DE NOVO CLASSIFICATION REQUEST FOR FLUOPTICS FLUOBEAM 800 CLINIC® IMAGING DEVICE WITH FLUOCASE 800™ CONTROL SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Autofluorescence detection device for general surgery and dermatological use: An autofluorescence detection device for general surgery and dermatological use is an adjunct tool that uses autofluorescence to detect tissues or structures. This device is not intended to provide a diagnosis.

NEW REGULATION NUMBER: 21 CFR 878.4550

CLASSIFICATION: Class II

PRODUCT CODE: QDG

BACKGROUND

DEVICE NAME: Fluobeam 800 Clinic Imaging Device used with Fluocase 800 Control System

SUBMISSION NUMBER: DEN170092

DATE DE NOVO RECEIVED: December 22, 2017

CONTACT: Fluoptics
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INDICATIONS FOR USE

The Fluoptics Fluobeam® Imaging system is intended to provide real-time near infrared (NIR) fluorescence imaging of tissue during surgical procedures. The Fluoptics Fluobeam® Imaging system is indicated for use in capturing and viewing fluorescent images for the visual assessment of blood flow in adults as an adjunctive method for the evaluation of tissue perfusion, perfused organs, and related tissue-transfer circulation in tissue and free flaps used in plastic, micro- and reconstructive and organ transplant surgeries.

The Fluoptics Fluobeam® Imaging system can also be used to assist in the imaging of parathyroid glands and can be used as an adjunctive method to assist in the location of parathyroid glands due to the auto-fluorescence of this tissue.

Use of the Fluobeam® device is intended to assist, not replace, experienced visual assessment, and biopsy with conventional histopathological confirmation per standard of care. The system is not to be used to confirm the absence of parathyroid tissue or glands and is only to be used to assist in location of visually identified gland/tissues.

LIMITATIONS

The sale, distribution, and use of the Fluobeam 800 Clinic Imaging Device used with Fluocase 800 Control System is restricted to prescription use in accordance with 21 § CFR 801.109.

The Fluobeam© 800 has not been evaluated in providing a diagnosis of parathyroid conditions including adenoma, carcinoma, and hyperplasia.

The clinical outcomes performance data was limited to total thyroidectomy patients and the impact of the device on clinical outcomes in patients with parathyroid disease (*i.e.,* adenoma) is not as clear. Caution must also be exercised to evaluate autofluorescent tissue to confirm identity as parathyroid gland because thyroid colloid nodules or other tissues may have enhanced autofluorescence in some patients.

The performance of this device has not been definitively established in certain disease states such as secondary hyperparathyroidism, tertiary hyperparathyroidism, malignant parathyroid disease, or certain genetic conditions including Multiple Endocrine Neoplasia 1/2A. Additionally, the device has not been adequately tested for use to differentiate normal from abnormal or pathologic parathyroid glands.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Fluobeam 800 Clinic Imaging Device Used With Fluocase 800 Control System is an autofluorescence imaging system that is capable of visualizing autofluorescent signals from the parathyroid glands. The device is a non-contacting imaging system that excites fluorescent molecules with non-ionizing near-infrared light at 750 nm and collects emissions from 800 nm to (b) (4) nm. The collected emissions are subsequently displayed as an image on a panel PC screen.

The Fluobeam device is composed of the following components:

1. The optical head (FluoBeam 800 Clinic® Device)
    a. Contains 750 nm laser (for fluorescence excitation), NIR LEDs (b) (4) and white LEDs (normal illumination $\lambda<800$)
    b. The excitation irradiance was measured as (b) (4) W/m^2 at a distance of 20 cm from the optical head.
    c. Contains a CCD camera to collect fluorescence emissions from 800 nm to (b) (4) nm
    d. The head is a multiple patient, multiple use device used in the sterile field with a disposable sterile sheath (K850959).

2. The electrical case (Fluocase™ 800)
    a. The electrical case remains in the non-sterile area and contains all supporting electronics to power, control, and monitor the optical head.
3. The software (Fluosoft™)
    a. Available as preinstalled software on the panel PC or as electronic media
    b. Enables real-time visualization of fluorescence and autofluorescence signals acquired by the optical head.
    c. Contains several modes (standard, advanced, perfusion, low signals, and time lapse) for visualizing fluorescence and autofluorescence images.

The optical head (left, top) and electrical case (left, bottom) are pictured below. Device accessories include sterile covers (K850959) and a panel PC mounted on the Fluocart™ a mobile cart (middle) and FluoPod™ arm (right) are pictured below.

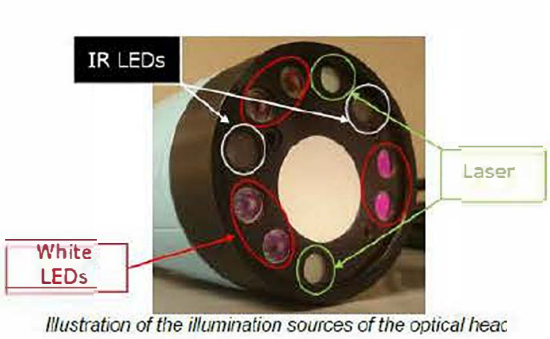
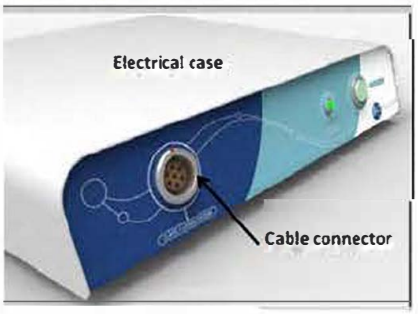


