

## **SUMMARY OF SAFETY AND EFFECTIVENESS DATA**

### **I. GENERAL INFORMATION**

**Device Generic Name:** Fiberoptic Diagnostic Analyzer (colon)

**Device Trade Name:** Optical Biopsy System

**Applicant's Name and Address:** *SpectraScience, Inc.*  
14405 21<sup>st</sup> Avenue, N. Suite 111  
Minneapolis, Minnesota 55447

**Premarket Approval Application (PMA) Number:** P990050

**Date of Panel Recommendation:** November 19, 1999

**Date of Notice of Approval to Applicant:** November 14, 2000

### **II. INDICATIONS FOR USE**

The SpectraScience™ Optical Biopsy™ System is indicated for use as an adjunct to lower gastrointestinal (GI) endoscopy. The device is intended for the evaluation of polyps less than 1 cm in diameter that the physician has not already elected to remove. The device is only to be used in deciding whether such polyps should be removed (which includes submission for histological examination).

### **III. CONTRAINDICATIONS**

The use of this device is contraindicated in patients who:

- Have pre-existing abnormalities of the coagulation system which contraindicate endoscopic biopsy and/or polypectomy.
- Have other conditions that prevent endoscopic biopsy or removal of colonic polyps.
- Have familial polyposis.

## IV. WARNINGS AND PRECAUTIONS

### Warnings

- If this device is used when the physician, absent this device, would remove all visualized polyps, this device will lead to an increase in the number of potentially pre-cancerous or cancerous polyps that are not removed (i.e., it will decrease the physician's sensitivity).
- If this device is used when a physician, absent this device, would only remove polyps that his/her visual assessment suggests are adenomatous, then this device will not only increase the number of removed polyps that turn out to be pre-cancerous or cancerous, but will also increase the number of removed polyps that turn out to be hyperplastic (i.e., while the device will increase the physician's sensitivity, it will also decrease her/his specificity).
- To properly use the device, the physician must move the fiber to three different regions of the same polyp and obtain three distinct spectral measurements. The accuracy of the device to distinguish between "suspect" and "not-suspect" polyps is dependent upon obtaining three distinct measurements from each polyp.
- To properly use the device, the physician must obtain a spectral reading from normal tissue within the patient's colon. The device cannot provide an evaluation without this information.

Other warnings and precautions can be found in the Physician Labeling.

## V. DEVICE DESCRIPTION

The Optical Biopsy System (OBS) is a laser-operated, diagnostic system that consists of the following main components:

- OBS console, which provides the primary interface between the user and device;
- OBS fiber, which transmits and collects laser light energy; and
- system software, which contains the analytical algorithm.

The OBS may be used with any lower-GI endoscope with a 2.8 mm inner diameter working channel. Accessories include biopsy forceps which are used to obtain tissue samples of the colonic polyps.

### **OBS Console**

The OBS console is housed in a transportable self-contained cabinet. The console includes the laser source, spectrophotometer, computer control module, display, keyboard, and power supply. The operation of the console is controlled by the user, who operates the keyboard and footswitch controls. The console includes a high resolution liquid crystal display which provides step-by-step instructions for the user to complete the procedure. The display also provides the results of the spectral analysis. The laser is a Class I laser device and conforms to the regulation outlined in 21 CFR Chapter 1, Subchapter J, 1040.10 (Laser Products) and 1040.11 (a) (Medical Laser Products).

### **OBS Fiber**

The optical fiber features three main layers: a silicone core, a silicone cladding, and a polyimide buffer. The core provides the conduit through which light energy is transmitted to and from the target polyp. The

cladding prevents the loss of light energy through the silica core. The buffer provides structural integrity for the silica core. The fiber is intended for single use only.

### **System Software**

The system software includes an algorithm which analyzes the spectra data collected by the OBS filter. Based upon the spectral data, the algorithm classifies the polyp as "suspicious" or "not suspicious." This information is displayed on the console screen.

### **Mechanism of Action**

The mechanism of action of this device is based on the principle of autofluorescence, i.e., when energy is applied to tissue, the tissue emits light energy at a specific wavelength intensity and pattern. Different tissues, i.e., hyperplastic and adenomatous polyps, emit this energy at different patterns that can be distinguished from one another. With the OBS, the energy originates with the laser source housed within the OBS console. The laser energy is delivered to the target polyp through the optical fiber at a pre-defined intensity and energy level. The energy is absorbed by the target polyp, which then emits autofluorescence back through the optical fiber. The autofluorescence is recorded and measured by the system software. By comparing the received spectral information to the spectra of adenomatous and hyperplastic tissue, the device determines whether the tissue is "suspicious" (adenomatous) or "not suspicious" (hyperplastic).

