

SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Name: Endoscope Accessory

Device Trade Name: Onco-LIFE™ Endoscopic Light Source and Video Camera (Onco-LIFE™)

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Premarket Approval application: P950042/S003

Date of Panel Recommendations: None

Date of Notice of Approval to Applicant: June 30, 2005

II. INDICATIONS FOR USE

This device is indicated for use with fluorescence imaging during bronchoscopy as an adjunct to white light imaging, to detect and localize tissue suspicious for moderate or severe dysplasia, carcinoma *in situ*, or invasive cancer in patients with suspected or previously treated lung cancer.

III. CONTRAINDICATIONS

Onco-LIFE should not be used with patients who are contraindicated for bronchoscopic examination. Contraindications typically include uncontrolled hypertension, unstable angina and known uncontrollable bleeding disorders.

For fluorescence examination, additional contraindications may include recent use of photosensitizing drugs, chemopreventative drugs, systemic cytotoxic chemotherapy agents and/or ionizing radiation treatment to the chest.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions for use of Onco-LIFE are listed under “General Warnings” in the Instructions for Use & Operator’s Manual and in the Onco-LIFE Labeling Summary.

V. DEVICE DESCRIPTION

Onco-LIFE consists of an endoscopic light source and video camera for use with conventional endoscopes. Onco-LIFE operates in two imaging modes: conventional white light imaging mode (also referred to as color imaging mode) and fluorescence imaging mode. In the white light mode, Onco-LIFE functions in the same way as currently marketed conventional endoscopic light sources and cameras.

In the fluorescence mode, Onco-LIFE functions in a similar manner to the Xillix LIFE-Lung™ Fluorescence Endoscopy System (PMA P950042) and images native tissue fluorescence to aid in the identification of potentially precancerous and cancerous tissue. Blue light is used to illuminate the tissue and excite fluorophors naturally present in the tissue. A real-time video image of the fluorescing tissue is acquired and displayed on the video monitor. Areas suspicious for disease are displayed in red in the video image. The principle of operation for Onco-LIFE is described in more detail below.

Onco-LIFE Endoscopic Light Source and Video Camera (Onco-LIFE) is designed as an accessory for conventional endoscopes. Onco-LIFE consists of:

- A light source (model OLLS) that attaches to the light guide of the endoscope and provides the illumination required for endoscopic examination. Light source is regulated under 21 CFR 874.4350, Class I.
- A camera (model OLCA) that attaches to the eyepiece of the endoscope and acquires images of the illuminated tissue with a color image sensor and a low light image sensor. Camera and accessories are regulated under 21 CFR 878.4160, Class I
- A camera controller (model OLCC) that controls the operation of the camera and the light source, and provides a real-time video output of the images acquired by the camera. Camera and accessories are regulated under 21 CFR 878.4160, Class I
- Bronchoscopes are regulated under 21 CFR 874.4680, Class II

In addition, Onco-LIFE is supplied with accessories including power cables, connecting cables, a footswitch, and a color reference standard. Onco-LIFE is used with conventional bronchoscopes and an analog color video monitor, which are not supplied. Onco-LIFE is also compatible with a number of optional image recording devices such as VCR, video printer and image management systems.

Onco-LIFE Light Source:

The Onco-LIFE light source provides both white light illumination and fluorescence excitation. The light source features include:

- Dual-mode operation for white light and fluorescence endoscopy
- 150 W super-high-pressure mercury (Hg) arc main lamp with halogen backup lamp
- Intensity adjustment from 5% to 100% of full scale

- Automatic control of light output intensity via digital communication with the Onco-LIFE camera controller. Manual control via front panel if the light source is not connected to the camera controller.
- An indicator for monitoring main lamp usage
- Main lamp replacement that can be performed without tools
- Safety features that include:
 - Lamp output filtered to limit emission of UV and IR light
 - Circuitry for over-temperature detection in case of blocked ventilation
 - Light guide shutter that closes automatically when the endoscope is removed from the light source

Onco-LIFE Camera:

The Onco-LIFE camera is used in conjunction with the Onco-LIFE camera controller and transduces endoscopic images. The camera features include:

- Dual-mode operation for white light and fluorescence endoscopy
- High-sensitivity, high-dynamic-range, color image sensor for the acquisition of color images
- Low light image sensor for the acquisition of fluorescence images
- Three switches on the camera that can be configured to operate selected functions

Onco-LIFE Camera Controller:

The Onco-LIFE camera controller provides control over the operation of the camera and provides video output for display. The camera controller features include:

- Automated color balance for realistic rendition of color
- Operator-selectable automatic gain control (AGC) modes
- Operator-selectable brightness of video signal output
- Operator-adjustable red and blue hue of video signal output (for white light mode only)
- Footswitch with three switches that can be configured to operate selected functions
- Output video signal and control signal compatible with analog color video monitors, video recorders, video printers, and image management systems
- Additional technical data and safety standards/classification information is provided in the Instructions for Use & Operator's Manual.