Illustration of the illumination sources of the optical heac



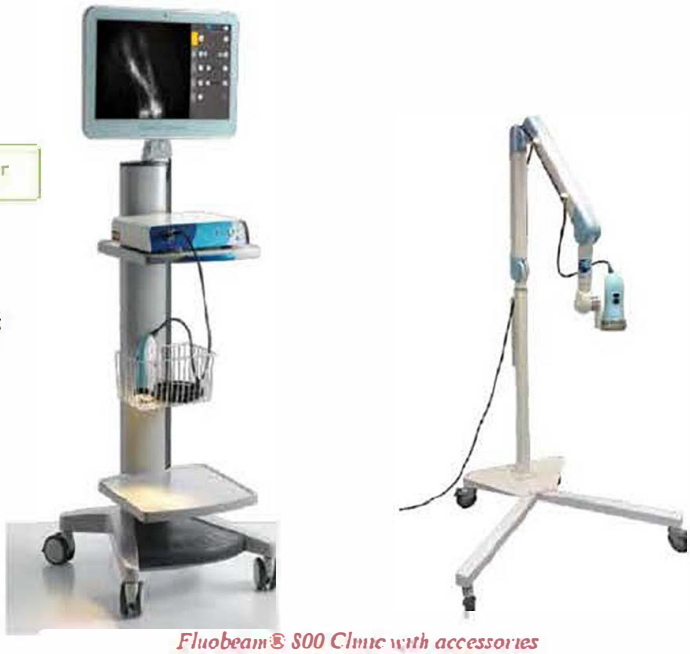

Fluobeam® 800 Clinic with accessories

Table 1: Fluobeam Regulatory Information

Device Trade/Proprietary Name	Fluobeam 800 Clinic® Imaging Device with Fluocase 800™ Control System
Device Common Name	Parathyroid Autofluorescence Imaging Device
Device Class	Class II
Classification Regulation	878.4550
Product Code	QDG

Table 2: Device Characteristics:

Device Technology Description:	DEN170092
General Device Characteristics	
Excitation Wavelength	750 nm
Emission Wavelength	>800 nm
Working Distance	20-30 cm
Focal plane depth	2 to 3 cm
Field of View	Minimum: 2.2 cm x1.5 cm Maximum: 20 cm x 14 cm
Resolution (focal plane)	300 µm to 50 µm depending on magnification
Magnification	X10 zoom
Maximum frame rate	25 images/sec
Minimum exposure time	1 ms
Maximum exposure time	1 s
Camera bit depth	8 bits
Image size (pixels)	696 x 576 pixels
Image format	PNG
Video format	MP4
Software operating system (OS) compatibility	Windows 7 or Windows 10
Laser power density	5 ± 1 mW/cm^2
Infrared LED	(b) (4) nm
White LED	Broadband LEDs with normal illumination λ<800

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

There are no direct or indirect patient contacting components.

SHELF LIFE/STERILITY/REPROCESSING

The Fluobeam 800 Clinic® Imaging Device with Fluocase 800™ Control System is a multi-patient, multi-use imaging system that is not provided sterile nor intended to be end-user sterilized. The Fluobeam 800 Clinic® imaging head is intended to be used in the sterile field with the use of a single-use, disposable, sterile sheath.

The Fluobeam device is labeled for use with, the disposable sterile sheath, Equipment Snap Kovers by Advance Medical Designs, Inc. (K8509590).

ELECTROMAGNETIC COMPATIBILITY AND ELECTROMAGNETIC SAFETY

The following Electrical/ Mechanical/Thermal Safety, electromagnetic compatibility (EMC) and laser safety testing has been performed:

- IEC 60601-1: 2005 (3rd Edition) + CORR.1:2006 + CORR.2:2007 + AM1:2012 or IEC 60601-1:2012 with US deviations, General safety standard: safety requirements for medical electrical systems

- IEC 60601-1-2: 2014 (Edition 4), Medical electrical equipment Part 1-2 – General requirements for basic safety and essential performance – Electromagnetic compatibility.

- IEC 60601-1-6: 2010 Collateral Standard: Medical electrical equipment Part 1-6 – General requirements for basic safety and essential performance - Usability

The Fluobeam 800 Clinic® Imaging Device with Fluocase 800™ Control System passed all relevant portions of the testing.

LASER/LIGHT SAFETY

The following laser and light safety testing has been performed:

- IEC 60825-1: Safety of laser products - Part 1: Equipment classification and requirements

- EN 62471:2008 Photobiological safety of lamps and lamp systems.

MAGNETIC RESONANCE (MR) COMPATIBILITY

Device is not compatible for Magnetic resonance (MR) environment.

SOFTWARE

The Fluosoft™ software controls access to the Fluobeam 800 Clinic® Imaging Device, the user interface, hardware components, and manages acquired images and videos.

The Fluobeam 800 Clinic® Imaging device has a 3 hardware buttons (function selection, setting adjustment arrows) that are used to navigate through the software menu and adjust imaging parameters and control when the white light, infrared LEDs, and excitation laser source are switched on and off and when the camera can capture images and vidoes.

The software user interface is where a user can begin a new session, review an old session, or export images and/or videos. The interface allows the user to enter user and patient information as well as identify the type of examination. There are 5 software acquisition modes, standard, advanced, perfusion, low signals, and time lapse. Each software mode has preset imaging parameters (e.g., background lighting, exposure time, brightness adjustment, zoom). All imaging parameters can be adjusted by the user regardless of the software mode that is used for the imaging session.

The agency considers the software to be a moderate level of concern (LOC) because inadvertent software errors could result in injury to the patient or delay in procedure time.

All elements of software and cybersecurity information as outlined in FDA's guidance documents *"Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices"* (issued May 11, 2005) and *"Content of Premarket Submissions for Management of Cybersecurity in Medical Devices"* (issued June 14, 2013) were provided.

Overall, the software documentation included in the De Novo request contains sufficient detail to provide reasonable assurance that the software will operate in a manner described in the specifications.

PERFORMANCE TESTING – BENCH

Performance testing to characterize device performance for the Fluobeam 800 Clinic® Imaging Device with Fluocase 800™ Control System was performed under K132475 and is summarized below.

- Laser Wavelength: The wavelength of the laser was measured with a monochromator through evaluation of standards EN60825-1 to ensure that the wavelength is within the pre-established design parameter (<800 nm).
- Laser Power and Irradiance: The maximum laser output power and irradiance at (b) (4) mm and (b) (4) mm was measured with a (b) (4)% uncertainty through evaluation of EN60825-1.
- Laser Illumination pattern: The laser illumination pattern was tested to ensure that when the output of the laser passed through a lens assembly and diffuser the illumination region was circular with a diameter of 10 cm at a distance of 20 cm.
- LED Spectra: The spectra of the infrared and white LEDs were measured through evaluation of standards EN62471.
- Emission Filters: The emission filters were tested to ensure that emission wavelengths from the target tissues from 800 to (b) (4) nm would be able to be collected. The emission filters prior to the detection camera include a long-pass filter with a cutoff wavelength close to 800 nm and a short pass filter with a cutoff wavelength close to (b) (4) nm.
- System Sensitivity: The system sensitivity was tested to demonstrate that the system is able to have a minimum detection limit of (b) (4) picomol of ICG diluted in (b) (4) uL sterile water drop.