## **VI. ALTERNATIVE PRACTICES OR PROCEDURES**

The evaluation of the colon for presence of colonic polyps pre-disposed toward colon cancer takes place primarily in one of these tests/procedures: fecal occult blood tests, and endoscopic examinations.

Fecal occult blood tests (FOBT) use chemical indicators on stool samples to detect the presence of blood (or its derivatives) not otherwise visible. A positive result may indicate the need for further diagnostic procedures. Possible medical conditions associated with a positive FOBT include colorectal and gastric cancer, ulcers, hemorrhoids, and inflammatory bowel disease.

Two types of endoscopic procedures are performed to evaluate the colon: sigmoidoscopy and colonoscopy. In sigmoidoscopy, the lower third of the colon is visually examined, whereas in colonoscopy, the entire length of the colon is examined.

## **VII. MARKETING HISTORY**

The OBS has not been marketed in the United States or any foreign country.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

There were no adverse effects observed or documented during the clinical evaluation of the OBS. Potential complications which were not seen during clinical evaluation include inadvertent perforation of colon with the optical fiber or components; excessive exposure of the patient to laser energy due to device malfunction; excessive bleeding; other risks associated with sigmoidoscopy or colonoscopy.

## **IX. SUMMARY OF PRE-CLINICAL TESTING**

The pre-clinical information submitted for the Optical Biopsy System consisted of laser safety, electrical safety/electromagnetic compatibility, biocompatibility, sterilization, *in vitro* bench testing, and software validation and verification information.

### **Laser Safety**

The laser safety information consisted of a computational evaluation of the maximum laser energy that may be delivered from the optical fiber. Based on the 337 nanometer (nm) pulsed nitrogen laser, the maximum laser energy delivered to the optical bulkhead per pulse was determined to be 40.7 microjoules ( $\mu\text{J}$ ) with a peak power of 8.14 kilowatts (kW) (minimum) and 10.85 kW (maximum). The total laser energy delivered to the tissue for one tissue examination (six pulses) was calculated to be 3.178 millijoules ( $\text{mJ}/\text{mm}^2$ ). This value is an order of magnitude below the threshold limit value for chemical substances, physical agents, and biological exposure indices, as specified by the American Conference of Government Industrial Hygienists (ACGIH). Although this threshold limit is specifically intended to address skin exposure to laser energy, FDA determined that this limit provided an adequate safety margin for exposure to mucosal tissue. It was concluded that the ultraviolet (UV) radiation exposure generated from the OBS does not pose an unacceptable risk for mutagenicity or carcinogenicity if used as intended.

### **Electrical Safety/Electromagnetic Compatibility**

The electrical safety/electromagnetic compatibility information consisted of testing performed by an independent laboratory to evaluate the electrical safety of the OBS. The laboratory tested the device for compliance with these standards: International Electrotechnical Commission (IEC) 60601-1, IEC 60601-1-2 and European Commission for Standardization CEN EN 55011. This evidence provides adequate characterization of electrical safety and electromagnetic compatibility of the device.

### **Biocompatibility**

The only patient-contacting component of the device is the optical fiber, composed of fused silica and polyimide. This fiber was cleared for marketing under a prior marketing application, K973611 for a duration and placement of use similar to its use with the OBS. Therefore, the biocompatibility of these materials was previously established for this intended use.

### ***In Vitro* Bench Testing**

The bench testing for the OBS focused on the integrity of the optical fiber when inserted into the endoscope. The specific tests conducted were assembly friction test, fiber fatigue test, pull test of the connector and optical fiber jacket, clamp force test, and energy transmission test. Five samples of the OBS fiber were used for each test. These tests are described in more detail below.

#### **A. Assembly Friction Test**

The purpose of this test was to assess whether the optical fiber could be passed through the endoscope without excessive resistance. In the test, the optical fiber was inserted into the biopsy forceps and was advanced until the end of the fiber slightly extended from the forceps. All 5 samples successfully passed this test.

**B. Fiber Fatigue Test**

The purpose of this test was to determine whether the optical fiber would retain its mechanical integrity and light transmission properties when subjected to axial movement through a 25 mm-radius tube. This test was intended to simulate movement of the fiber through an endoscope. In the test, the fiber was subjected to 50 cycles of movement through the length of the tube. All five samples successfully passed this test.