Onco-LIFE Software:

- The Onco-LIFE software consists of embedded modules that are responsible for controlling the hardware components of the device and generating a real-time image of the tissue on a video monitor, viewed by the endoscope.

Onco-LIFE Accessories:

Onco-LIFE is supplied with accessories including power cables, a cable for the light source and camera controller communication, cables for the video outputs, a color reference standard, that ensures realistic and consistent color image rendition from endoscope to endoscope, a spare endoscope guide for the color reference standard, a spare lamp cartridge, and a footswitch.

Principle of Operation:

Onco-LIFE may be used in white light or in fluorescence mode. In white light imaging mode, Onco-LIFE functions in the same way as conventional endoscopic light sources and cameras. The light source produces a full visible spectrum output (approximately 400-700 nm) that is projected through the light guide of the bronchoscope and illuminates the tissue to be examined. This light is subsequently reflected by the tissue and an image is projected back through the bronchoscope image guide and acquired by the Onco-LIFE camera color image sensor. The camera controller encodes the image and outputs it as a real-time color video signal. The video signal is displayed on an analog color video monitor such as those commonly used in bronchoscopy.

In fluorescence mode, Onco-LIFE excites and images native tissue fluorescence (“autofluorescence”). When the blue light from the Onco-LIFE filtered (395-445 nm) arc lamp illuminates epithelial tissue, fluorophors naturally present in the tissue are excited and light of longer wavelengths (green through red) is emitted. Differences in the autofluorescence emitted by tissue at green (470-560 nm) wavelengths allow the discrimination between healthy and diseased tissue. Specifically, tissue suspicious for moderate or severe dysplasia, carcinoma *in situ* (CIS) or invasive carcinoma are associated with progressively reduced green autofluorescence.

In addition to providing blue excitation light, the Onco-LIFE light source simultaneously illuminates the tissue with a red (650 – 700 nm) light which is diffusely reflected by the epithelial tissue. This reflected red light does not vary with tissue pathology like the green fluorescence. However, both the fluorescence and the reflectance light will vary similarly with geometry, such as being closer to or further away from the tissue or in the presence of shadows.

In fluorescence mode, the Onco-LIFE camera simultaneously acquires two separate endoscopic images: The first is an image of the green fluorescence emitted from the tissue and the second is an image of red tissue reflectance. Contrasting colors are assigned to the two acquired images (green for fluorescence image and red for reflectance image), which are then combined and displayed as a single multi-color image on a video monitor. In the combined video image, areas of normal tissue will be dominated by the green fluorescence and will appear green and areas of diseased tissue will be dominated by the red reflectance and appear red. Areas that are far away or in shadows will appear dark.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative tests used to detect lung cancer include tests such as chest X-rays, sputum cytology, CT scans, PET scans, MRI, transbronchial needle aspiration, mediastinoscopy and thoracotomy.

VII. MARKETING HISTORY

The predecessor device to Onco-LIFE is the Xillix LIFE-Lung Fluorescence Endoscopy System™ (Xillix LIFE-Lung™), which was approved for commercial sale in the United States in 1996 (PMA # P950042) and marketed worldwide.

Onco-LIFE is Xillix's latest fluorescence endoscopy device which incorporates conventional white light and fluorescence endoscopy. Onco-LIFE devices are sold in Europe and approved for sale in Canada in 2004. To date, no Onco-LIFE or Xillix LIFE-Lung devices have been withdrawn from the market for any reason related to the safety or effectiveness and no medical device reports (MDRs) have been issued for these products.

VIII. POTENTIAL ADVERSE EVENTS

Potential adverse events are those normally associated with standard bronchoscopic procedures. These include infection, bleeding, pneumothorax, hypoventilation, arrhythmia, hypotension, reaction to medication used during the procedure (including local and intravenous anesthetics, anti-arrhythmics, medication used to control biopsy site bleeding etc.), postoperative soreness of the throat and bloody sputum.

The addition of fluorescence examination (FL) to white light examination (WL) may increase the duration of the bronchoscopy procedure, resulting in a potential increase in anesthetic/analgesia administration. The addition of FL to WL may also result in additional biopsies. However, there have been no reported adverse events attributable to use of Onco-LIFE. The small number of complications/adverse events observed in the OL-L01 clinical study were those typically seen with conventional bronchoscopy, and were unrelated to Onco-LIFE. Complications/adverse events were reported for 9 patients (none associated with the Onco-LIFE device). These included fever (5), hypoxia (4), hypertension (1), anxiety (3), hemoptysis (2), chills (4), pneumonia (2) and dyspnea (1). The length of the WL+FL bronchoscopic examination may be longer than that for standard bronchoscopy. In the Onco-LIFE study the average duration of bronchoscopy (WL+FL examination) was 21.9 minutes. The probability of adverse events while using the device may be increased by the additional biopsies and potentially longer examination time, however, all adverse events should be similar to those encountered with white light examination.