SUMMARY OF CLINICAL INFORMATION

Five literature articles about clinical studies were provided to support the safety and effectiveness of the Fluoptics Fluobeam System for the detection of parathyroid glands during thyroid surgery.

STUDY 1: *Falco et al* 2016

The first included study (Falco et al 2016) was designed to test the relative levels of autofluorescence of parathyroid gland tissue compared to thyroid gland and background *in vivo*. The authors used the sponsor's device for this study. Twenty-eight patients were enrolled at a single institution between June 2015 and August 2015 were prospectively included (19 female, 9 male). The indications for surgery were varied: seven primary hyperparathyroidism, four hyperthyroidism, three goiter, and 11 thyroid cancer. Patients underwent the indicated surgery for their respective disease processes. During the surgical procedure, the Fluobeam 800 device was used in a single instance to evaluate intra-operative levels of autofluorescence of parathyroid glands, thyroid gland, and surrounding background tissues (fat, lymph nodes, and muscle).

Autofluorescence images were acquired with the room lights off. For patients with primary hyperparathyroidism, adenomas were resected, and normal gland biopsy was performed, allowing histologic confirmation of tissues suspected to be parathyroid glands. Other surgical procedures did not have histology confirmation.

Image J image processing software was used to quantify the amount of fluorescence by each structure (ie. Parathyroid gland, thyroid gland, background tissue). No units for autofluorescence values are provided. Statistical Package of the Social Sciences software 19 was used for analysis with ANOVA.

Table 1. Patient Demographics, Surgery, and Average Autofluorescence (No units provided)

Patient	Sex	Age, (y)	Diagnosis	Surgery	Normal parathyroid	Thyroid	Background
1	*Female*	*35*	*Primary HPT*	*Parathyroidectomy*	*N/A*	*41.8*	*16.8*
2	*Female*	*60*	*Primary HPT*	*Parathyroidectomy*	*N/A*	*46.9*	*33.2*
3	Female	43	Primary HPT	Parathyroidectomy & biopsy normal gland	32.3	26.4	20.4
4	Female	37	Primary HPT	Parathyroidectomy & biopsy normal gland	47.3	39.3	29.3
5	Female	48	Primary HPT	Parathyroidectomy & biopsy normal gland	12.9	7.8	3.2
6	Female	55	Primary HPT	Parathyroidectomy & biopsy normal gland	29.1	11.1	8.0
7	Female	59	Primary HPT	Parathyroidectomy & biopsy normal gland	27.1	15.7	13.0
8	Female	32	Hyperthyroidism	Thyroidectomy	26.6	28.2	12.7
9	Female	28	Hyperthyroidism	Thyroidectomy	46.7	19.2	11.8
10	Male	45	Hyperthyroidism	Thyroidectomy	58	69.0	26.2
11	Male	32	Hyperthyroidism	Thyroidectomy	37	69.0	26.2
12	Female	28	Goiter	Thyroidectomy	19.8	17.9	5.6

13	Female	39	Goiter	Thyroidectomy	38.2	26	13.0
14	Female	42	Goiter	Thyroidectomy	32.4	31.9	18.0
15	Female	46	Goiter & Primary HPT	Thyroidectomy & Parathyroidectomy & biopsy normal gland	48.9	45.4	35.1
16	Male	54	Thyroid cancer	Thyroidectomy	33.6	30.6	15.2
17	Female	49	Thyroid cancer	Thyroidectomy	32.3	18.1	15.4
18	Female	37	Thyroid cancer	Thyroidectomy	84.3	78.7	73.0
19	*Male*	*49*	*Thyroid cancer*	*Thyroidectomy*	*N/A*	*85.9*	*40.3*
20	Male	56	Thyroid cancer	Thyroidectomy	26.4	29.8	10.3
21	Male	48	Thyroid cancer	Thyroidectomy	10.8	7.6	6.7
22	Male	52	Thyroid cancer	Thyroidectomy	51.4	28.2	14.4
23	Female	38	Thyroid cancer	Thyroidectomy	40.9	17.8	12.0
24	Male	53	Thyroid cancer	Thyroidectomy	41.0	N/A	1.02
25	Male	49	Thyroid cancer	Thyroidectomy	134.7	N/A	2.5
26	Female	45	Thyroid cancer	Thyroidectomy	23	N/A	0.8
27	*Female*	*39*	*Thyroid cancer & Primary HPT*	*Thyroidectomy & parathyroidectomy & biopsy normal gland*	*N/A*	*2.2*	*1.4*
28	Female	46	Thyroid cancer & Primary HPT	Thyroidectomy & parathyroidectomy & biopsy normal gland	30.0	1.1	1.1
Mean (SD)		44.4 (8.9)			40.6 (26.5)	31.8 (22.3)	16.6 (15.4)
Range		28-60			10.8-134.7	1.1-85.9	1.1-73.0
HPT, hyperparathyroidism; N/A, data not available.							

The results of the study were as follows: The mean intensity signal of parathyroid glands was 40.6 ± 26.5; thyroid glands, 31.8 ± 22.3; and background, 16.6 ± 15.4. Parathyroid glands showed significantly higher fluorescence intensity on average compared with thyroid glands and background ($p < 0.0014$). However, in four out of 21 patients (19%) with available fluorescence values from normal parathyroid and thyroid tissue, there was higher average autofluorescence from the thyroid than parathyroid. Additionally, 13 glands in 28 patients were observed to be false positives. No hypocalcemia or other complications related to the surgery were reported.

