

**DE NOVO CLASSIFICATION REQUEST FOR
PILLCAM COLON 2 CAPSULE ENDOSCOPY SYSTEM**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Colon Capsule Imaging System: A prescription, single-use ingestible capsule designed to acquire video images during natural propulsion through the digestive system. It is specifically designed to visualize the colon for the detection of polyps. It is intended for use only in patients who had an incomplete optical colonoscopy with adequate preparation, and a complete evaluation of the colon was not technically possible.

NEW REGULATION NUMBER: 21 CFR 876.1330

CLASSIFICATION: II

PRODUCT CODE: PGA

BACKGROUND

DEVICE NAME: PillCam COLON 2 Capsule Endoscopy System

SUBMISSION NUMBER: K123666

DATE OF DE NOVO: NOVEMBER 21, 2012

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REQUESTER'S RECOMMENDED CLASSIFICATION: II

INDICATIONS FOR USE

The PillCam COLON 2 Capsule Endoscopy System is indicated to provide visualization of the colon. It is intended to be used for detection of colon polyps in patients after an incomplete optical colonoscopy with adequate preparation, and a complete evaluation of the colon was not technically possible.

LIMITATIONS

The sale, distribution, and use of the device are restricted to prescription use in accordance with 21 CFR 801.109.

Limitations on device use are also achieved through the following statements included in the Instructions for Use Manual:

Colon capsule endoscopy (CCE) is not a treatment. The device is intended to provide visualization of the colon for detection of polyps in patients after an incomplete optical colonoscopy with adequate preparation, and a complete evaluation of the colon was not technically possible. Common causes for failure to complete the colonoscopy procedure include looping and anatomic variations resulting in tortuosity, angulation, redundancy and decreased colonic mobility. The value of CCE in this limited population is not known, as the clinical trial was conducted in “normal subject” subjects who were able to undergo optical colonoscopy.

The primary risks of the Given PillCam Colon 2 Capsule Endoscopy System are the possibilities of false positive and false negative results. Patients with a false negative CCE result would not be identified as having a colon polyp or cancer, and would have possible histologic progression of the lesion or the development of a cancer would be possible during the surveillance period. In addition, patients with a false positive CCE result may be advised to undergo unnecessary additional evaluation, although it is likely that CT Colonography (CTC) would be utilized in these cases for confirmation of a lesion.

Undergoing an MRI while the PillCam video capsule is inside the patient’s body may cause damage to the intestinal tract or abdominal cavity. If the patient did not positively verify the excretion of the PillCam capsule from the body, contact the physician for evaluation and possible abdominal X-ray before undergoing an MRI examination.

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

DEVICE DESCRIPTION

The PillCam® COLON 2 capsule endoscopy system includes a single-use ingestible capsule designed to acquire video images during natural propulsion through the digestive system. It is specifically designed to visualize the complex anatomy of the colon. The PillCam COLON 2 capsule is designed to withstand the mechanical forces and chemical environment of the digestive system.

Technological Characteristics

The PillCam® COLON 2 capsule endoscopy system is comprised of four main subsystems; (1) the ingestible PillCam COLON 2 capsule, (2) the DR 3 PillCam® Recorder, (3) the RAPID® software, and (4) the Given® Workstation.

1. Ingestible PillCam COLON 2 Capsule

The PillCam COLON 2 video capsule (Figure 1 and Table 1) is a single-patient use, ingestible capsule designed to acquire video images during natural propulsion through the digestive system. The basic characteristics and components of the PillCam COLON 2 capsule are similar to the Small Bowel (PillCam SB) and Esophagus (PillCam ESO) capsules. However the software of the PillCam Colon 2 Capsule Endoscopy System is designed for the detection of polyps. The software also adjusts the time the capsule is on to preserve battery life during the transit through the small bowel.

The capsule consists of the following main components:

1. Capsule envelope (case and 2 domes)
2. 2 optical heads
3. 2 Complementary metal oxide semiconductor (CMOS) based Imagers
4. 8 Light Emitting Diodes (LEDs)
5. Application Specific Integrated Circuit (ASIC) Transmitter
6. Full Flex Printed Circuit Board (PCB)
7. Battery pack

The capsule is swallowed by the patient and turns off while it travels through the stomach and small bowel. It then turns on again and begins recording images of the distal small bowel and colon. This action is accomplished by an image processing algorithm which is designed to detect the capsule transit to small bowel. The frame rate increases with more rapid movement and slows while movement is slower.