**C. Pull Test of SMA Connector and Optical Fiber Jacket**

The purpose of this test was to determine whether the joint between the SMA connector and optical fiber jacket will stay intact when subject to a pull force of 10 lb., an acceptable specification given the device's intended use. The results of the test showed that the force at which separation occurred was 85.1 lb. Thus, the device successfully passed this test.

**D. Clamp Force Test**

The purpose of this test was to determine that the clamp force on the tubing was greater than 1 lb., an acceptable specification given the device's intended use. The results of the test showed that the force of the clamp was 6.45 lb. Thus, the device successfully passed this test.

**E. Energy Transmission Test**

The purpose of this test was to determine how efficient the optical fiber was in transmitting the energy delivered from the laser source. In this test, the optical fiber was connected to the laser source at one end. The other end was connected to a calibrated Molectron JD2000 Joulemeter. A series of 15 laser pulses were sent through the fiber and the energy input and output were measured. The pass criterion was that the energy loss from the optical fiber is less than 30% of the initial energy output sent from the laser source. The results of the test showed that the energy loss from the fiber was 17%. Thus, the device successfully passed this test.

**Sterilization**

The sterilization information was provided on the OBS optical fiber, which is the only component provided sterile. The fiber is sterilized with 100% ethylene oxide (EtO) to a sterility assurance level of  $10^{-6}$ . The sterilization method was validated in accordance with International Organization for Standardization (ISO) 11135: 1994 "Medical devices -- Validation and routine control of ethylene oxide sterilization." The residual levels for EtO, ethylene chlorohydrin, and ethylene glycol were within acceptable limits as specified in the 1978 Proposed Rule for maximum residual levels. The device is packaged in a Tyvek/Mylar pouch and heat sealed. The package integrity was validated in accordance with ANSI/AAMI/ISO 11607:1998 "Packaging of terminally sterilized medical devices." The device was tested for and successfully passed the shipping and handling durability test requirements of ASTM D4169-96 "Standard Practice for Performance Testing of Shipping Containers and Systems."

**Shelf Life**

The only component of the OBS which required a shelf life was the optical fiber, which was previously cleared for marketing under K973611 with a 1-year shelf life. Since no changes in product package, materials, or design were made from the device cleared under K973611, no changes in shelf life for the optical fiber were required.

**Software**

The software of the device was considered to present a moderate risk, given that the software controls the delivery of energy from a 337 nm laser, which, if not properly controlled, may cause injury to the patient. Software validation and verification information included software description, hazard analysis, software requirements specification, architectural design chart, design specification, and traceability analysis. The verification and validation testing confirmed that the device software performed as designed.

## X. SUMMARY OF CLINICAL STUDIES

The clinical studies of the OBS system were conducted in two phases.

### *Phase I*

In the first phase (Phase I), data were collected to develop the diagnostic algorithm to be validated in the Phase II study. A total of 183 specimens from 86 subjects at three investigational sites were evaluated in the Phase I study. Background information on these study participants is listed in Table 1. Complete spectral characterization, the endoscopist's visual assessment, and consensus pathology diagnoses were obtained for 97 polyps and 86 "normal" control tissue samples.

**TABLE 1 - BACKGROUND INFORMATION FROM PHASE I STUDY**

<b>Characteristic</b>	<b>Male</b>	<b>Female</b>	<b>Total</b>
Number of subjects	56	30	86
Age, range (years)	45-86	40-86	40-86
mean + SD	63.39 ± 9.52	64.86 ± 15.93	63.89 ± 12.06
Number of polyps evaluated	64	33	97
true adenomas biopsied	35	21	56
true hyperplastic polyps biopsied	19	8	27
polyps classified as "normal"	10	4	14

The "true" status of each polyp, as classified above, was determined by histological examination. Polyps were classified as adenomatous, hyperplastic, or "normal" and ranged in size from 3 - 25 mm. The "normal" classification refers to those tissue samples which during endoscopic evaluation were thought to be polyps, but were determined to be normal tissue during the histological exam.

Based on the data obtained from this study, an algorithm was developed that evaluated the spectral characteristics to distinguish between adenomatous and hyperplastic polyps.

### *Phase II*

The purpose of the Phase II study was to validate the algorithm developed from the Phase I study, i.e., to measure the ability of the OBS device during colonoscopy to discriminate between adenomatous and hyperplastic polyps by classifying them as "suspect" and "not suspect," respectively.