STUDY 2: Falco *et al* 2017

The second study was designed to reproduce the findings of study 1, and to determine whether the use of the subject device could improve the number of parathyroid glands found during thyroid and parathyroid gland surgery. They prospectively included all patients undergoing thyroid and parathyroid surgery at a single institution between October 2015 and February 2016 (no overlap with study 1). The parathyroid glands were identified intraoperatively, first with direct visual inspection under white light, and then with autofluorescence using the sponsor device. Parathyroid adenomas were resected for histology. Normal glands were not resected for histology due to ethical concerns with removing normal gland tissue. Fluorescent intensity for parathyroid gland, thyroid gland, and background tissue was quantified from videos for each

patient using Image J software. Patient demographic and descriptive variables were extracted from patient charts.

The number of parathyroid glands identified with the device compared to with direct inspection was compared using a Wilcoxon Signed-Rank for paired samples. An ordered logit model was fit to the difference in the number of parathyroid glands visualized between the device and direct inspection and fixed for effects of other variables. The mean fluorescent intensities were compared using a linear mixed model, although how intensity was quantified is not mentioned.

Seventy-four patients were included in the study, with average age 48.4. Cohort description is available in Table 2.

Table 2 Cohort description

	N = 74
Diagnosis [*N* (%)]	
Thyroid Cancer	35 (47%)
Papillary	30 (85.5%)
Follicular	1 (3%)
Cancer + Primary HPT	3 (8.5%)
Not specified	1 (3%)
Goiter	22 (30%)
Goiter + Primary HPT	1 (1%)
Hyperthyroidism	3 (4%)
Primary HTP	13 (18%)
Age (years)	
Mean (SD)	48.4 (13.5)

HPT hyperparathyroidism, *SD* standard deviation, *n* sample size

The number of parathyroids visible with the device (NIRL) and direct inspection (WL) are available in Table 3.

Table 3 Number of parathyroid gland visualizations with NIRL and WL

	Mean (SD)	Median
Visualizations with WL	2.5 (0.8)	2
Visualizations with NIR	3.7 (0.7)	4
Difference NIRL–WL	1.2 (0.8)	1

WL white light, *NIRL* Near Infrared Light, *SD* Standard Deviation

The Relative intensity of autofluorescence of the surgical tissues is available in Table 4.

Table 4 Comparison of the fluorescent intensities of the different tissues

Comparison	Estimated Mean Difference (SD)	P Value
Parathyroids versus background	38.327 (2.6)	<0.0001
Thyroids versus background	13.051 (2.6)	<0.0001
Parathyroids versus thyroids	25.276 (2.6)	<0.0001

The authors of the study state that the number of parathyroid glands visualized with the device was significantly higher than with direct light, with a P value from Wilcoxon Signed-Rank test of < 0.0001. They further state that, in 86.5% (n=64) of patients, four parathyroid glands were visualized with the device, compared to 12.2% (n=9) under direct white light. However, because the device was used sequentially after direct inspection in all patients, by design, more parathyroid glands would likely be observed using the device than with direct inspection. Additionally, they do not state that glands identified as parathyroids during autofluorescence were ever verified to be parathyroid glands. They do not have any confirmation that the autofluorescent tissue is parathyroid gland, and do not provide results of histological assessment. It is not clear if some or many of these identified glands may represent false positives.

The authors then state that the intensity of auto-fluorescence is higher in parathyroid glands. They state that the mean fluorescence intensity for parathyroid glands was 47.6 (±26.9), thyroid glands was 22.2, and background was 9.1. No units are provided. They note that these differences are all significant with p value <0.0001.

They then note that no parathyroid auto transplantations were performed, and that no permanent hypocalcemia was observed in the study cohort at six months. There is no control comparison. They do not report a follow up rate among the cohort.

STUDY 3: Benmiloud *et al*

The third study aims to assess clinical endpoints in patients who are treated with the sponsor's device compared to multiple control groups. Because identification of all parathyroid glands during surgery is not considered mandatory, clinical outcomes are the ultimate important consideration for effectiveness for this device. There are four study groups. All patients underwent a total thyroidectomy for various indications, with completion thyroidectomy's, concurrent parathyroid pathology, and/or simultaneous lymph node dissections excluded. The study design is a before and after controlled study using the device with one surgeon (surgeon 1). The authors include an additional surgeon (surgeon 2) before and after group, with neither receiving the device, as a means of further control. Period 1 is defined as January 2015-January 2016, and period 2 is defined as February 2016 to September 2016. Surgeon 1 period 1 group did not receive the device and is labeled NIR- group. Surgeon 1 period 2 received the device and was labeled NIR+. Surgeon 2 period 1 and surgeon 2 period 2 groups were labeled control groups 1 and 2 respectively. Both surgeons operated out of the same institution. Surgeon one had five years of experience in the field, while surgeon 2 had twenty-five. The main outcomes assessed were postoperative hypocalcemia, parathyroid identification intra-operatively, parathyroid gland autotransplantation, and inadvertent parathyroid resection.

The control groups (NIR-, Control 1, Control 2) that did not receive intervention with the sponsor's device underwent operative removal of the thyroid gland with attempted preservation of parathyroid glands using standard visual evaluation alone. However, no explicit attempt was made to identify parathyroid glands during surgery. If parathyroid glands were impossible to preserve during the operation, they were diced and auto-transplanted into the ipsilateral sternocleidomastoid muscle.

In the treatment group (NIR+), a visual inspection of the thyroid gland was performed before any dissection of the gland from surrounding structures was performed. Before dissection of each lobe, the operating room lights were then turned off, and the sponsor device was used to attempt to locate potential parathyroid glands. Videos were taken using the device. Then the lobe dissection was performed, and potential parathyroid glands were "confirmed" or "disconfirmed" by detailed surgeon inspection. No tissue biopsies were performed.

The authors prospectively collected patient demographic data, as well as medically relevant history. For each surgery, the number of parathyroids observed by the surgeon, number of auto-transplanted parathyroids, duration of the operation, corrected calcium nadir on postoperative days one and two, treatment for hypocalcemia, duration of hypocalcemia, occurrence of other complications, number of inadvertently resected parathyroids, thyroid weight, and of the largest nodule, and definitive diagnosis were all recorded. Parathyroids were only recorded as observed if the surgeon had "no doubts" that the tissue was parathyroid. Postoperative hypocalcemia was defined as a corrected calcium (measured calcium mg/dL – 0.8*(albumin g/dL - 40)) less than 8 on postoperative days one or two. This definition of hypocalcemia was used as threshold for starting calcitriol. Calcium gluconate was injected if symptoms of hypocalcemia occurred. Postoperative hypocalcemia was considered permanent if it persisted past six months.

