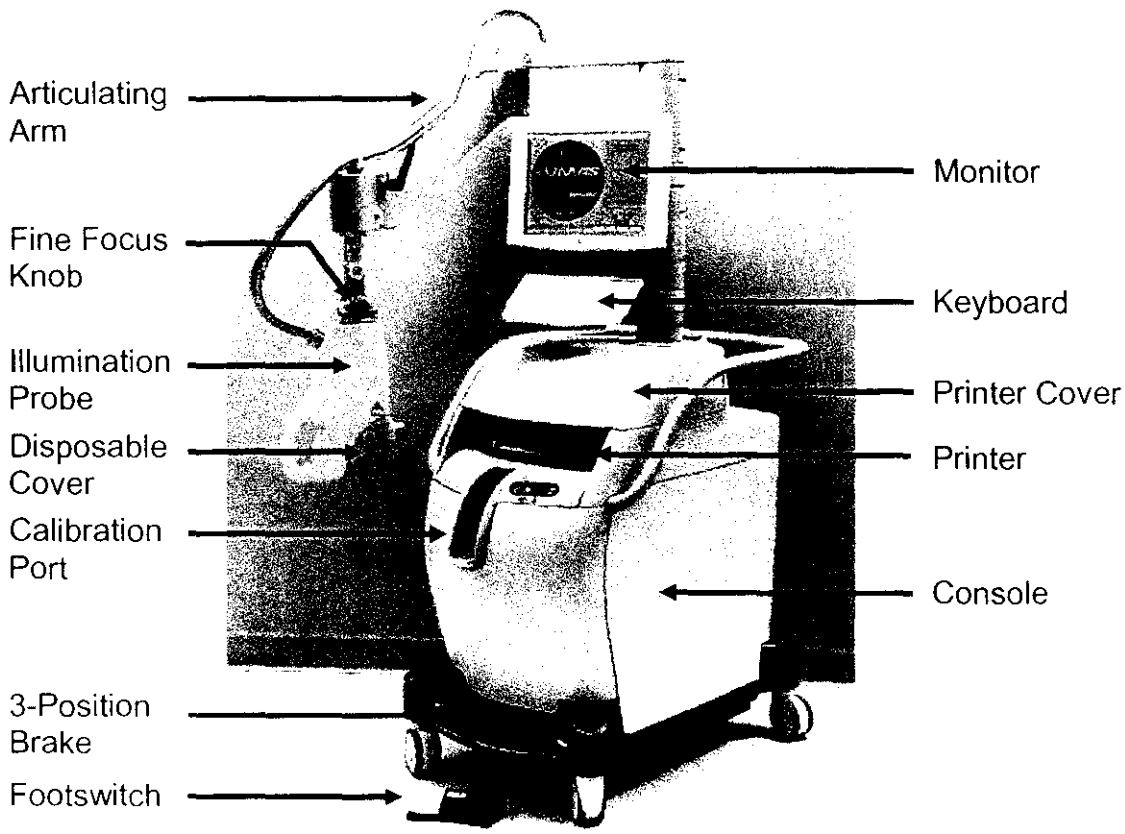
The MediSpectra LUMA™ Cervical Imaging System is a stand-alone, non-contact optical analysis system. Scans of the cervix are performed by interrogating a 25 mm diameter circular area of the ectocervix in a dense grid pattern using laser-induced fluorescence spectroscopy, white light diffuse reflectance spectroscopy, and video

fluorescence spectroscopy, white light diffuse reflectance spectroscopy, and video imaging. The cervix is scanned by the illumination probe, which is positioned near the proximal opening of the speculum as part of a colposcopy examination, following the application of acetic acid. The scan is a hands-free operation that takes approximately 12 seconds.

The key elements of the system are:

- console (and accessories) and
- illumination probe and disposable probe cover.

The **console** contains a computer, control electronics, ultraviolet laser, broadband flashlamp assembly, camera controller, spectrometer, and the visible "targeting" laser used for centering and focusing. Interaction with the system is by way of a keyboard, touchpad and/or foot-actuated dual-pedals. The touchpad allows the user to control system operations by drawing a finger across the pad to position the screen cursor, and then clicking either the left or right touchpad button. The foot pedals allow hands-free operation of the software screens.



Output data are provided to the user by way of an LCD monitor and a printer. The LCD monitor is used to display the software control screens and cervical images captured during the scan. A color printer produces a report containing the cervical image captured during the scanning process.

A **calibration port** is located in the front center of the console and is used to calibrate the system prior to each patient exam; it can also be used to store the probe when not in use.

The **illumination probe** is attached to the console by way of an articulating arm. The articulating arm allows the user to manipulate and position the illumination probe during the exam. The probe can be moved in several different axes for optimum positioning, and contains the fine focus assembly. The **disposable probe cover** is a single-patient use accessory that minimizes the risk of contamination to the system. It consists of a molded plastic housing with an anti-fog coated optical window. A protective plastic strip over the anti-fog window is removed after the disposable cover is placed on the probe, but prior to inserting into the calibration port.

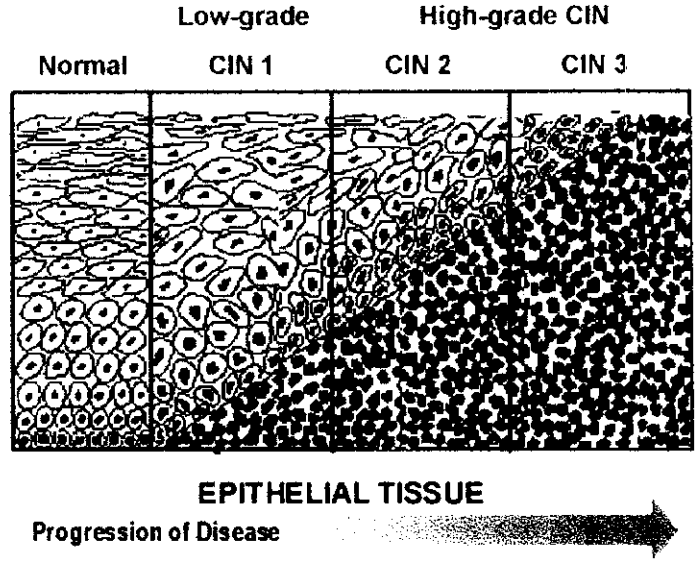
Cervical Neoplasia and the Role of Colposcopy

Development of Cervical Cancer

Prospective follow-up studies have documented that cervical cancer develops from histologically-defined precursor lesions that are referred to as cervical intraepithelial neoplasia or CIN (reviewed in Wright 2002). These precursor lesions are caused by infection with anogenital types of human papilloma virus (HPV) (IARC 2005). Although criteria for identification of cervical intraepithelial neoplasia (CIN) vary somewhat among pathologists, the common pathological differences identified in CIN lesions are epithelial immaturity, cellular disorganization, nuclear abnormalities, and increased mitotic activity (Wright 2002). The degree of CIN is determined from the extent of the mitotic activity, delayed maturation, and nuclear atypia.