IX. SUMMARY OF NONCLINICAL STUDIES

Onco-LIFE conforms to the following standards as confirmed by third party inspection/testing. Onco-LIFE was designed and tested according to established design control procedures.

Testing/Analysis	Standard	Title
General Safety including Electrical Safety	UL 60601-1 (1 st Edition)	Medical electrical equipment – Part 1, General requirements for safety
	IEC 60601-2-18:1996 (Amendment 1:2000-07)	Medical electrical equipment – Part 2, Particular requirements for safety; Section 2.18 Specification for endoscopic equipment
EMC	IEC 60601-1-2:2001 (ANSI/AAMI/IEC 60601-1-2-2001)	Medical electrical equipment – Part 1, General requirements for safety; Section 1.2 Collateral standard: Electromagnetic compatibility – Requirements and tests
Hazard Analysis	ISO 14971:2000	Medical devices -- Application of risk management to medical devices

Light Source Spectral Power Distribution:

The Onco-LIFE endoscopic light source utilizes a 150 W super-high-pressure mercury arc lamp. Xillix employed an independent contractor to make measurements of the spectral power distribution at the distal end of the bronchoscope for an endoscopic light source containing such a lamp. The measurement range covered wavelengths from 250 nm to 2000 nm for both white light (color mode) and fluorescence illumination modes. The light output in both modes was shown to be limited to the visible spectrum. In addition, total light power output (brightness) was measured using the Onco-LIFE light source in both white light (color mode) and fluorescence illumination modes with various models of endoscopes. The total light output power in all cases was shown to be the same or less than the same brightness measurement performed using a commercially available endoscopic light source and bronchoscope.

Endoscope Compatibility:

Onco-LIFE is compatible and factory configured for optomechanical fit with endoscopes from leading manufacturers. Optical compatibility with Onco-LIFE, particularly in terms of color response in fluorescence mode has been evaluated as follows: the results of spectral transmission measurements showed that the illumination and imaging optics of representative bronchoscopes had similar spectral transmission properties; the Onco-LIFE auto-balance procedure ensures that color fidelity is maintained independent of any residual differences in optical transmission properties of a particular endoscope; the results of intrinsic fluorescence measurements showed that representative bronchoscopes produced acceptably low levels of fluorescence; the results of an evaluation of Moiré (interference) patterns showed that representative endoscopes exhibited acceptably low levels of Moiré; results of safety measurements showed that, when used in conjunction with the Onco-LIFE light source, representative bronchoscopes from all manufacturers produced a

similarly uniform illumination and that their maximum temperature remained below recommended limits.

Software Validation:

Onco-LIFE software was validated in accordance with the “*General Principles of Software Validation; Final Guidance for Industry and FDA Staff*” and “*Off-the-Shelf Software Use in Medical Devices*”. All software requirements for the custom embedded software modules were established and documented in a device-level requirements specification. A device-level hazard analysis was used to generate and/or identify safety-related requirements. Traceability was maintained between hazard analysis, safety-related software requirements and code segments designed to address these requirements. Safety related code was subjected to documented code-reviews in addition to routine verification activities. Test protocols and acceptance criteria were generated for the verification of requirements and the results of all custom software testing was documented in test reports. All testing was carried out and successfully concluded in this manner.

Off- the-shelf software used in Onco-LIFE is limited to compilers and low-level operating systems and has been successfully validated.

Nonclinical Laboratory Studies:

Onco-LIFE is an illumination and imaging accessory for medical endoscopes. Since Onco-LIFE does not come into direct contact with patients, non-clinical laboratory studies involving animal modeling, or examination of sterilization, biological/microbiological, immunological, toxicological or biocompatibility properties were not carried out. Onco-LIFE also does not contain any component with a limited shelf-life, eliminating the need for shelf-life studies.

Onco-LIFE was tested to recognized consensus standards for electro-medical devices. Certification to UL 60601-1, IEC 60601-2-18 and IEC 60601-1-2 incorporates the relevant electrical, electromagnetic and mechanical stress tests applicable to such electro-medical devices.

X. SUMMARY OF CLINICAL STUDY

Onco-LIFE provides both a conventional white light (WL) imaging mode and a fluorescence (FL) imaging mode in a single endoscopic imaging device. The Onco-LIFE pivotal study OL-L01 was designed to evaluate the safety and effectiveness of the device. Physicians used fluorescence as an adjunct to white light imaging and conducted the study using white light examination followed by fluorescence examination. In the Onco-LIFE study 68% of the patients evaluated were male (32% female), the mean age was 61.7 years (range 45 – 75 years), 99% were current or former smokers. These patient demographics are consistent with the patient population at risk for lung cancer.