Statistical analysis was described by the authors as follows: "Continuous data was recorded as mean and standard deviation (SD), while categorical data was recorded as frequency (%). The Chi-square test was used to assess percentage comparisons (after verification of the use assumptions), and the Kruskal-Wallis test was used for mean comparisons. The post-hoc Tukey-type multiple comparison test for unpaired multiple groups was used to compare proportions in each pair of groups. Similarly, the Dunn's nonparametric comparison test was used for post hoc testing after the Kruskal-Wallis test for continuous data. The Kappa index was used to assess agreement between parathyroids visualized with the naked eye and parathyroids visualized using NIR light. Factors associated with hypocalcemia were assessed using multiple logistic regression. Univariate analysis for hypocalcemia was performed prior to multivariate analysis. Among the following variables (age, gender, BMI, initial diagnosis, preoperative calcium level, number of parathyroids seen by the naked eye, number of autotransplanted parathyroids, duration of the operation, hypocalcemia event, other complications, number of inadvertently resected parathyroids, thyroid weight, size of the largest nodule and definitive diagnosis), those with p value of less than 0.20 in univariate analysis were selected as potential covariates for multiple logistic regression analysis. There was no selection method applied in the multivariate model, all covariates had a p-value assessed. Correlation analysis was performed in order to detect significant collinearity between covariates. Odds ratios [95% confidence interval (CI)] for hypocalcemia were reported. All tests were assessed using a significant criterion of α=0.05."

The authors report 513 total patients with 93 in NIR+ group, 153 in NIR- group, 180 in Control 1 group, and 87 in control 2 group. They report differing age and body mass index among the groups by global analysis. However, they state that there were no significant differences among groups by multiple comparison pairwise testing, although the data is not presented. 100% follow up rate is reported. The operative duration was shorter in control group 1 compared to NIR+ or NIR- with a provided p value of <0.0001. The authors report that for the same surgeon (surgeon 1) there was no difference in operative time with the use of the device (NIR+ compared to NIR-). They report no significant difference in weight of specimens between NIR+ and NIR-.

Related to clinical outcomes, the authors report reduced incidence of postoperative transient (<6 months) hypocalcemia in the NIR+ group compared to all other groups with a significant Tukey type test of < 0.05. (NIR+: 5.3%, NIR-: 20.9%, Control 1: 16.1%, Control 2: 19.5%). They further state a 2/153 (1.3%) rate of permanent (>6 months) hypocalcemia in the NIR- group, but do not state the rate in the NIR+ group.

In this study, parathyroid identification rates were higher in the NIR+ group compared to NIR- group with significant Dunn's test p<0.05 (76.3% vs. 65.7% of theoretically present parathyroids). The authors then state that "245/320 (68%)" of the theoretically present parathyroids in the NIR+ group were identified with the sponsor device prior to visualization with white light. This represents a typo – there were three patients with missing data, so the theoretically present parathyroids would be 360 (90*4). The percent provided is accurate (245/360 = 68%). However, study design dictated that the surgeon use the device prior to initiating any dissection in the area of parathyroid tissue, so initial observation with the device is relatively expected. The authors further state that 100% of parathyroid glands identified by the device were confirmed to be parathyroids by visual inspection. Patient level data is not available to corroborate this claim. It does vary significantly from the results obtained from other groups using this device in which several false positives were observed (Falco 2016, 13 glands/28 patients). There was no histology confirmation in this study.

The authors then state that parathyroid autotransplantation rates were significantly reduced in the NIR+ group compared to all other groups with a p value of 0.0034 by Dunn's multiple comparison pairwise test (NIR+: 2.1%, NIR-: 15.0%, Control 1: 16.7%, Control 2: 16.1%). These baseline auto-transplantation rates are significantly higher than in Study 1 and Study 2, in which 100 patients received surgery without autotransplantation. The rate of inadvertent parathyroid resection also occurred less frequently in the NIR+ group (1.1%) compared to the other groups (NIR-: 7.2%, Control 1: 8%, Control 2: 6.9%), although statistical significance (p< 0.05) was only achieved compared to control group 1 with Dunn's testing.

The authors then note that postoperative hypocalcemia appeared to be more common among patients with three or more parathyroid glands identified, compared to patients with less than three identified (Table 5)

Table 5. Hypocalcemia rates depending on number of PG identified during surgery

Study Group	**Hypocalcemia rate if 3 or more PG identified (% of patients)**	**Hypocalcemia rate if less than 3**	**P Value**

		PG identified (% of patients)	
NIR+	6%	4%	1.00
NIR-	26%	15%	0.11
Control 1	22%	10%	0.045
Control 2	28%	3%	0.0046

PG, Parathyroid gland

These data suggest that inadvertent resection of unidentified parathyroid glands is not responsible for postoperative hypocalcemia, but rather that traumatic insult or devascularization of identified parathyroid glands during dissection is responsible for inadequate parathyroid function after surgery. Because the sponsor device is associated with increased number of parathyroid glands identified, the advantages of the sponsor device, according to this study, are a reduction in hypocalcemia among patients with three or more identified glands. This may suggest that surgical identification of glands is a more traumatic process for parathyroid tissue without the use of the device, or that attempts at parathyroid gland identification via surgical dissection is not a beneficial approach to these surgeries.

Finally, the authors report that patients in whom two parathyroids were autotransplanted were at relatively higher risk of hypocalcemia. (OR 15.15, p =0.03)

Overall the study appears to be appropriately controlled with a single surgeon treating two groups (one using the device and one not). Ideally these groups would have been assigned by randomization rather than a before-and-after design. However, the authors attempt to control for before-and-after effects by incorporating control groups consisting of a second surgeon's patients during the same time periods. Additionally, this is a single institution study and the generalizability of the results is unclear.