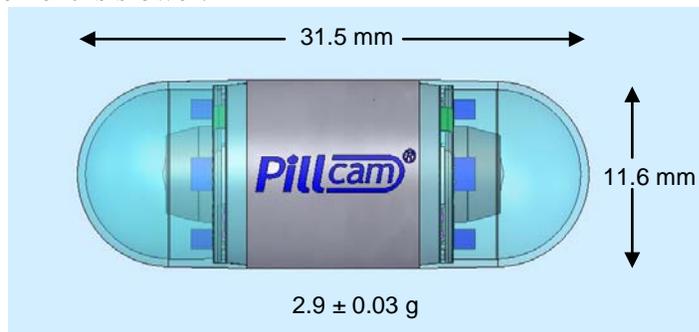


Figure 1: PillCam Colon 2 capsule

Table 1: PillCam Colon 2 Capsule, Basic Specifications

PillCam COLON 2 Capsules			
Physical	Dimensions:	Length:	31.5 mm \pm 5%
		Diameter:	11.6 mm \pm 5%
		Weight:	2.9 gr \pm 5%
	Material:	Biocompatible plastic	
Optical	Illumination:	4 white light emitting diodes for each head	
	# of imaging heads	2	
	Effective Visibility Distance:	0-30 mm	
Operational	Frame Rate:	Up to 35 Frames per Second per head	
	Operating Time:	10 hours	
	Chemical Safety:	Resistant to dissolution in pH=2 to pH=8	
	Battery Type:	Silver Oxide batteries	
	Operating Temperature:	20-40°C	
	Storage Temperature:	0-30°C	

2. Data Recorder 3 (DR3) PillCam Recorder

The DR 3 PillCam Recorder (Figure 2) is an external receiving/recording unit worn by the patient that receives and stores the acquired images from the capsule. The recorder supports patient/physician real time alerts for different aspects of the procedure such as the time for additional laxative intake and the time for procedure termination. The alert is done by (1) vibration on the sensor array, (2) visual indication on the LCD screen, and/or (3) audio indication. The DR 3 consists of the following main components:

1. Dual core CPU
2. Storage – Removable Secure Digital High Capacity (SDHC) card
3. Battery (Internal, Rechargeable, Li-Ion)
4. LCD screen with navigation keys
5. Sensor array to supports uplink channel
6. Sensor loop to support down link channel
7. Cradle with Li-Ion battery charger and status indicators



Figure 2: DR 3 PillCam Recorder

3. RAPID Software

The RAPID software is proprietary software that supports the capsule endoscopy examination in all of its phases: Patient check-in, PillCam Recorder initialization, copying data from the PillCam Recorder, video creation, viewing of the RAPID video, and generation of a Capsule Endoscopy Report. The software also includes in-service training videos, and patient instruction forms that may be printed.

4. Given Workstation and other accessories

The Workstation is a modified standard personal computer that is the operational platform for the RAPID software. Other accessories include a flat panel LCD monitor, a high-capacity mass storage device, and a high-capacity USB portable storage device.

Principles of operation

The PillCam COLON 2 capsule endoscopy system acquires video images of the colon during natural propulsion through the digestive system. Figure 3 illustrates the data flow from the PillCam COLON 2 capsule through the antennas of the Sensor Array and PillCam Recorder to the workstation that utilizes the RAPID software to output an image of the colon.



Figure 3: Data flow of Given PillCam endoscopy system

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The patient-contacting components of the PillCam COLON 2 capsule were evaluated with respect to their intended use per ISO 10993-1:2003. Testing was performed on finished devices. Below is a table of all patient contacting and non-contacting materials (Table 2), as well as a summary of the biocompatibility tests conducted, and the results.

TABLE 2: PILLCAM COLON 2 CAPSULE MATERIAL LIST

No.	Name	Raw material	Body contact
1	Optical dome	Polycarbonate material	Surface device contacting the mucosal membrane for prolonged duration (>24 hours to 30 days)
2	Capsule case	Polycarbonate material	
3	Optical head	General electric component	No body contact
4	LED	General electric component	
5	CMOS image sensor	General electric component	
6	Printed circuit	General electric component	
7	MEMS magnetic switch	General electric component	
8	Battery	General electric component	
9	ASIC/receiver - transmitter	General electric component	
10	Receiving antenna (inductor)	General electric component	

The PillCam COLON 2 capsule was evaluated for cytotoxicity (ISO 10993-5), sensitization (ISO 10993-10), and irritation or intracutaneous reactivity (ISO 10993-11). The device was shown to be biocompatible per ISO 10993-1:2003.