Currently, several different classification systems for CIN are in use by pathologists. The one most widely used and the one that correlates best with clinical management divides CIN lesions into low-grade CIN (CIN 1) and high-grade CIN (CIN 2,3), which combines what was previously referred to as CIN 2, and CIN 3 together into a single entity (see figure)(Wright 2002). Low-grade CIN (CIN 1) lesions are heterogeneous with respect to their associated HPV types and, most importantly, biological behavior (IARC 2005). CIN 1 lesions represent the cytopathic effects of HPV infections and usually spontaneously regress in the absence of clinical intervention. In contrast, high-grade cervical neoplasia including invasive cancer (CIN 2,3+) lesions are usually associated with infection with specific "high-oncogenic risk" types of HPV which are the HPV types that are found in invasive cervical cancers. These are HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. CIN 2,3 lesions are much more likely to persist than are

CIN 1 lesions and CIN 2,3 lesions place a patient at risk for developing invasive cervical cancer if not detected and appropriately treated (IARC 2005).



Progression of Disease and Corresponding Cell Morphology Changes

Role of Colposcopy in the Prevention of Cervical Cancer

Cervical cancer prevention programs utilize cervical cytology, with or without adjunctive "high-risk" HPV DNA testing, to identify women at risk for having CIN 2,3 lesions. Women who have abnormal cervical cytology results or persistent "high-risk" HPV infections are referred for a colposcopic evaluation at which time the clinician examines the cervix using a colposcope which is a long-focal point magnifying device that illuminates the cervix using broadband white light. The cells in CIN 2,3 lesions are smaller and more crowded, with more notable condensed nuclear material compared to the cells of the normal epithelium or CIN 1 lesions. These changes alter the optical properties of the tissues, and as a result CIN 2,3 lesions typically appear densely white after the application of a solution of 3% to 5% acetic acid (i.e., acetowhite) (Sakuma 1985, Burke 1991). In addition, CIN 2,3 lesions often result in neovascularization and have characteristic vascular changes which can be identified with the colposcope. This combination of acetowhitening and vascular changes allows the clinician to identify areas of the cervix that may represent CIN 2,3 lesions using the colposcope. Once such areas are identified the clinician obtains a cervical biopsy in order to allow a definitive histopathological diagnosis. Typically, one to two biopsies are taken. If a CIN 2,3 lesion is identified by histopathology, the patient can be treated using a variety of ablative or excisional techniques. If a cancer is identified either by colposcopy or on histopathology the patient is usually referred for definitive therapy.

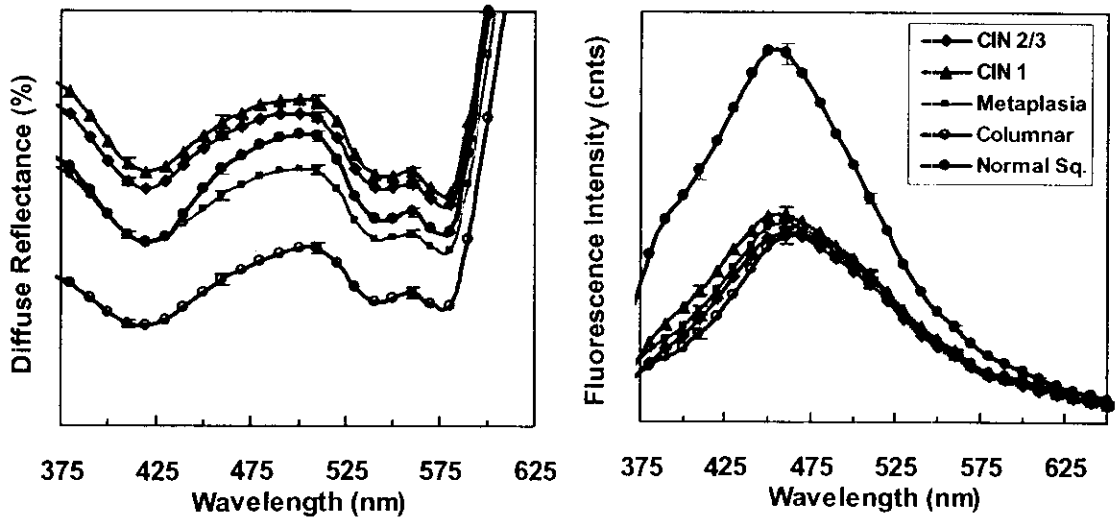
LUMA Principle of Operation

Optical Characteristics of Cervical Tissue

The structural and biochemical properties of the tissue that change with the development of CIN lead to corresponding changes in the optical characteristics of the tissue. These optical changes have been investigated extensively in the literature (Richards-Kortum 1996, Wagnieres 1998, Ramanujam 2000, Drezek 2003). For example, the development of high-grade CIN is associated with nuclear condensation that results in the acetowhitening effect. These changes also affect the properties of optical signals in general. Optical absorption of hemoglobin is also observed in tissue reflectance spectra, and these signals can change with CIN development. Reflectance optical signals measured from various intact cervical tissues are shown in the accompanying figures. The effect of hemoglobin absorption is seen in the reflectance spectra as minima near 415, 540 and 575 nm.

The predominant biochemical effect of CIN development is seen in the fluorescence optical signals. Fluorescence signals from diseased tissue are significantly reduced compared to those for normal squamous tissue. This is interpreted as a shift in the oxidation-reduction equilibrium of the metabolic protein nicotinamide adenine dinucleotide phosphate (NADPH), which is characterized by an emission maximum near 460 nm following excitation by 337 nm light. Acetowhitening also affects the fluorescence signals, resulting in a reduction of the observed fluorescence signal overall. The combined result is that the fluorescence signals from normal squamous tissue are significantly more intense than those from most other tissues (see figure).

In these ways the morphological and biochemical changes associated with CIN development are exhibited in the optical measurements of intact cervical tissue. Optimally exploiting these characteristics can therefore be used to provide enhanced identification of CIN 2,3 tissue.