### Study Design

The Phase II trial was a prospective, non-randomized, multi-center study of 101 subjects at 5 sites. Patients who participated in the study had been previously referred to colonoscopy and had at least one polyp identified. The patient's participation in the study was limited to the single colonoscopy procedure where the device was used (i.e., the patient was not followed after the completion of the procedure). The results of the OBS analysis were not known to the physician; therefore, patient treatment was not affected.

### Patients Studied

Characteristics of the patients studied, stratified by sex, are presented in Table 2.

**TABLE 2 - BACKGROUND INFORMATION FROM PHASE II STUDY**

<b>Characteristic</b>	<b>Male</b>	<b>Female</b>	<b>Total</b>
Number of subjects	61	40	101
Age, range (years)	30-91	50-83	30-91
mean + SD	60.99 ± 6.53	67.22 ± 4.36	63.57 ± 6.12
Number of polyps identified	107	70	177
Number of polyps evaluable <sup>†</sup>	79	56	135
true adenomas biopsied	45	36	81
true hyperplastic polyps biopsied	20	15	35
polyps classified as "normal"	14	5	19

<sup>†</sup> The number of polyps evaluable is defined as those polyps for which a complete spectral analysis was performed and for which a normal tissue biopsy was obtained. The number of subjects is based on the number of polyps evaluable, and not the total number of polyps identified.

The inclusion criteria for the study included:

- presence of at least 1 polyp on prior endoscopic examination.

The exclusion criteria included:

- coagulopathy or other conditions contraindicating endoscopic biopsy or polypectomy;
- other conditions which prevent the removal or biopsy of colonic polyps;
- presence of familial polyposis.

### Methods

Patients were prepared for a standard colonoscopy procedure according to the practice at each investigational site. The optical fiber and forceps were inserted through the working channel of the colonoscope.

When a polyp was identified, the physician documented: (1) whether they believed the polyp was adenomatous (or pre-cancerous, pre-malignant) or hyperplastic based on their visual assessment; and (2) whether they would remove the polyp. The OBS probe was then applied to the polyp.

The "test" spectral measurements were obtained in the following manner: The optical fiber was placed on a region of the polyp; the OBS pedal was depressed, triggering the release of laser energy to the polyp; the tissue's autofluorescence was reflected back through the fiber and evaluated by the analytical software. This step was repeated twice, such that spectral information from three different locations on the polyp were obtained. If the OBS was unable to decipher all three measurements, then the diagnostic procedure was not completed and the polyp was considered unevaluable. A "normal" control spectral measurement was obtained on a region of "normal" mucosa near the location of the target polyp. Once three spectral polyp readings and a "normal" reading were obtained, the data were processed through the system algorithm. During the study, the physician performing the procedure was blinded to the system results. The polyp was then biopsied.

All tissue samples were evaluated by two pathologists to confirm histology. This included a "reference" pathologist who evaluated all specimens, as well as the institutional pathologist who regularly evaluated



specimens at that site. If the diagnoses by the pathologists differed, then the tissue sample was reevaluated by each pathologist. If the diagnoses differed a second time, then the specimen was excluded from further analysis.

Effectiveness Results

The effectiveness of the OBS was characterized by its ability to correctly identify adenomatous polyps as adenomatous (characterized as sensitivity of the machine) and to correctly identify hyperplastic polyps as hyperplastic (characterized as the specificity of the machine). The data presented below include those polyps which were 1 cm or smaller in size that were evaluable in the Phase II study. Polyps were considered "evaluable" if a complete spectral data set was obtained on both the target polyp and the adjacent "normal" tissue, and if all documentation was complete.

***Sensitivity/Specificity Results***

The sensitivity and specificity of the device alone (OBS), physician alone (based on visual assessment), and combined device and physician are presented in Tables 3, 4, and 5, respectively.