The authors examine relevant clinical endpoints and determine a decreased rate of auto-transplantation and transient postoperative hypocalcemia among patients in the device group. However, they do not state rates of permanent hypocalcemia (>6 months) for comparison. These significant reductions are primarily observed in patients with more than three identified parathyroid glands. The authors posit that the use of the device enables earlier identification of parathyroid glands and enables surgeons to avoid injuring the parathyroid glands or their vascular supply. There was no observed increase in operative time with the use of the device, which the authors attribute to expedited dissection due to earlier identification of the parathyroid glands. This study offers support for the use of the device with observed improvement in clinically relevant outcomes, which are the most important consideration in effectiveness of the device.

STUDY 4: Kahramangil *et al*

The purpose of the fourth study was to compare the rate of detection of parathyroid glands with and without the sponsor device among patients undergoing thyroid and parathyroid surgery. This was a retrospective review of 210 prospectively-enrolled patients from three centers. One of the study sites the same hospital as Study 3 above. The authors of Study 4 do not provide the

years for data acquisition, and it cannot be determined if this study includes duplicate patients, although the included surgeries were broader in Study 4 (*ie* parathyroid and thyroid in study 4, just thyroid surgery in study 3). Patients were used as their own control, with the device used in every patient. The patient demographics is available in the table:

TABLE 6 Description of study patients

Parameter	All patients (n = 210)	Center 1 (n = 70)	Center 2 (n = 70)	Center 3 (n = 70)	p value
Age, years [mean (SD)]	53.1	53.0 (12.0)	51.6 (15.4)	54.8 (14.2)	0.31
BMI, kg/m^2 [mean (SD)]	26.5 (6.5)	21.4 (1.8)	27.0 (5.4)	31.3 (6.9)	<0.001
Sex [n, (%)]					0.26
Female	183 (87)	62 (89)	61 (87)	60 (86)	
Male	27 (13)	8 (11)	9 (13)	10 (14)	
Pathology [n, (%)]					<0.001
Benign thyroid nodule/MNG	83 (40)	16 (23)	37 (53)	30 (43)	
Hyperthyroidism	10 (4.8)	1 (1.4)	4 (5.7)	5 (7)	
Thyroid cancer	43 (20)	16 (23)	19 (27)	8 (11)	
Primary hyperparathyroidism	74 (35)	37 (53)	10 (14)	27 (39)	
Surgery [n, (%)]					<0.001
Total thyroidectomy	95 (45)	33 (47)	22 (31)	40 (57)	
Thyroid lobectomy	41 (20)	0 (0)	38 (54)	3 (4.3)	
Parathyroidectomy	74 (35)	37 (53)	10 (14)	27 (39)	

MNG multinodular goiter, *BMI* body mass index, *SD* standard deviation

Similar to Study 3, surgery was conducted per standard of care until the thyroid gland was encountered. At this time, the surgeon attempted to locate as many parathyroid glands as possible in standard room light without further dissection. The operating room lights were then turned off, and the sponsor device was used to identify parathyroid glands by autofluorescence. Parathyroids were confirmed with either frozen section histology, or if they met the following three visual criteria: 1) yellow brown color, 2) a discrete shape (typically ovoid) in contrast to amorphous fat, and 3) distinct vasculature seen along its substance. It was then recorded how many parathyroid glands were first detected with direct inspection, and how many were first detected with the autofluorescence. All clinical and intra-operative parameters were compared using Kruskal-Wallis and Chi square testing.

A total of 594 parathyroid glands were located at the three centers. The reported overall sensitivity for the device to detect parathyroid glands was 98%. However, a sensitivity value cannot truly be reported without a gold standard confirmatory test to determine the true number of parathyroid glands present in each patient. Of the parathyroid glands ultimately identified, 272 (46%) were not identified on the initial visual inspection. Further, the authors report that, in 161 (77%) patients, at least one parathyroid gland was detected with autofluorescence without

further dissection after visual inspection. Lastly, they report that a median of one parathyroid gland per patient was detected by autofluorescence before being identified with direct inspection.

STUDY 5: De Leeuw *et al*

The purpose of the fifth study was to calculate a sensitivity and specificity for the Fluoptics system for detecting parathyroid tissue. The study was a prospective single-center investigation including all patients over eighteen years of age undergoing total or partial thyroidectomy, or parathyroid surgery, between December 2014 and March 2015. The surgery was performed with the surgeon using the Fluoptics system to help identify parathyroid glands intra-operatively. The patient specimens were then removed per standard of care for each patient disease process. The removed specimen was then evaluated on a back table with the Fluoptics system *ex vivo* by a blinded investigator labeled as a "scientist". The scientist distinction was intended to imply that the investigator was not a clinician and was therefore unfamiliar with typical anatomy or gland appearance. The scientist would decide, based on the Fluoptics autofluorescence, whether the resected specimen contained parathyroid tissue, and where the parathyroid tissue was. However, it is unclear how the scientist could be informed of the purpose of the experiment without a basic understanding of the difference between the tissues being identified. It is possible that the scientist unintentionally used visual inspection to bias his decisions.

Portions of the specimens that were identified by the scientist as positive for parathyroid or negative for parathyroid were then sent for pathology. The process of selecting specific areas of tissue as positive for parathyroid gland is understood. However, how the specific areas considered to be negative were chosen for inclusion is not clearly explained. For example, if a large thyroid gland with some adjacent tissue was removed *en bloc*, then there should theoretically be numerous areas (*ie* the majority of the relatively large specimen) that are "not parathyroid gland". It may have been the case that specific areas with highest autofluorescence and lowest were chosen, and any area with intermediate autofluorescence was avoided and never evaluated, which may falsely enhance the accuracy of the device. The selected areas were then processed by conventional histology (Hemotoxylin Eosin Saffron staining) and the tissue was identified by a blinded pathologist. The histology results were compared to the scientist determination using Fluoptics, and a sensitivity and specificity was calculated.

In total, 28 specimens were included from 35 patients. It is unclear why seven patients did not have specimens. From the 28 specimens, 32 areas were identified for histology (19 considered positive and 13 considered negative). There were 16 true positives, 3 false positives, 12 true negatives, and 1 false negative. The authors then calculate a sensitivity of 94.1% and a specificity of 80%. Of note, all 3 of the false positives were noted to be colloid nodules on histology. The small study size and potential biases limit the utility of these calculated values. This study reiterates the idea that most parathyroid glands autofluoresce, but autofluorescence is not unique to parathyroid tissues.