Tissue Reflectance Spectra **Tissue Fluorescence Spectra**

The LUMA Optical Scan

With the LUMA device, diagnostic scans of the cervix are performed by interrogating the ectocervix using a combination of laser-induced fluorescence spectroscopy, white light diffuse reflectance spectroscopy, and video imaging. The cervix is scanned by the illumination probe, which is positioned near the proximal opening of the speculum as part of a colposcopy exam, following the application of acetic acid. The scan is a hands-free operation that takes approximately 12 seconds.

The fluorescence measurements are made by illuminating the cervix with ultraviolet (UV) light pulses at 337 nm from a nitrogen laser and recording the spectrally resolved intensities (spectra) of longer wavelength UV and visible light (360-720 nm) emitted from the cervix. Reflectance measurements are made by illuminating the cervix with pulses of broadband light from xenon flash lamps and recording the spectra of reflected light at those same wavelengths. Fluorescence and reflectance spectra are obtained from 499 distinct, closely-packed sites on the cervix by way of a computer-controlled scanning mechanism.

Prior to and during the measurement sequence, the cervix is also illuminated with the flashlamps for capturing video images of the cervix. The video images prior to the measurements provide a method to align the device, with four green spots of 532 nm visible light. The video images are used for alignment, to control for movement during a scan, and as an element in the overall device output. An interrogation point is rescanned if there is movement greater than 0.55 mm; an entire rescan is performed if accumulated movement is greater than 2.5 mm.

Following the optical scan of the cervix, the device analyzes the calibrated spectra and images of the cervix with a mathematical algorithm encoded in its software. Final output results are then calculated and displayed within approximately 30 seconds.

LUMA Algorithm

The LUMA algorithm combines the fluorescence, white light backscatter and video measurements in an integrated real-time algorithm. The LUMA classification algorithm consists of three main components: image masks, spectral masks, and a spectral classifier. The "masks" identify areas of the cervix to be marked as "no evidence of disease." A logistic classification with fluorescence spectra is combined with a multivariate statistical analysis of backscattered white light employing principal component and feature extraction analyses methods to yield a final tissue classification and associated LUMA score. The algorithms were optimized to differentiate high-grade cervical intraepithelial lesions (CIN 2,3+) from all other tissue types.

Results are displayed as a false-color overlay superimposed on a digital image of the cervix obtained during the scan. This overlay is color-coded to indicate the classifier score for identifying high-grade disease (CIN 2,3+) at different locations on the cervix as follows:

- Blue: highest score for CIN 2,3+;
- Yellow: lower score for CIN 2,3+;
- Green square cross-hatching: necrotic tissue (rare); and
- Gray diamond-shaped cross-hatching: indeterminate, i.e., a LUMA result is not being made.

This color coding corresponds to a LUMA score representing the likelihood that high grade disease is present. It does not represent a definitive diagnosis of CIN 2,3+.

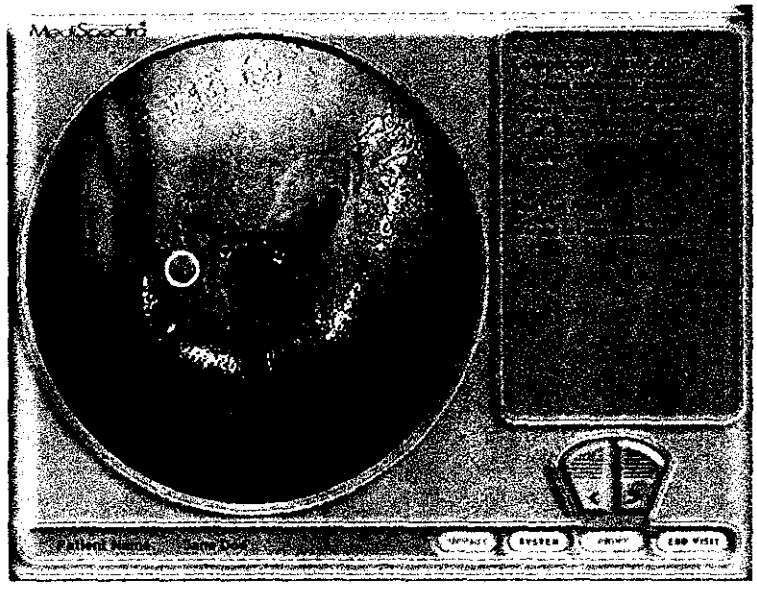
Biopsy Site Annotation Software

The colposcopist is asked to commit to any colposcopically-directed biopsy sites prior to viewing the LUMA display by annotating an electronic image.

Colposcopy Directed Annotations

Using the touchpad on the system keyboard, the colposcopist annotates biopsy site (s) by centering the green annotation circle over the targeted tissue. Left clicking or tapping the touchpad places the circle onto the displayed image of the cervix. Once annotated, the colposcopically directed site is depicted as a yellow circle. The colposcopist is allowed to adjust location of biopsy sites while in the colposcopy biopsy site selection mode. Once the colposcopist confirms (by pressing a keypad or foot pedal) that all colposcopically-directed biopsy sites have been entered, the annotated colposcopy biopsy

sites cannot be changed. These sites should be biopsied regardless of the subsequent LUMA display.

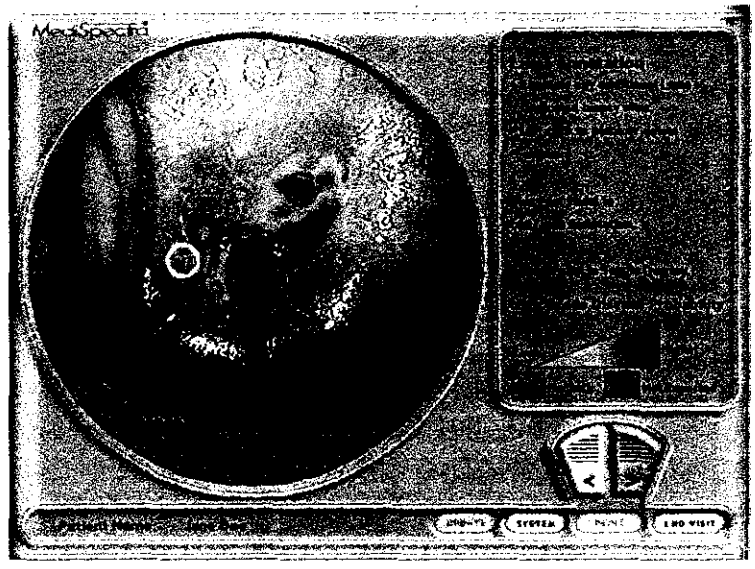


LUMA Directed Annotations

The colposcopist commits to any LUMA-directed biopsy sites using the same process. With respect to the second annotation (after the LUMA display is viewed), the device software will:

- Allow placement of annotation circles on the cervical image in areas marked with green crosshatch, blue or yellow false-color overlay;
- Allow the colposcopist to change LUMA biopsy site locations while in the LUMA biopsy site location mode; and
- Disallow annotation of LUMA biopsy sites that would overlap with any previously annotated colposcopically-directed or LUMA-directed biopsy site

Once annotated, the LUMA-directed site is depicted as a green circle.