Safety was assessed by evaluating adverse events, if any, attributable to Onco-LIFE. All patients were monitored during the bronchoscopy and followed-up by telephone call or office visit within 1 week after bronchoscopy to identify any complications/adverse events. Patients experiencing an adverse event received appropriate medical care.

Efficacy assessments were based on the comparison of visual classifications made during the bronchoscopy and the corresponding pathology classification of the biopsies taken from those areas. From these assessments, the study objectives of determining the sensitivity and specificity of WL+FL versus WL alone were calculated. Thirty-five positive patients were required to power the study.

Primary Objectives

- To demonstrate that the sensitivity of WL+FL bronchoscopic examination is better than WL examination alone for the localization of biopsy sites suspicious for moderate/severe dysplasia, carcinoma *in situ* (CIS) or invasive cancer (includes per-lesion and per-patient analysis), and the hypothesis tested that the relative sensitivity is at least 1.15.
- To demonstrate that WL+FL bronchoscopic examination conducted with Onco-LIFE is safe.

Secondary Objectives

- To quantify the difference in false positive rate (1 – specificity) between WL+FL bronchoscopic examination and WL examination alone for the localization of biopsy sites suspicious for moderate/severe dysplasia, CIS or invasive cancer (includes per-lesion analysis), and
- To demonstrate that the sensitivity of WL+FL bronchoscopic examination is better than WL examination alone for the localization of biopsy sites suspicious for moderate/severe dysplasia and CIS (includes per-lesion and per-patient analysis).

Study Design:

Study OL-L01 was a prospective, comparative, single arm, multi-center study that ultimately encompassed 204 patients at seven centers. In brief, the study required that all patients undergo a WL bronchoscopic examination followed by a FL examination. Anatomical sites of interest were recorded and visually classified by the investigator during both examinations. Clinical monitoring verified compliance with this imaging sequence. Visual classifications (Table1) were developed in conjunction with the study's Medical Advisor and the FDA.

Table 1 Description of Visual Tissue Classifications

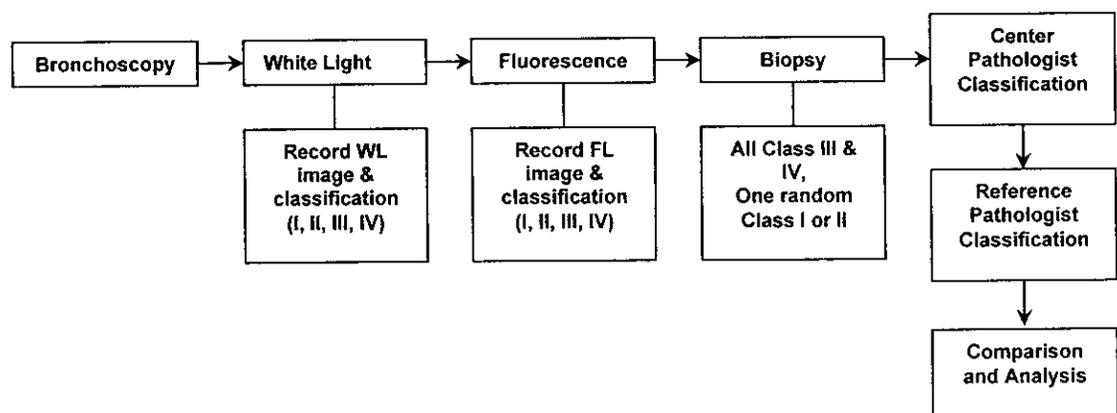
Classification	Description
Class I	Normal: not visually abnormal or suspicious
Class II	Abnormal: appearance of inflammation, trauma, anatomical

	abnormalities, metaplasia or mild dysplasia
Class III	Suspicious for pre-invasive cancer: suggestive of moderate dysplasia, severe dysplasia, or carcinoma <i>in situ</i>
Class IV	Suspicious for invasive cancer: appearance of gross, visible tumor

Visual classifications of Class I and II were considered negative (-) and Class III and IV were considered positive (+) as suspicious for cancer by the bronchoscopist. Biopsies were taken of sites visually classified as Class III or IV under either WL or FL, as well as at least one random site classified as either Class I or II under both WL and FL. Pathology slides were then examined by a center pathologist and a reference pathologist.

Both center and reference pathologists were blinded from the bronchoscopist evaluation, and independently graded the tissue biopsies. Pathology classifications of normal to mild dysplasia were considered negative, and classifications of moderate dysplasia or worse were considered positive. Biopsy samples that could not be evaluated were graded as unsatisfactory. If there was a discrepancy between the center and reference pathology scores, the biopsy sample was reread by the reference pathologist and this score became the final pathology score. The exception was when both the center and reference pathology scores were negative, in which case the highest score was used.