Clinical Conclusions:

The five provided studies consistently demonstrate that parathyroid glands do autofluoresce with an average intensity that is typically greater than nearby and surrounding tissues. Further, these

clinical reports suggest improved parathyroid gland localization with the use of autofluorescence. In general, the property of autofluorescence appears to be highly consistent for parathyroid glands (98% of ultimately identified parathyroid glands autofluoresced in study 4). Additionally, autofluorescence appears to allow detection of parathyroid glands earlier in the surgical procedure. Study 3 provides reasonable affirmation that the earlier detection of parathyroid glands can result in reduced postoperative hypocalcemia, inadvertent resection, and autotransplantation. While the authors of Study 3 do not report long term postoperative hypocalcemia rates in groups other than the NIR- control group, a reduction in transient postoperative hypocalcemia represents a clinical improvement for patients.

However, it is also noted that thyroid gland tissue, which sits immediately adjacent to parathyroid glands in many cases, also autofluoresces in the spectrum visualized by the device. Detailed visualization of autofluorescent tissue did not always confirm identity as a parathyroid gland (13 autofluorescent "glands"/28 patients in Study 1 were ultimately realized to not be parathyroid), and the representative images provided by the sponsors show multiple examples of false positives, although false positives are reported to have never occurred in 93 patients in the NIR+ group from Study 3. Current techniques for parathyroid identification include: visual identification of parathyroid gland tissue, intra-operative parathyroid hormone measurement, and frozen histology. Histological confirmation, which provides definitive parathyroid identification, was not available in the majority of the patients included in the studies. Therefore, no true sensitivity and specificity can be calculated to support the performance of this device as a diagnostic modality. No clinical endpoints were examined in any of the studies related to false positives (*i.e.,* accidental preservation of thyroid tissue falsely identified as parathyroid)

Ultimately, it can be accepted that the sponsor device has clinical applicability in assisting with the identification of parathyroid glands during thyroid or parathyroid gland surgery but cannot be used as a reliable indicator for confirmation of a structure as parathyroid gland, or for concluding the absence of more unidentified parathyroid glands. Therefore, the presented clinical data support the use of the sponsor device for adjunct purposes for the stated indication for use.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The labeling includes a Fluobeam® 800 imaging device system instruction manual, Fluosoft manual (software), Fluobeam® Clinical System Quick Start guide, a Fluobeam Refill Kit Instructions for Use manual and 3 manuals for each additional software module (time lapse mode, perfusion mode, low signals mode).

The Fluobeam® 800 imaging device system instruction manual includes a description of the device with technical parameters, and instructions for use for the device. The instruction manual also includes relevant findings from the supporting clinical studies to demonstrate the detection performance characteristics of the device when used as intended. Finally, the document also states the shelf life for (b) (4) components.

Together these documents summarize the steps required to use the device as well as necessary measures to maintain sterility (with use of recommended disposable sterile sheath) and clean or disinfect the device.

The user manual includes a warning that the device has not been evaluated in providing any diagnosis for parathyroid conditions including adenoma, carcinoma, and hyperplasia or differentiation of normal from abnormal or pathologic parathyroid glands. Additional warning statements include that the clinical outcomes performance data was limited to total thyroidectomy patients and outcomes in patients with parathyroid disease (i.e., adenoma) is not clear. Furthermore, caution must be exercised to evaluate autofluorescent tissue to confirm identity of the parathyroid gland because thyroid colloid nodules and other tissues may have enhanced autofluorescence in some patients. Lastly, there is a warning stating that the performance of the device has not been definitively established in disease states such as: secondary hyperparathyroidism, tertiary hyperparathyroidism, malignant parathyroid disease, or other circumstances when prophylactic thyroidectomies are performed in individuals at high-risk for certain diseases such as MEN2A.

Labeling for this device is in accordance with the special controls listed below.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of autofluorescence detection and imaging devices for surgical and dermatological use and the measures necessary to mitigate these risks.

Table 6 – Identified Risks to Health and Mitigation Measures

Identified Risks to Health	**Mitigation Measures**
Electrical, mechanical, or thermal hazards leading to user injury or discomfort	Electromagnetic compatibility testing Electrical, mechanical and thermal safety testing Software verification, validation, and hazard analysis Labeling
Tissue, skin burn, or eye injury due to light and laser exposure	Light and laser exposure safety testing Labeling
Infection and cross-contamination	Sterilization validation Shelf life testing Labeling
Adverse tissue reaction	Biocompatibility evaluation
False identification of target tissues or structures leading to errors in patient management (e.g., removal of healthy tissue or not removing diseased tissue)	In vivo performance testing Software verification, validation, and hazard analysis Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the autofluorescence detection device for general surgery and dermatological use is subject to the following special controls:

(1) In vivo testing under anticipated conditions of use must characterize the ability of the device to detect autofluorescent signals from tissues or structures consistent with the indications for use.
(2) The patient-contacting components of the device must be demonstrated to be biocompatible.
(3) Performance testing must demonstrate the electromagnetic compatibility and electrical, mechanical and thermal safety of the device.
(4) Software verification, validation, and hazard analysis must be performed.
(5) Performance testing must demonstrate the sterility of patient-contacting components of the device.
(6) Performance testing must support the shelf life of device components provided sterile by demonstrating continued sterility and package integrity over the labeled shelf life.
(7) Performance testing must demonstrate laser and light safety for eye, tissue and skin.
(8) Labeling must include the following:
    (i) Instructions for use;
    (ii) The detection performance characteristics of the device when used as intended; and
    (iii) A shelf life for any sterile components.

BENEFIT-RISK DETERMINATION

Risks:
The risks of the device are based on data collected in clinical studies described above.