VI. ALTERNATIVE PRACTICES OR PROCEDURES

Colposcopy is the current method for assessing areas of the ectocervix most likely to represent high-grade neoplasia (CIN 2,3+) and is the method used to direct the taking of biopsies.

VII. MARKETING HISTORY

The MediSpectra LUMA™ Cervical Imaging System has not been previously marketed.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

In all clinical studies to date, involving 3527 enrolled subjects, there were 17 reports of adverse events. None of these events were serious and none was believed to be related to the LUMA device.

The 17 reported minor adverse events occurred in 11 women and consist of the following:

- cramping (2)
- vomiting (1)
- weakness (1)
- vaginal bleeding (3)
- dizziness/fainting (6)
- nausea (1)
- abdominal pain (1)
- dysuria (1)
- burning sensation after application of acetic acid (1)

Risks associated with the intended use of the LUMA device are inadvertent contact of the probe with the vaginal speculum, resulting in minor discomfort. While not observed in

clinical studies, failure to follow operating instructions could result in ocular damage, hazardous optical radiation, electrical shock, damage to the system, or other hazard.

IX. SUMMARY OF PRECLINICAL STUDIES

Bench/Engineering Testing

The LUMA Cervical Imaging System and subassembly verification testing was conducted to demonstrate that the system fulfills the requirements identified in the product specification, risk management guidelines and associated failure modes and effects analyses, and the design requirements document. Verification testing included, as an example, testing of the optical sources to ensure that the exposures to the cervix were within their design ranges previously determined to be safe. Tests were categorized into one of six groups: electrical, optical, mechanical, software, disposable probe cover and miscellaneous.

All designs were verified by one or more of the following means: inspection, engineering measurement, user feedback, or software test. A minimum of 3 samples were tested to verify those specifications that require engineering measurement, not including wear testing. A traceability analysis tracking the Design Requirements, Product Specification, risk control measures, and testing of the device was maintained to assure proper test coverage.

Optical Exposure

A complete optical radiation assessment was performed. The worst-case maximum laser single pulse exposure is 35 μJ (mean+6SD) corresponding to a maximum radiant dose of 0.36 mJ/cm2 when using a 3.5 mm limiting aperture as recommended by the American Conference on Governmental Industrial Hygienists (ACGIH). This value is more than a factor of 10 below the ACGIH Threshold Limit Value (TLV) for exposure to a single pulse. The worst-case radiant power from the xenon broadband lamps is 4.6 mW/cm^2, which is more than a factor of 40 below the ACGIH Threshold Limit Value. An evaluation of the total effective dose between 300 and 400 nm from all sources was also evaluated, including a worst-case 10-minute exposure from the xenon source optics, a 10-minute exposure to the colposcope, and a worst-case 10-scan exposure from the UV laser. The maximum optical emission was found to be a factor of 70 below the ACGIH Threshold Limit Value. Appropriate engineering fail-safes, together with labeling and training, have been implemented to minimize the risk of any cervical or optical damage. An independent test laboratory performed additional laser testing. The LUMA System is rated as a Class 1 laser based on the IEC 60825-1: 2001 standard.

Electrical, Thermal and Mechanical Testing

The LUMA console was evaluated for electric shock, fire and mechanical safety including as examples leakage current tests, rigidity and rough handling tests, and environmental temperature and humidity tests. All tests were performed by independent laboratories. The LUMA console was found to be compliant with the following standards: UL 60601-1, IEC 60601-1, and CAN/CSA-C22.2 No. 601.1-M90.

EMC Testing

The LUMA device was evaluated for electromagnetic compatibility including emissions and immunity tests performed by an independent laboratory. The LUMA device was found to be compliant with IEC 60601-1-2.

Environmental Stress and Lifetime Testing

Packaging and shipping containers for the console and the disposable covers were evaluated to ensure that they can withstand the expected distribution environment. Ship testing was successfully conducted on the LUMA single-use disposable containers, as well as on the console-shipping container. Testing was performed to the standard ASTM D4169-01.

Biocompatibility

The only component of the LUMA device that has the potential in normal use to contact the patient is the LUMA disposable probe cover. The disposable probe cover is used to cover the front of the probe and is positioned near the proximal opening of the speculum during cervical scanning. The LUMA probe cover is non-invasive and contacts neither sterile tissue nor any mucosal membrane. Testing per the ISO 10993 matrix for an externally communicating, skin contact, short duration device was performed by an independent laboratory using good laboratory practices (21 CFR Part 58). All testing passed.

Disinfection

Risk analysis determined that a user could accidentally insert the probe with a used disposable cover into the calibration port of the console. To mitigate this risk, (1) instructions are provided both in the User's Guide and on the system display to discard the disposable cover after use and (2) the LUMA device was designed with an electronic eye that checks the disposable bar code; if the bar code has been used before, the software will prompt the user to disinfect the calibration port door. The calibration port has been designed such that, if a used disposable cover is inserted into the port, only the calibration port door could become contaminated. Instructions for disinfection are provided in the User's Guide.

The disinfection procedure for the calibration port door was evaluated by an independent laboratory based on AAMI TIR No. 12-1994, Designing, Testing and Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities: A Guide for the Device Manufacturer, 24 November 1994. The calibration port door assembly was effectively disinfected when challenged with the test microorganisms, Bacillus subtilis and Pseudomonas aeruginosa.

Software Testing

System level software quality assurance (SQA) testing, unit level testing and integration testing were performed on the LUMA and manufacturing software. User test cases were developed for SQA testing to verify all LUMA software. Due to the complexity of the system, SQA testing could not fully exercise algorithm implementation or low level acquisition, calibration and video functionality. Thus, extensive unit and integration testing were performed to ensure proper test coverage.

Traceability analysis was used to ensure that tests covered all requirements, risk control measures, etc. Tracing was performed backwards and forwards to ensure that (1) every software requirement was derived from either a design requirement, risk requirement or product specification, (2) that each software design requirement is a consequence of a software requirement, and (3) that testing is designed to exercise and verify software design elements, software requirements, product specifications, and risk requirements. An automated test environment for unit and integration testing was constructed to permit extensive regression testing. All unit/integration tests were rerun with each software release. The combination of automated unit and integration testing and manual system testing verify that the software should work as intended. Although software tests were divided into unit, integration and system-level test plans, functional tests as well as white box/structural tests were performed at the unit/integration level on the full final software release.