Each patient enrolled in the study underwent a single bronchoscopic procedure followed by post-bronchoscopy observation. Patients were followed-up by telephone call or office visit within 1 week after bronchoscopy to identify any complications or adverse events.



Study Flow Diagram:

Patient Assessment:

Inclusion Criteria:

To be included in this study, patients were required to meet all of the following criteria:

- Current or past smoking history of >20 pack-years or exposure to known occupational risk factors
- Age 45-75 years
- At least ONE of the following:
 - > Suspected lung cancer based on either:
 - i Sputum atypia
 - ii Evidence of airflow limitation on spirometry with an FEV1: FVC ratio of less than 0.70 and/or FEV1 <75 % of the predicted value
 - iii Suspected lung cancer on the basis of X-ray or CT scan
 - > Or previous(within 2 years) curative therapy for primary lung cancer or head and neck cancer (excluding nasopharyngeal cancer) and currently thought to be disease-free, or suspected for second primary or recurring tumor
- Signed and dated informed consent from patient

Exclusion Criteria:

Patients experiencing any of the following were to be excluded from the study:

- Uncontrolled hypertension (systolic BP >200 mmHg; diastolic BP >120 mmHg)
- Unstable angina
- Known or suspected pneumonia
- Acute bronchitis within the previous one month
- Known uncontrollable bleeding disorder
- Undergone one or more bronchoscopy(ies) with biopsy within the previous 3 years, where the bronchoscopy report or other means of localizing the previous biopsy sites are not available, OR undergone one or more bronchoscopy(ies) with multiple biopsies (> 4 sites) within the previous 3 years
- Treatment with fluorescent photosensitizing drugs within the previous 12 months
- Treatment with retinoid chemopreventative drugs within the previous 12 months
- Treatment with ionizing radiation to the chest within the previous 6 months
- Treatment with cytotoxic chemotherapy agents within the previous 6 months
- Known allergy to topical xylocaine

- Known allergy to fentanyl, morphine, midazolam, diazepam and/or codeine, if any of these are planned to be used
- Treatment with anticoagulants within the previous 6 days (e.g., warfarin, heparin)
- Pregnancy

Demographic Data:

Thirty-five positive patients were required to power the study. Due to the lag time in receiving final pathology results from both center and reference pathologists an additional 8 positive patients (total 43 positive patients) were enrolled, resulting in a total of 204 study subjects at 7 centers.

Of 204 study subjects, 34 patients were excluded from the efficacy analysis because of the following, 18 were training cases, 6 were ineligible according to inclusion criteria and the remaining 10 had incomplete data, e.g., pathology. The remaining 170 evaluable patients are included in the efficacy analyses. Table 2 shows the distribution of gender. Table 3 presents the minimum, maximum and mean age of patients.

Table 2 Distribution of Patients by Gender

N=170 (100%)	
Males	Females
115 (68%)	55 (32%)

Table 3 Age of Patients

Age Range	Age (yrs)
Minimum	45
Maximum	75
Mean	61.7

Table 4 represents the smoking status of the patients at the time of enrollment into the study. Patients enrolled in the study were required to have a smoking history of >20 pack years or exposure to known occupational risk factors.

Table 4 Smoking Status at Enrollment

Smoking Status	Number of Patients (N=170)
Current Smoker	49
Ex-Smoker	120
Occupational Risk Factor	1

Patients were also required to have at least one of the criteria presented in Table 5.

Table 5 Distribution of Study Subjects by Reason of Enrollment

Reason for Enrollment	Number of Patients (N=170)*
Positive Sputum Cytology	76 evaluable patients (45%)
Airflow Limitation	56 evaluable patients (33%)
Previous Curative Therapy	23 evaluable patients (14%)
Suspected Lung Cancer**	78 evaluable patients (46%)

* Note: patients may have more than one reason for enrollment

** On the basis of X-ray or CT Scan

Final pathology results identified 43 of the 170 patients (25%) to have 76 lesions positive for moderate/severe dysplasia, CIS, or invasive carcinoma. Table 6 provides the distribution of the 776 evaluable lesions by final pathology.

Table 6 Distribution of Evaluable Lesions by Final Pathology

Pathology	Total (N= 776)
Normal – Mild Dysplasia	700 (90%)
Moderate Dysplasia	33 (4%)
Severe Dysplasia	6 (1%)
CIS	2 (<1%)
Microinvasive Carcinoma	4 (1%)
Invasive Carcinoma	31 (4%)

Analysis of Primary Efficacy Objectives:

Per-Lesion Analysis (Includes Invasive Cancer): Relative Sensitivity for Detection of Moderate/Severe Dysplasia, CIS or Invasive Cancer

The per-lesion relative sensitivity calculation compares the visual classification of an area of interest identified during the bronchoscopic examination with the pathology classification of the biopsy obtained from that area.