No device or procedure related adverse events (AEs), serious adverse events (SAEs), or unanticipated adverse device effects (UADEs) were reported in the clinical studies provided by the sponsor. Not all end users (non-endocrine surgeon-specialists) were tested in these studies and no additional human factors testing was performed. The main probable risks of the device are false diagnoses (*i.e.,* false positive and false negative). A true histologically confirmed sensitivity, specificity, positive predictive value, and negative predictive value cannot be calculated due to absence of histological confirmation and missing patient level data for most studies. The patient outcomes that could be potentially adversely affected by false negatives (erroneous removal/injury of parathyroid gland thought to be not parathyroid gland) or false positives (erroneous preservation of non-parathyroid gland tissue thought to be parathyroid gland) are the following:

- Erroneous removal of parathyroid tissue during surgical procedures (4-20%)
- Erroneous injury to parathyroid tissue during surgical procedures
- Hypocalcemia(hypoparathyroidism) after thyroid/parathyroid surgery (20-30%)
- Increased operative time due to prolonged identification/confirmation of parathyroid glands (use of frozen histology or PTH blood testing)

However, the clinical studies have demonstrated a reasonable assurance that false negative results are not frequent (98% reported sensitivity in Study 4 compared to surgeon expertise confirmation), and clinical endpoints are not affected by accidental mis-identification of true parathyroid tissue (reduced inadvertent parathyroid resection, auto-transplantation, and postoperative hypocalcemia in Study 3). False positive results represent a more frequent occurrence (13 glands in 28 patients in Study 1), and these clinical endpoints were not directly addressed in any of the studies. Therefore, there is moderate uncertainty of the risk of false diagnoses using the device. This risk can be mitigated by using the subject device as an adjunct to current techniques of parathyroid identification (visual inspection, frozen section histology, and intra-operative parathyroid blood level measurements). Adjunctive medical devices are defined as: Therapeutic or diagnostic products used in conjunction with but not required by another medical assessment or intervention and not intended to be a sole therapy or stand-alone diagnostic. The Fluobeam device is indicated as an adjunct to assist with initial localization of possible parathyroid tissue but not to be used for confirmation of tissue as parathyroid or for concluding an absence of further parathyroid tissue.

An additional risk is increased operative time by using the device. However, the device is intended for single or brief episodic use during a procedure, and study 3 reported no significant change in operative time with the use of the device.

Benefits:

The benefits of the device are supported by clinical studies. Because identifying all parathyroid glands is not mandatory for all parathyroid and thyroid surgery, the endpoints of highest importance are postoperative clinical outcomes. In Study 3 the sponsors have provided evidence that their device can reduce transient postoperative hypocalcemia, inadvertent parathyroid resection, and parathyroid auto-transplantation. The robustness of this study is modest because this study is limited to single surgeon (with control surgeon not using the device), single institution, and only total thyroidectomy patients. However, erroneous removal of parathyroid tissue during surgical procedures is often reported as 4-20% and risk of hypocalcemia after thyroid/parathyroid surgery is often reported as 20-30%. A reduction to 1.1% and 5.3% respectively represents a benefit for this patient population.

The remainder of the supporting clinical studies rely on identification of parathyroid glands without histologic confirmation, and present significantly weaker support for the benefits of the sponsor device. A sensitivity, specificity, positive predictive value, and negative predictive value cannot be calculated and, therefore, the device is intended for adjunct use.

Ultimately, the benefits of reduced postoperative adverse outcomes after thyroid surgery outweigh the risks related to potential false positives or negatives when the risks are mitigated by the use of the device as an adjunct tool in addition to standard methods to identify the parathyroid glands.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> The Fluoptics Fluobeam® Imaging system is intended to provide real-time near infrared (NIR) fluorescence imaging of tissue during surgical procedures. The Fluoptics Fluobeam® Imaging system is indicated for use in capturing and viewing fluorescent images for the visual assessment of blood flow in adults as an adjunctive method for the evaluation of tissue perfusion, perfused organs, and related tissue-transfer circulation in tissue and free flaps used in plastic, micro- and reconstructive and organ transplant surgeries.
>
> The Fluoptics Fluobeam® Imaging system can also be used to assist in the imaging of parathyroid glands and can be used as an adjunctive method to assist in the location of parathyroid glands due to the auto-fluorescence of this tissue.
>
> Use of the Fluobeam® device is intended to assist, not replace, experienced visual assessment, and biopsy with conventional histopathological confirmation per standards of care. The system is not to be used to confirm the absence of parathyroid tissue or glands and is only to be used to assist in locating of visually identified glands/tissue.

The probable benefits outweigh the probable risks for the Fluoptics Fluobeam 800 Clinical Imaging Device. The device provides benefits and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the Fluobeam 800 Clinic Imaging Device used with Fluocase 800 Control System is granted and the device is classified as follows:

> Product Code: QDG
> Device Type: Autofluorescence detection device for general surgery and dermatological use
> Class: II
> Regulation Number: 21 CFR 878.4550

REFERENCES

1. Falco J, Dip F., Quadri, P., Fuente M., Rosenthal R. Cutting Edge in Thyroid Surgery: Autofluorescence of Parathyroid Glands. *J Am Coll Surg.* 2016 Apr; 223(2): 374-380.
2. Falco J, Dip F., Quadri P., de La Fuente M., Prunello M., Rosenthal R.. Increased Identification of Parathyroid Glands using Near Infrared Light during Thyroid and Parathyroid Surgery. *Surg. Endosc.* 2017 Mar; 31:3737-3742.
3. Benmiloud F., Rebaudet S., Varoquax A., Penaranda G., Bannier M., Denizot A., Impact of Autofluorescence-based Identification of Parathyroids During Total Thyroidectomy on

Postoperative Hypocalcemia: a Before and After Controlled Study. *Surg.* 2018 Jan; 163(1):23-30.
4. Kahramangil B., Dip F., Benmiloud F., Falco J., de La Fuente M., Verna S., Rosenthal R., Berber E. Detection of Parathyroid Autofluorescence Using Near-Infrared Imaging: A Multicenter Analysis of Concordance Between Different Surgeons. *Ann Surg. Oncol.* 2018 Apr; 25(4): 857-962.
5. De Leeuw F., Breuskin I., Abbaci M., Casiraghi O., Mirghani H., Lakhdar A.B., Laplace-Buillhe C., Hartl D. Intraoperative Near-infrared Imaging for Parathyroid Gland Identification by Auto-fluorescence: A Feasibility Study. *W. J. Surg.* 2016 May;40(9); 2131-2138.