Failure Mode and Effects Analysis (FMEA) and Hazard Analysis

Risk Management was initiated in the Definition and Requirement phases of product development and conducted throughout the design and development activities for the LUMA device. The purpose of the Risk Management activities was to identify and control potential hardware and software hazards associated with LUMA. Risk Management involved identifying potential hazards, estimating and evaluating the associated risks, and reducing these risks to acceptable levels.

The two greatest areas of risk are: (1) unintentional light exposure due to a hardware or software anomaly, and (2) tissue misclassification due to a hardware or software anomaly. Specifically, a software or hardware defect could cause unintended ultraviolet, visible or broadband light overexposure resulting in tissue damage. The resulting injury

would be tissue erythema that is considered minor. Tissue misclassification is possible due to incorrect or incomplete calibration data due to a software anomaly or corrupted calibration targets. A variety of control measures were implemented to mitigate these and other potential risks. The criteria for risk acceptability were based on ISO 14971. The risks from all considered hazards have been mitigated to the lowest possible reasonable levels.

X. SUMMARY OF CLINICAL STUDIES

Background: Overview of Colposcopy Performance

Colposcopy with colposcopically-directed biopsy is considered the standard of care for diagnosing significant cervical cancer precursors and invasive cervical cancer (CIN 2,3+). However, colposcopy is a subjective clinical science, with an accuracy that is dependent upon the training and experience of the colposcopist [Buxton 1991, Massad 2003]. Estimates for the performance of colposcopy in clinical practice vary widely depending on a number of factors, including the grade of the referral cytologic abnormality and whether or not women with negative colposcopic findings are followed prospectively.

Cox *et al.* recently analyzed the data from the ASCUS/LSIL Triage Study (ALTS) clinical trial specifically to address the performance of initial colposcopy among the ASCUS/LSIL referral population [Cox, 2003]. They concluded that in the ASCUS/LSIL referral population 18% of women would have biopsy-confirmed CIN 2,3+ identified at initial colposcopy, and that cumulatively about 27% of the women would be diagnosed with CIN 2,3+ over a two year period. Therefore the sensitivity of a single colposcopic examination in the ALTS study was only about 67% (18%/27%). Similarly, histopathologic correlation studies between the preoperative diagnosis and the diagnosis made on loop electrosurgical excision (LEEP) specimens demonstrate that colposcopically-directed cervical biopsies miss approximately a third of cases of CIN 2,3. Massad *et al.* summarized the findings of eight histopathologic correlation studies correlating histopathology findings in LEEP specimens in women undergoing a LEEP for a preoperative diagnosis of CIN 1 (based on preoperative colposcopically-directed cervical biopsy) [Massad 1996]. The prevalence of CIN 2,3+ in the LEEP specimens in the eight studies ranged from 18% to 55%. In six of the eight studies, a third or more of the women with a preoperative diagnosis of CIN 1 were subsequently found to have undiagnosed CIN 2,3+, and the average detection of CIN 2,3+ in the eight studies, combined, was 36%. Other studies have reported false negative rates of colposcopy ranging from 15% to 31% for CIN 2,3 lesions [Skehan 1990, Denny 1995].

LUMA Clinical Studies

A total of nine clinical studies, enrolling over 3500 subjects, have been completed to date. The first seven studies were executed to support system development and

optimization of the LUMA algorithm. One study included data that can be used to assess instrument reproducibility, as described below. Two additional studies provided clinical evaluation in the colposcopy referral population of the safety and efficacy of LUMA when used in combination with colposcopy as reported in more detail below.

LUMA Reproducibility

To assess the reproducibility of the LUMA results, fifty women with no evidence of cervical disease underwent multiple LUMA procedures, once per week for four to five weeks. Two to five regions of each woman's cervix were monitored to determine if the LUMA classifications for those regions changed from no evidence of disease to a blue or yellow LUMA reading or vice versa. The study had data on 189 regions, and a total of 899 assessments, 28 of which were falsely positive. An indirect measure of reproducibility is the probability of a falsely positive outcome in these putatively negative women. The false positive rate was estimated by a generalized estimating equation (GEE) model for the probability of a positive (yellow or blue) reading that takes into account that repeated measures within each woman are correlated. From the model, the false positive rate was estimated to be 3.02% with 95% confidence interval 1.75% to 5.12%. Reproducibility can be directly estimated as the probability of discordant results within women between all possible pairings of visits for each region. The total number of visit pairings was 1707, of which 71 were discordant. The probability of discordance between visit pairs was estimated from a GEE model that takes into account that repeated measures within each woman are correlated. The probability of discordance between visit-pairs was estimated to be 4.03% with 95% confidence interval from 2.08% to 6.29%.

This study did not include women known to have cervical disease, so no conclusions can be made regarding the repeatability of the LUMA System for women with cervical disease. That is, no information is available on how many true positives could become false negatives, or vice versa, upon repeated LUMA procedures in women with cervical disease.

Concurrent-use Clinical Study (Pivotal Study I)

An initial clinical study was designed to evaluate the performance of the LUMA system in an alternate use model in which LUMA is used concurrently with colposcopy. In this study women were randomized to one of two arms: Routine Colposcopy (a LUMA scan was performed but the colposcopist was blinded to the results) or Colposcopy with LUMA (the colposcopist was able to visualize the LUMA result while performing the colposcopic examination). While this does not reflect the adjunctive intended use of the LUMA system, it does provide supporting evidence of the safety and effectiveness of the LUMA system when used in a colposcopy referral population.

Study Sites, Patient Characteristics and Exclusions

A total of 2299 women referred to colposcopy on the basis of an abnormal Pap test (ASC, LSIL, HSIL, or cancer) were enrolled at 13 centers with a total of 51 participating colposcopists. One hundred thirteen (113) subjects (4.9%) were lost because of either investigator withdrawal or exclusions, leaving 2186 evaluable subjects. Of the 113 subjects removed, 27 subjects (1.2%) were withdrawn by the investigator before randomization. There were a total of 86 (3.7%) subjects excluded after randomization; 37 subjects (1.6%) were lost from the Routine Colposcopy arm and 49 subjects (2.1%) from the Colposcopy with LUMA arm. The primary reasons for subject loss were no majority pathology diagnosis (1.8%) and device malfunctions (1.6%). The median age of women was 30.4 years. The most common reason for referral to colposcopy was a LSIL cytology (44%), followed by ASC cytology (36%) and HSIL/Cancer (20%). Other demographic data is similar to that for the intended use study reported below.