The data analyzed for the main study objective are presented in Table 7. A total of 76 of the 776 evaluable lesions were classified as positive (moderate/severe dysplasia, CIS or invasive cancer) by pathology. Thirty-six of these lesions were identified and classified as Class III or IV during WL examination. An additional 18 Class III or IV lesions were identified by FL, for a total of 54 Class III or IV lesions identified during WL+FL examination. Random biopsy (WL-FL-) identified an additional 22 Class III or IV lesions. The proportion of identified lesions that were Class III or IV was greater for adjunctive WL-FL+ biopsy (18/151, 12%) than for random biopsy (22/537, 4%), with the difference being statistically significant ($p= 0.0011$). The relative sensitivity is 1.50, indicating that the addition of an Onco-LIFE FL examination to WL bronchoscopy resulted in a 50% increase in detection of precancerous and cancerous lesions. The 95% lower 1-sided confidence limit is 1.29.

This exceeds the requirement for clinical significance (1.15) as set by the protocol. Thus the combination of WL + FL shows both statistically and clinically increased sensitivity over WL alone.

Table 7 Per-Lesion Sensitivity Analysis (Includes Invasive Cancer)

		Pathology Classification of Corresponding Biopsy		Totals per visual classification
		+	-	
WL classification of area of interest	+ (III or IV)	36	52	88
	- (I or II)	40	648	688
WL+FL classification of area of interest	+ (III or IV)	54	185	239
	- (I or II)	22	515	537
		WL	WL+FL	
Sensitivity		0.47†	0.71†	
Relative Sensitivity (95% 2-sided Confidence Interval) (95% 1-sided Confidence Limit)			1.50† (1.26, 1.89) (1.29)	

† Sensitivity is overestimated because intrinsically its denominator is undercounted. However, the ratio of the sensitivities of WL + FL and WL alone (the relative sensitivity) is an unbiased estimate of the true ratio.

Per-Patient Analysis (Includes Invasive Cancer): Relative Sensitivity for Detection of Moderate/Severe Dysplasia, CIS or Invasive Cancer

Results of the relative sensitivity per-patient analysis are presented in Table 8. A total of 43 of the 170 evaluable patients were confirmed by pathology to have at least one lesion positive for moderate/severe dysplasia, CIS or invasive cancer. Twenty-four patients had at least one lesion identified and classified as positive for Class III or IV with WL examination. An additional 8 positive patients were identified by FL, for a total of 32 patients found with at least one Class III or IV lesion during WL+FL examination. Random biopsy identified an additional 11 positive patients. The proportion of patients identified for biopsy for whom at least one positive lesion was found was greater for adjunctive WL-FL+ (8/37, 22%) than for random biopsy (11/84, 13%), but the difference did not attain statistical significance ($p= 0.2805$). The observed relative sensitivity is 1.33, indicating that the addition of an Onco-LIFE FL examination to WL bronchoscopy resulted in a 33% increase in detection of patients with precancerous and cancerous lesions.

The 95% lower 1-sided confidence limit is 1.15. This meets the requirement for clinical significance (1.15) as set by the protocol. Thus, the combination of WL + FL shows both statistically and clinically increased sensitivity over WL alone.

Table 8 Per-Patient Sensitivity Analysis (Includes Invasive Cancer)

		Pathology classification of patient	
		+	
WL classification for patient	+ (III or IV)	24	
	- (I or II)	19	
WL+FL classification for patient	+ (III or IV)	32	
	- (I or II)	11	
		WL	WL+FL
Sensitivity		0.56†	0.74†
Relative Sensitivity (95% 2-sided Confidence Interval) (95% 1-sided Confidence Limit)			1.33† (1.13, 1.70) (1.15)

† Sensitivity is overestimated because intrinsically its denominator is undercounted. However, the ratio of the sensitivities of WL + FL and WL alone (the relative sensitivity) is an unbiased estimate of the true ratio.

Analysis of Secondary Efficacy Objectives Per Protocol:

Per-Lesion Relative False Positive Rate (1 – Specificity) Calculation: Detection of Moderate/Severe Dysplasia, CIS or Invasive Carcinoma

The secondary objective of quantifying the difference in false positive rate, or 1 – specificity, between WL+FL versus WL was fulfilled by calculating the ratio of 1 – Specificity of WL+FL versus WL examinations on a per-lesion basis. Results are presented in Table 9.

Table 9 Specificity Analysis (Includes Invasive Cancer)

	WL	WL+FL
1 – Specificity	0.07†	0.26†
Ratio of 1 – Specificity 95% 2-sided Confidence Interval		3.56† (2.7, 4.9)

† 1 – specificity is overestimated because intrinsically its denominator is undercounted. However, the ratio of the sensitivities of WL+FL and WL alone (the relative sensitivity) is an unbiased estimate of the true ratio.