**TABLE 3 - SENSITIVITY/SPECIFICITY OF DEVICE ALONE  
n = 135 evaluable polyps ≤ 1 cm**

		Pathology	
		adenomatous	hyperplastic
Device Alone	adenomatous	64	24
	hyperplastic	17	30
Sensitivity		79.0% (68.5-87.3)	
Specificity		55.6% (41.4-69.1)	
False Positive Rate		44.4%	
False Negative Rate		21.0%	

**TABLE 4 - SENSITIVITY/SPECIFICITY OF ENDOSCOPIST'S VISUAL ASSESSMENT ALONE  
n = 135 evaluable polyps ≤ 1 cm**

		Pathology	
		adenomatous	hyperplastic
Physician Alone	adenomatous	67	27
	hyperplastic	14	27
Sensitivity		82.7% (72.7-90.2)	
Specificity		50.0% (36.1-63.9)	
False Positive Rate		50.0%	
False Negative Rate		17.3%	

**TABLE 5 - SENSITIVITY/SPECIFICITY OF COMBINED OBS AND ENDOSCOPIST'S VISUAL ASSESSMENT<sup>†</sup>  
n = 135 evaluable polyps ≤ 1 cm**

		Pathology	
		adenomatous	hyperplastic
Combined Device and Physician	adenomatous	78	36
	hyperplastic	3	18
Sensitivity		96.3% (89.6-99.2)	
Specificity		33.3% (21.1-47.5)	
False Positive Rate		66.7%	
False Negative Rate		3.7%	

<sup>†</sup> For Table 5, if either the device classified the polyp as "suspect" or the physician classified the polyp as adenomatous, then the combined classification for that polyp was adenomatous. Thus, the only case where the polyp was classified as hyperplastic was when the device classified the polyp as "not suspect" and the physician classified the polyp as hyperplastic.

The results presented above demonstrated a statistically significant improvement in sensitivity when the OBS was used in conjunction with the physician's visual assessment during colonoscopy, according to the approved Indications for Use.

#### Safety Results

No adverse events (i.e., patient complications) were observed by study investigators or reported by study subjects.

## **XI. CONCLUSIONS DRAWN FROM THE STUDIES**

The pre-clinical studies included laser safety, electrical safety, electromagnetic compatibility, biocompatibility, and functional testing. The bench tests validated the safety of the device for the proposed intended use. The software documentation validated that the device algorithm performs according to its set specifications.

The pivotal (Phase II) clinical study demonstrated that the combined discriminatory ability of the OBS device and physician was improved over the discriminatory ability of the physician alone.

The effectiveness of the OBS device was demonstrated for the clinical setting in which the physician bases the decision to remove a polyp on his/her discriminatory ability. In this setting, the physician's sensitivity to remove adenomatous polyps is less than 100%. As a result, when labeled as an adjunctive tool, this device will increase the number of adenomatous polyps that are biopsied (i.e., increase the physician's sensitivity). However, the device will also increase the number of hyperplastic polyps that are biopsied (i.e., decrease the physician's specificity).

In contrast, the effectiveness of the OBS device was not demonstrated for the clinical setting in which the physician removes all polyps which are visualized. In this setting, the physician's sensitivity to identify adenomatous polyps is 100% (with a specificity of 0%). As a result, the device cannot improve this physician's sensitivity. The risk of not removing an adenomatous polyp outweighs the benefit of reducing the number of hyperplastic polyps that are biopsied. The risk of removing a polyp < 1 cm is minimal.

Regarding device safety, the clinical study suggested that the device will not expose patients to an unreasonable or significant risk of illness or injury, as the most likely adverse events would not be directly associated with the use of this device, but with the lower GI endoscopic procedure.

Overall, the pre-clinical and clinical studies provide reasonable assurance that, when used in a manner consistent with the indications, contraindications, warnings, and precautions specified in the labeling, the OBS device is safe and effective.

## **XII. PANEL RECOMMENDATION**

At an advisory meeting held on November 19, 1999, the Gastroenterology and Urology Devices Advisory Panel recommended that *SpectraScience's* PMA for the Optical Biopsy System be approved, subject to submission of and approval by the Center for Devices and Radiological Health (CDRH) of a post-approval study. This post-approval study would evaluate the performance of the OBS device in the context of sigmoidoscopy and by physicians who are less experienced and skilled than those who participated in the Phase II clinical study.

## **XIII. CDRH DECISION**

CDRH concurred with the Panel's recommendation regarding device approval. However, CDRH determined that a post-approval study was not required to evaluate the performance of the device when used in a different clinical setting. CDRH determined that the sponsor submitted sufficient safety and effectiveness data on the device's performance and that the performance of the device during the conditions described by the Indications for Use statement can be reasonably extrapolated from the existing clinical data.

FDA inspection determined the manufacturing facility to be in compliance with the device Quality System regulations.

## **XIV. APPROVAL SPECIFICATIONS**

Directions for use: See the labeling.

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