Study Results

The primary trial endpoints were the comparison of subject-level true positives (TP) (women with CIN 2,3+ on cervical biopsy) and subject-level false positives (FP) (women with cervical biopsies but no CIN 2,3+ diagnosed) between the two arms.

The primary TP hypothesis was that the TP (detection) rate would be significantly greater in the Colposcopy with LUMA arm compared to the Routine Colposcopy arm. Overall, TP rates were 19.9% in the Routine Colposcopy arm versus 21.8% in the Colposcopy with LUMA arm, corresponding to a 1.9% (95% CI -1.5% to 5.3%) increase (Table 1). This increase represents a 9.8% relative gain (95% CI -6.8% to 29.3%) in the TP rate. The overall study hypothesis was not met because both 95% CI's include 0% and therefore do not indicate a statistically significant increase.

While pooling of ASC/LSIL subjects was not pre-specified, the TP findings were similar in the ASC and LSIL Pap strata, as might be expected since these groups have similar CIN 2,3+ disease prevalence and associated clinical management practices. Among women referred for evaluation of ASC and LSIL combined, the TP rate was 11.4% for Routine Colposcopy versus 14.4% for Colposcopy with LUMA arm. This represents a 3.0% (95% CI -0.1% to 6.1%) difference in TP rate, corresponding to a 26.5% relative gain (95% CI -1.1% to 61.8%). The 95% CI's include 0%, indicating that the increase was not statistically significant. In any case, the analysis is exploratory because statistical tests of significance for this and other subgroups were not pre-specified in the protocol.

Table 1: Concurrent-use Study - Subject-level True Positive Rates

Pap Strata (% total)	Routine Colposcopy Arm % (n/N)	Colposcopy with LUMA Arm % (n/N)	Difference (95% CI)
Overall (100.0%)	19.9% (218/1096)	21.8% (238/1090)	1.9% (-1.5%, 5.3%)
ASC (36.3%)	10.9% (42/387)	13.8% (56/407)	+2.9% (-1.7%, 7.5%)
LSIL (43.6%)	11.8% (57/484)	14.9% (70/469)	+3.1% (-1.2%, 7.4%)
HSIL (20.1%)	52.9% (119/225)	52.3% (112/214)	-0.6% (-9.9%, 8.7%)

The primary FP hypothesis on the FP (non-detection) rate was that it would be greater in the Colposcopy with LUMA arm compared to the Routine Colposcopy arm by an amount significantly less than 8%. Overall, the FP rate was 57.4% in the Routine Colposcopy arm versus 60.5% in the Colposcopy with LUMA arm, for a FP difference of 3.1% (95% CI -1.0% to 7.2%) (Table 2). The entire 95% CI is less than 8%, indicating that the FP rate hypothesis was met.

Overall, 22.7% of subjects had no biopsies in the Routine Colposcopy arm, while 17.7% had no biopsies in the Colposcopy with LUMA arm. Thus 5% more women received biopsies in the Colposcopy with LUMA arm. The average number of biopsies for all subjects was also greater in the Colposcopy with LUMA arm than in the Routine Colposcopy arm. In the Routine Colposcopy arm, the average number of biopsies per patient was 1.03, while in the Colposcopy with LUMA arm it was 1.30, for an average gain of 0.27 biopsies per patient. The proportion of biopsies that were positive for CIN 2,3+ was 24.0% (268/1115) in the Routine Colposcopy arm and 21.9% (306/1397) in the Colposcopy with LUMA arm.

Table 2: Concurrent-use Study - Subject-level False Positive Rates

Pap Strata (% Total)	Routine Colposcopy Arm % (n/N)	Colposcopy with LUMA Arm % (n/N)	Difference (95% CI)
Overall (100.0%)	57.4% (629/1096)	60.5% (659/1090)	3.1% (-1.0%, 7.2%)
ASC (36.3%)	54.3% (210/387)	62.4% (254/407)	+8.1% (1.3%, 14.9%)
LSIL (43.6%)	66.7% (323/484)	67.6% (317/469)	+0.9% (-5.1%, 6.9%)
HSIL (20.1%)	42.7% (96/225)	41.1% (88/214)	-1.6% (-10.8%, 7.6%)

The effectiveness of LUMA in PSI appeared to decrease with increasing age. Overall, LUMA increased the TP rate by 100% (from 10% to 20%) in the youngest age group, but increased the TP rate minimally in age groups 21-29 years and > 29 years. The large TP rate increase in the age group < 21 years was not accompanied by a concomitant increase in the FP rate. (This effect was not observed in PSII.) A post-approval study is being conducted to further evaluate the possibility of an age effect on LUMA performance.

Intended Use Pivotal Trial (Pivotal Study II)

In the intended use pivotal trial, examination of the LUMA results was preceded by colposcopy. A commitment was made to biopsy colposcopically-indicated lesions prior to revealing the LUMA display. The number of enrolled subjects was intended to be 788, with 670 per protocol subjects. The study was stopped early at 227 enrolled and 193 per protocol. The decision to stop the study was made before any analysis of the data could be made. A single analysis was made after the study ended. Of the 193 per protocol women, 21.2% had CIN 2,3+ diagnosis from the colposcopically-directed biopsies and an additional 4.7% had CIN 2,3+ diagnosis from the LUMA-directed biopsies, which were indicated subsequent to colposcopy. This corresponds to a relative gain of 22.0% (95% CI 6.1% to 37.8%). On average, women in this study had one colposcopically-directed biopsy and one LUMA-directed biopsy.

This study was not designed to determine the relative contribution of LUMA compared to the value of additional colposcopically-directed biopsies after initial colposcopy was completed.

The intended use study was a single-arm evaluation of the ability of LUMA to identify additional cases of women with CIN 2,3+ who had been definitely missed by the initial colposcopic examination.

Study Sites, Patient Characteristics and Exclusions

This trial enrolled 227 subjects at 7 centers with a total of 16 participating colposcopists, including nurse practitioners, generalist obstetrician/gynecologists, and gynecologic oncologists. The subjects were at least 18 years of age (or age of consent) and referred to colposcopy on the basis of an abnormal Pap test (ASC, LSIL, HSIL or cancer). Thirty-four (15%) of the 227 subjects were not evaluable, including 7 subjects (3.0%) withdrawn by the investigator before examination was completed and 27 (11.9%) subjects excluded post examination. The primary reason for post examination exclusions was incomplete pathology (16 subjects). The final evaluable population was 193 subjects. Demographic and clinical information of the enrollees is presented in Table 3. The mean age was 28.5 years. The most common reason for referral to colposcopy was LSIL cytology (47%), followed by ASC cytology (39%) and HSIL/Cancer cytology (14%).