The ratio of 1-Specificity was 3.56, indicating an increase in the false positive rate found with WL+FL compared to WL alone. In this study, thirty-six positive lesions were detected with WL alone and fifty-four with WL+FL. These additional positive lesions were associated with an increase in the number of false positive biopsies. This increase in the false-positive rate is consistent with increased false-positive rates in other studies, for example the Xillix LIFE-Lung study reported a 1-Specificity of 3.40.

Per-Lesion Analysis (Excludes Invasive Cancer):Relative Sensitivity for Detection of Moderate/Severe Dysplasia or CIS

For this analysis that excludes invasive cancer, lesions with visual classifications of Class IV under either WL or FL and lesions with final pathology scores indicative of invasive carcinoma (N=49) were removed. This reduced the lesion dataset from 776 to 727 evaluable lesions.

The data analyzed are presented in Table 10. A total of 39 of the 727 evaluable lesions were classified as positive (moderate/severe dysplasia or CIS) by pathology. Four of these were identified and classified as Class III during WL examination. An additional 13 Class III lesions were identified by FL for a total of 17 lesions identified and classified as Class III during WL+FL examination. Random biopsy (WL-FL-) identified 22 Class III lesions. The proportion of identified lesions that were Class III was greater for adjunctive WL-FL+ biopsy (13/145, 9%) than for random biopsy (22/537, 4%), with the difference being statistically significant ($p= 0.0311$). The relative sensitivity is 4.25, indicating that the addition of an Onco-LIFE FL examination to WL bronchoscopy results in a 325% increase in detection of moderate/severe dysplasia and CIS. The 95% lower 1-sided confidence limit is 2.22.

This exceeds the requirement for clinical significance (1.15) as set by the protocol. Thus the combination of WL + FL shows both statistically and clinically increased sensitivity over WL alone.

Table 10 Per-Lesion Sensitivity Analysis (Excludes Invasive Cancer)

		Pathology classification of Corresponding biopsy		Totals per visual classification
		+	-	
WL classification of area of interest	+ (III)	4	41	45
	- (I or II)	35	647	682
WL+FL classification of area of interest	+ (III)	17	173	190
	- (I or II)	22	515	537
		WL	WL+FL	
Sensitivity		0.10†	0.44†	
Relative Sensitivity (95% 2-sided Confidence)		4.25†		
(95% 1-sided Confidence Limit)		(2.00, 16.00)		
		(2.22)		

† Sensitivity is overestimated because intrinsically its denominator is undercounted. However, the ratio of the sensitivities of WL + FL and WL alone (the relative sensitivity) is an unbiased estimate of the true ratio.

Per-Patient Analysis (Excludes Invasive Cancer):
Relative Sensitivity for Detection of Moderate/Severe Dysplasia or CIS

Results of the relative sensitivity per-patient analysis are presented in Table 11. A total of 25 patients were confirmed by pathology to have at least one lesion positive for moderate/severe dysplasia or CIS. Four patients had at least one lesion classified as Class III under WL examination. An additional 10 patients were identified by FL for a total of 14 patients with at least one lesion identified and classed as Class III during WL+FL examination. Random biopsy identified 11 positive patients. The proportion of patients identified for biopsy for whom at least one positive lesion was found was greater for adjunctive WL-FL+ biopsy (10/49, 20%) than from random biopsy (11/93, 12%), but the difference did not attain statistical significance ($p=0.2140$). The relative sensitivity is 3.50, indicating that the addition of an Onco-LIFE FL examination to WL bronchoscopy results in a 250% increase in detection of patients with moderate/severe dysplasia or CIS. The 95% lower 1-sided confidence limit is 1.86. This exceeds the requirement for clinical significance (1.15) as set by the protocol. Thus, the combination of WL + FL shows both statistically and clinically increased sensitivity over WL alone.

Table 11 Per-Patient Analysis (Excludes Invasive Cancer)

		Pathology classification of patient
		+
		+ (III)
		- (I or II)
WL+FL classification for patient	+ (III)	14
	- (I or II)	11
	WL	WL+FL
Sensitivity	0.16†	0.56†
Relative Sensitivity	3.50†	
(95% 2-sided Confidence Interval)	(1.63, 12.00)	
(95% 1-sided Confidence Limit)	1.86	

† Sensitivity is overestimated because intrinsically its denominator is undercounted. However, the ratio of the sensitivities of WL + FL and WL alone (the relative sensitivity) is an unbiased estimate of the true ratio.

Gender-Based Analysis:

In the Onco-LIFE study 68% of the patients evaluated were male (32% female), the mean age was 61.7 years (range 45 – 75 years), 99% were current or former smokers. These patient demographics are consistent with the patient population at risk for lung cancer.

Relative sensitivity of Onco-LIFE was 1.62 in males and 1.33 in females. While the relative sensitivity was higher in males, there was no statistically significant difference ($p = 0.38$) between the gender-based cohorts, indicating that Onco-LIFE was equally effective for both gender groups. Ratio of 1-specificity was similar in both gender groups (3.25 in males, 3.61 in females, $p = 0.81$).

Age-Based Analysis:

Median age in the study population was 62 years. Patients were stratified for analysis by less than or equal to 62 years of age and greater than age 62. Relative sensitivity of Onco-LIFE was 1.63 in patients 62 years or younger and 1.40 in patients older than 62 years of age. While the relative sensitivity was higher in the 62 years and younger patient subgroup, there was no statistically significant difference ($p = 0.57$) between the age groups, indicating that Onco-LIFE was equally effective for both age groups. Ratio of 1-specificity was better in the greater than 62 patient population (2.74 as compared to 5.24 in the 62 years and younger age group). The difference is statistically significant ($p = 0.009$), indicating that fewer false positive biopsies were obtained from patients greater than 62 years of age.

XI. DEVICE FAILURES

During the clinical study, there were three reported Onco-LIFE failures:

- a. One reported case of the light source unexpectedly switching from main lamp to back-up lamp mode during setup prior to bronchoscopy. When re-started, the light source functioned normally and was used without incident for subsequent bronchoscopies. It was later determined that the malfunction was caused by an intermittent solder connection of a connector in the light source. In response, the manufacturing process was revised to minimize strain on that connection during assembly. The connector was also changed to a crimped, instead of a soldered, connection.
- b. One reported case of the light source failure to start during setup prior to bronchoscopy set-up. This was caused by a component failure in the lamp ballast, a subassembly supplied by the lamp vendor. The vendor was notified of the failure.
- c. One reported case of problem switching from WL to FL during a bronchoscopy. The camera was fully functional in WL mode and the bronchoscopy was completed in WL. It was determined that the ribbon cable in the camera controller had been strained and developed an intermittent short circuit after being threaded through a circular ferrite during assembly. In response, the ferrite

specification was modified such that ferrites specifically shaped for ribbon cables are used.

XII. CONCLUSIONS DRAWN FROM STUDY

Clinical Benefits:

Based on the Per Protocol analysis, Onco-LIFE WL+FL examination improved the detection of cancerous and precancerous lesions on a per-lesion basis by 50% overall and 325% for moderate/severe dysplasia, or *CIS*. On a per-patient basis, the WL+FL improvement was 33% overall and 250% for patients with moderate/severe dysplasia or *CIS*.

This improved detection, especially at an earlier stage, may allow patients earlier access to diagnosis and treatment.

Clinical Risks:

The addition of FL to WL may increase the duration of the bronchoscopy procedure, resulting in a potential increase in anesthetic/analgesia administration. The addition of FL to WL may also result in additional biopsies.

There were no safety issues identified with the use of Onco-LIFE in this clinical study. Also, there were no reported increased risks associated with the use of Onco-LIFE. The small number of complications/adverse events observed, such as fever and hypoxia, (9 of 204 patients) were those typically seen with conventional bronchoscopy and were unrelated to Onco-LIFE.

Benefit versus Risk:

An overall assessment of benefits and risks associated with FL imaging is presented in the recent Guidelines from the American College of Chest Physicians. Specifically, it is reported that "Fluorescence techniques used with bronchoscopy have demonstrated detection of dysplasia, carcinoma *in situ*, and early invasive cancers not visible by standard white light bronchoscopy..."¹

In addition it is noted that, "There have been no untoward risks reported in the series utilizing autofluorescence bronchoscopy. Considering that fluorescence inspection simply uses light of a different wavelength and that bronchial biopsy attainment is the same as in conventional bronchoscopy, there is no increase in risk to the patient over a standard WLB [white light bronchoscopy] flexible bronchoscopy technique. Autofluorescence inspection following WLB generally adds 5 to 10 minutes to the overall bronchoscopic procedure."¹

The Onco-LIFE pivotal study results are consistent with the Guidelines' observations. That is, the Onco-LIFE clinical study met its objective for clinical significance and

¹ Ernst A, Silvertri A, Johnstone D. *Interventional Pulmonary Procedures: Guidelines from the American College of Chest Physicians*. Chest 2003; 123: 1693-1717.

demonstrated a statistically significant improvement in the detection of precancerous and cancerous lesions. This improvement is greatest in the detection of early-stage lung cancer, and was attained without any reported increased risk. Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ear Nose and Throat Devices panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CDRH DECISION

FDA issued an approval order on June 30, 2005. The applicant's manufacturing facility was inspected on January 13, 2005, and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XV. 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.

Postapproval Requirements and Restrictions: See approval order.

XVI. REFERENCES

Ernst A, Silvertri A, Johnstone D. *Interventional Pulmonary Procedures: Guidelines from the American College of Chest Physicians*. Chest 2003; 123: 1693-1717.