Table 3: Intended Use Study - Demographic and Clinical Characteristics

Characteristic	Overall
N, evaluable	193
Age (years)	
Mean (SD)	28.5 (10.6)
Range	18 - 64
Race	
Caucasian	83 (43.0%)
Hispanic	60 (31.1%)
African American	41 (21.2%)
Native American	3 (1.6%)
Asian	3 (1.6%)
Other	3 (1.6%)
Clinical History	
Referral Pap	
ASC*	76 (39.4%)
LSIL	91 (47.2%)
HSIL/Cancer	26 (13.5%)
Menstrual status	
Menstrual (cycling)	181(93.8%)
Post-menopausal	12 (6.2%)

Characteristic	Overall
No prior history of abnormal Pap	99 (51.3%)
Mean gravidity (SD)	2.0 (2.1)
Mean parity (SD)	1.5 (1.8)

*Includes ASC-US and ASC-H cytology

Definition of Study Endpoints

The primary trial endpoints were the incremental true positive (TP) subjects (subjects with CIN 2,3+ on a LUMA-directed biopsy, but no CIN 2,3+ detected on a biopsy indicated by colposcopy) and incremental false positive (FP) subjects (subjects with LUMA-directed cervical biopsies that were not diagnosed as CIN 2,3+, and who did not have a biopsy indicated by colposcopy). The primary trial hypothesis for the TP (detection) rate was that the overall TP rate for the LUMA increment would be significantly greater than 2%. The primary trial hypothesis for the FP (non-detection) rate was that the overall FP rate for the LUMA increment would be significantly less than 15%.

True Positive Detection Rate

Initial colposcopy identified 41 cases of CIN 2,3+ for a TP rate of 21.2% (see Table 4). Among those women not identified by colposcopy to have CIN 2,3+ an additional 9 cases were identified by the use of the LUMA system. This corresponds to an incremental LUMA TP rate of 4.7% (95% CI 2.2% to 8.7%). In this *intended use* trial the overall TP hypothesis was therefore met (p = 0.0164). Use of the LUMA system therefore resulted in a 22.0% (95% CI 6.1% to 37.8%) relative gain in the number of subjects with CIN 2,3+ compared to colposcopy alone.

The study results can be used to estimate the sensitivity of LUMA-aided colposcopy relative to colposcopy alone. Sensitivity is the percent of women with CIN 2,3+ disease that are detected to have CIN 2,3+ from colposcopy-indicated biopsies. While the sensitivities of colposcopy and LUMA cannot be estimated directly from the study because the total number of women with CIN 2,3+ is unknown, the relative increase in sensitivity when LUMA is added to colposcopy can be estimated by the ratio of the incremental TP rate to the initial colposcopy TP rate. The estimate of a 22% relative gain in TP rate reported above therefore also corresponds to the same relative gain in the sensitivity.

Table 4: Counts of TP, FP and Negative (no biopsy) Subjects by Phase (initial colposcopy, colposcopy + LUMA)

	Colposcopy and LUMA Combined			
Initial Colposcopy	**True Positive (TP)**	**False Positive (FP)**	**Negative**	**Total**
True Positive (TP)	41	0	0	41
False Positive (FP)	7	93	0	100
Negative	2	35	15	52
Total	50	128	15	193

Table 5: Intended Use Study - Subject Level Outcomes

Strata	Outcome	Initial Colposcopy		LUMA Increment	
		Rate (n/N)	95% CI	Rate (n/N)	95% CI
Overall	True Positive	21.2% (41/193)	15.7%, 27.7%	4.7% (9/193)	2.2%, 8.7%
	False Positive	51.8% (100/193)	44.5%, 59.0%	18.1% (35/193)	13.0%, 24.3%

False Positive (Non-Detection) Rate

The FP rate for initial colposcopy was found to be 51.8% (100 of 193 subjects) (Table 5). An additional 35 subjects had a LUMA-directed biopsy that was not diagnosed as CIN 2,3+, yielding an incremental FP rate of 18.1% (95% CI 13.0% to 24.3%). In this case, the 95% CI includes 15%, indicating that the FP hypothesis was not met.

Because of the clinical consequence of a false positive LUMA reading is an increase in the number of biopsies taken, the impact of the FP rate on the patient can best be assessed based on the increase in biopsy rates. The mean biopsy rate for the LUMA increment was 1.02 (197 biopsies in 193 subjects), which was comparable to the mean biopsy rate for colposcopy of 0.89 (172 biopsies in 193 subjects). The percent of subjects not biopsied in the LUMA increment was 22.3% (43/193), which was comparable to the no biopsy rate in the colposcopy phase of 26.9% (52/193). The percent of subjects biopsied increased from 73.1% (141/193) for initial colposcopy to 92.2% (178/193) with the addition of the LUMA increment.

The study results can be used to obtain limited information on the specificity of colposcopy with adjunctive LUMA relative to colposcopy alone. Specificity is the percent of women without CIN 2,3+ that are not biopsied. While the specificities of colposcopy and LUMA cannot be estimated directly from the study, the relative increase in (100%-specificity) when LUMA is added to colposcopy can be estimated by the ratio

of the incremental FP rate to the initial colposcopy FP rate. The estimate is 18.1%/51.8%, or 35.0% (95% CI 21.5% to 48.5%).

True Positive and False Positive Trade-off

Taken together, the incremental TP and FP rates of 4.7% and 18.1% for the LUMA phase represent a trade-off of approximately 4:1 (18.1/4.7) in the ratio of the number of subjects regarded as unnecessarily biopsied in search of CIN 2,3+ to the number of subjects in which incremental biopsy detected CIN 2,3+. By comparison, this ratio was approximately 2.5:1 (51.8/21.2) in the initial colposcopy phase. A smaller ratio for the colposcopy phase than the LUMA phase is expected, because by virtue of going last, the LUMA phase is a search only for the remainder of women with CIN 2,3+ disease that were not detected to have disease in the colposcopy phase.

The proportion of biopsies that were positive for CIN 2,3+ was 26.2% (45/172) in the colposcopy phase and 18.3% (36/197) in the incremental LUMA phase. That is, the ratio of true positive to false positive biopsies was approximately 3:1 in the colposcopy phase and 4.5:1 in the LUMA phase. The larger ratio in the LUMA phase is expected because in that phase a search is made only for the remainder of high-grade disease that was not detected in the colposcopy phase.

Analysis of LUMA Readings

The LUMA score is a measure between 0 and 1 of the LUMA system reading at a specified biopsy location, and was calculated using the LUMA output data from the intended use study. Although a specific score is not reported to the user, the "strength" of the score is reflected in the color display (i.e., blue areas represents those with highest LUMA scores). The LUMA score was evaluated in relation to the likelihood of a positive biopsy by mixed effect logistic regression models with biopsy as the unit of analysis. The goal was to assess the degree of relationship between the LUMA score and the logarithm of the odds of a positive biopsy while taking into account Pap referral stratum (ASC, LSIL, HSIL), study phase (colposcopy or LUMA), interactions between stratum, study phase, and LUMA score, and clinical site and colposcopist variability.

The primary finding from these analyses is that the LUMA score is significantly related to the likelihood of a positive biopsy ($p = 0.0135$). This relationship was consistent among Pap referral strata. According to the model, the odds of a positive biopsy are estimated to increase 1.39 fold (95% CI 1.07-1.80) for every 0.25 increase in the LUMA score. The increase in the odds was greater in the LUMA phase than in the colposcopy phase ($p = 0.0622$ for interaction between study phase and the LUMA score). Using a model that includes the interaction between the study phase and the LUMA score, the odds of a positive biopsy for LUMA phase biopsies is estimated to increase 2.46 fold (95% CI 1.27 to 4.78) for every 0.25 increase in the LUMA score. The corresponding

estimate for Colposcopy phase biopsies is 1.28 (95% confidence interval from 0.96 to 1.72).

XI. CONCLUSIONS DRAWN FROM THE CLINICAL STUDIES

The Intended Use Study (PSII), where the LUMA System was used in sequence after colposcopy, showed a relative gain of approximately 22.0% (95% CI 6.1-37.8) in the identification of true-positive cases of high-grade CIN 2,3+ across the study population. This benefit was observed with the cost of approximately one additional biopsy per subject, about 20% of which were positive for CIN 2,3+ (compared to about 25% for colposcopically-directed biopsies). This study was not designed to determine the relative contribution of LUMA compared to the value of additional colposcopically-directed biopsies after initial colposcopy was completed.

Biopsy-level data from the Intended Use Study (PSII) was analyzed to provide further evidence of the effectiveness of the LUMA device. This analysis showed a statistically significant relationship between the LUMA scores underlying the color image and a positive biopsy (i.e., CIN 2,3+), with positive biopsy locations tending to have higher LUMA scores across all Pap strata and for both LUMA-directed and colposcopically-directed biopsies.

The Concurrent-Use Study (PSI), a much larger randomized study where the LUMA System was used simultaneous with colposcopy, failed to show a statistically significant difference for the overall study population in the identification of true-positive cases, when compared to colposcopy used alone. However, a positive trend was seen in the important subpopulation of patients with a pap referral of ASCUS and LSIL.

A total of 2379 patients underwent the LUMA exam procedure in PSI and PSII and no significant adverse events were reported.

XII. PANEL RECOMMENDATION

At an FDA advisory meeting held on May 17, 2005, the Obstetrics and Gynecology Devices Panel recommended that MediSpectra Inc.'s PMA for the LUMA™ Cervical Imaging System not be approved. The primary reason for the not approval decision was the failure of both PSI and PSII to reject their respective null hypotheses.

Other reasons given for not approval included questions about a possible age effect seen in PSI, concerns about how representative the clinical investigators were of the general colposcopist population, whether LUMA performance would be affected if subjects were stratified by HPV status, and questions about over-treatment of patients with a CIN 2,3+ diagnosis today in the U.S.

Some panelists cited concern about the risk of over-reliance on the LUMA technology at the expense of losing their colposcopic skills. All of the panel members acknowledged that the risk of extra cervical biopsies was very low.

XIII. CDRH DECISION

Following the panel meeting, FDA looked carefully at the panel rationale and conducted additional analyses of the clinical data. In particular, FDA recognized that the two co-primary outcome measures of PSII are highly dependent on each other and should not be viewed independently as configured in the study hypothesis. The diagnostic performance of the LUMA device was viewed as a trade-off of unnecessary biopsies (false-positive increment, ΔFP) against extra cases identified with high-grade disease that colposcopy missed (true-positive increment, ΔTP) and expressed as a ratio:

false-positive increment (ΔFP) ÷ true-positive increment (ΔTP)

In PSII, the study hypothesis included two outcomes: (1) the CI lower limit on ΔTP rate > 2% and (2) the CI upper limit on ΔFP rate < 15%. The *observed* ΔFP rate was 18.1% (95% CI 13.0-24.3%), and the *observed* ΔTP rate was 4.7% (95% CI 2.2-8.7%). Expressing this as a ratio gives 18.1% ÷ 4.7% = 3.9 (1.87, 8.09), meaning approximately one new case of true disease detected for every four cases where women with normal tissue were unnecessarily biopsied. FDA concluded that this diagnostic trade-off was clinically significant and supported approval of the PMA approval. The risk to a patient of one additional (and unnecessary) cervical biopsy was considered minor.

In addition, FDA asked MediSpectra to perform a biopsy-level analysis from PSII of the numerical LUMA output ("score") for each colposcopic and LUMA selected biopsy site. This analysis showed that the frequency of biopsies having CIN 2,3+ disease increased significantly with increasing LUMA score (the numerical value corresponding to the color on the LUMA display). Additionally, the median LUMA score for the LUMA TPs was 0.882 whereas the median score for the colposcopy TPs was 0.444. In summary, this analysis showed that the LUMA score was positively correlated with the probability of a positive biopsy (CIN 2,3+).

FDA's review acknowledged that reader variability was not accounted for and these studies could not answer whether a more aggressive biopsy regimen would have found a comparable true-positive increment. However, these were questions the original protocol, developed after extensive discussions with FDA, did not address.

In summary, FDA concluded that the data from PSI and PSII support approval of the PMA, and that labeling mitigations and a post approval study will adequately address the remaining concerns.

A large post approval study (n=950) will address the effects of age, HPV status, and colposcopy experience on LUMA performance. Reader variability will be accounted for.

Labeling mitigations included refinement of the indication for use, a warning about first performing a thorough colposcopic exam, and a precaution advising users that it is unknown whether taking additional colposcopically-directed biopsies would achieve similar results.

The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820). FDA issued an approval order on March 16, 2006.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See the Information for Prescribers labeling.

Hazards to Health from Use of the Device: See Indications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

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