- Cytotoxicity**
 Cytotoxicity testing was performed in L-929, mouse fibroblast cells and 5% serum supplemented media with 2% antibiotics. The three samples tested all demonstrated a cytotoxicity grade of zero.
- Sensitization**
 Tests performed in mice (strain CBA/J). The test substance was regarded as a skin sensitizer if the Stimulation Index (SI) for the test group was greater than 3.0. The saline and DMSO test extracts had an SI of < 3 and therefore met the acceptance criterion to pass
- Irritation or Intracutananeous Reactivity**
 Test extracts were prepared and agitated in 0.9% sodium chloride USP solution (SC), or sesame oil (SO). Rabbits were injected intracutaneously into 5 separate sites on the left side of the back with a 0.2 ml dosage of the test extract. The primary irritation score in SC and SO treated rabbits was 0.0 and 0.4 (negligible), respectively.

SHELF LIFE/STERILITY

The PillCam COLON 2 capsule is not provided sterile, and sterilization for this use is not necessary because the device is not being used in a sterile environment.

The shelf-life of the device is determined by battery performance and the mechanical integrity of the capsule. Taking into consideration factors such as the specified battery capacity, battery self-discharge, the capsule OFF current monthly consumption, and the capsule working time, the calculated capsule shelf-life was determined to be 12 months when stored at 40°C.

The firm also provided real-time aging data obtained from the small bowel capsule (PillCam SB2 Capsule), in support of the 12 month shelf life. This documentation is acceptable since the PillCam SB2 and PillCam COLON 2 capsules are composed of the same materials.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

Test reports and labeling were provided demonstrating the device’s compliance with the standards listed in Table 3 below.

TABLE 3: ELECTRICAL AND ELECTRICAL STANDARDS MET

Capsule:

STANDARD NO.	STANDARD NAME	REQUIREMENT	RESULT
IEC 60601-2-18:2009	Particular requirements for the basic safety and essential performance of endoscopic equipment	All requirements were met	Pass

IEC 60601-1:2005/ (R) 2012 and CI: 2999/(R) 2012	Medical Electrical Equipment- Part 1: General Requirements for Safety and Essential Performance	All requirements were met	Pass
IEC 60601-1-2:2007	Medical Electrical Equipment- Part 1-2: General Requirements for Safety – Collateral Standard: Electromagnetic Compatibility Requirements	Radiated RF emissions, Class B	Pass
		Immunity to electrostatic discharge (ESD)	Pass
		Radiated immunity to radio frequency electromagnetic field	Pass
		Radiated immunity to power frequency magnetic field, 50/60 Hz	Pass
		Effective radiated power	Pass
		Transient power	Pass
		Range of modulation bandwidth	Pass
		Radiated	Pass
FCC CFR 47Part 15 Subpart C	Radio Frequency Devices – Intentional radiators	Fundamental radiated emissions	Pass
		Unwanted radiated emissions	Pass
FCC CFR 47Part 15 Subpart B	Radio Frequency Devices – Unintentional radiators	Radiated emissions, Class B	Pass
EN 300 220-2 V.2.4.1:2012	Electromagnetic compatibility and Radio spectrum Matters (ERM); Short Range Devices (SRD); Radio equipment to be used in the 25 MHz to 1,000 MHz frequency range with power levels ranging up to 500 mW; Part 2: Harmonized EN covering essential requirements under article 3.2 of the R&TTE Directive	Frequency error	Pass
		Effective radiated power	Pass
		Transient power	Pass
		Range of Modulation bandwidth	Pass
		Radiated Spurious emissions	Pass
		Frequency stability under low voltage (wide band transmitter)	Pass
		Duty cycle	Pass
EN 300 330-2 V1.5.1:2010	Electromagnetic compatibility and Radio spectrum Matters (ERM); Short Range Devices (SRD); Radio equipment in the frequency range 9 kHz to 25 MHz and inductive loop systems in the frequency	Hi-field (radiated), product	Pass
		Receiver spurious radiation below 30MHz	Pass

	range 9 kHz to 30 MHz; Part 2: Harmonized EN covering the essential requirements of article 3.2 of the R&TTE Directive	
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DR 3:

STANDARD NO.	STANDARD NAME	REQUIREMENT	RESULT
FCC CFR 47Part 15 Subpart C	Radio Frequency Devices – Intentional radiators	In band radiated emissions	Pass
		Out of band radiated emissions	Pass
		Frequency Stability	Pass
		Occupied Bandwidth	Pass
		Antenna requirements	Pass
FCC CFR 47Part 15 Subpart B	Radio Frequency Devices – Unintentional radiators	Radiated emissions, Class B	Pass
EN 300 220-2 V.2.4.1:2012	Electromagnetic compatibility and Radio spectrum Matters (ERM); Short Range Devices (SRD); Radio equipment to be used in the 25 MHz to 1,000 MHz frequency range with power levels ranging up to 500 mW; Part 2: Harmonized EN covering essential requirements under article 3.2 of the R&TTE Directive	Receiver Spurious emissions radiated	Pass
EN 300 330-2 V1.5.1:2010	Electromagnetic compatibility and Radio spectrum Matters (ERM); Short Range Devices (SRD); Radio equipment in the frequency range 9 kHz to 25 MHz and inductive loop systems in the frequency range 9 kHz to 30 MHz; Part 2: Harmonized EN covering the essential requirements of article 3.2 of the R&TTE Directive	Hi field (radiated), Product Class1	Pass
		Permitted range of operation frequencies	Pass
		Permitted frequency range of modulation bandwidth	Pass
		Radiated field strength	Pass
		Effective radiated power	Pass

SOFTWARE

The Agency considers capsule imaging systems to be of a moderate level of concern (LOC) because a malfunction of, or a latent design flaw in the software device could, if relied upon, lead to an erroneous diagnosis or a delay in delivery of appropriate medical

care, which is considered at least a minor injury.

All the elements of software information corresponding to moderate LOC devices as outlined in FDA's *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (May 11, 2005) has been provided. The sponsor provided adequate documentation describing the software development program. In addition, the sponsor provided documentation that they performed a hazard analysis from both the patient's and user's standpoint, addressed those hazards, and carried out an appropriate validation process. The verification and validation testing documentation provided an acceptable description of the validation and verification activities at the unit, integration and system level(s), which included system level test protocols, including the pass/fail criteria, and the results of these activities. In addition, the sponsor provided a description of the cybersecurity issues involved in the control and use of the device, and the mitigation of the risks arising therefrom.

Overall, the software documentation included in the *de novo* request is in sufficient detail to provide reasonable assurance that the software performs as intended and all software-related risks have been adequately mitigated.

PERFORMANCE TESTING – BENCH

To evaluate the mechanical and structural integrity of the PillCam COLON 2 capsule, the following bench testing has been performed:

1. Resistance to incidental biting test
2. Resistance to pH test
3. Image Quality
4. Imaging chain performance and color reproducibility
5. Battery life

A summary of each test is provided below:

- **Resistance to incidental biting test**

The purpose of this test was to ensure that the PillCam COLON 2 Capsule is able to withstand extreme cases of accidental biting. The capsule's integrity was evaluated in a simulated model to ensure that the capsule enclosure does not split or break so the capsule will not have sharp edges which could injure the digestive tract. The biting simulation in the tested range did not cause the capsules to break or crack. The applied forces caused only a small and local plastic deformation without producing any sharp edges that could injure the digestive tract. Therefore, it was concluded that the PillCam COLON 2 capsule is able to withstand accidental biting of up to 60 kg of force.

- **Resistance to pH test**

During the passage of the PillCam Capsule through the entire digestive tract, it will experience a range of pH values from as low as 2 to as high as 8.5.

The purpose of this testing is to evaluate the integrity of the PillCam COLON 2 capsule during exposure to simulated conditions of extreme pH variations (pH2 and pH8) in comparison to a control group submerged in distilled water (pH 7.0). After 48 hours, the capsules were inspected visually for cracks/leaks, and were also weighed and measured to ensure that there was no loss in material. The results showed no evidence of leakage or physical degradation in any of the capsules. Therefore, it is concluded that the PillCam COLON 2 capsule is resistant to extreme pH conditions, including both acidic and basic conditions (pH2 and pH8), for a period of 48 hours.

- **Image quality**

The purpose of this test is to verify the optical and illumination models of the PillCam COLON 2 capsules. It shows that, for the capsule tested, the field of view (FOV) model is valid within <2% error. The optics FOV in water and in air is very similar.

The FOV measurements originally provided by the sponsor determined the FOV to be 172°. However, this calculation was based on ISO 8600-3—3: Optics and optical instruments-Medical endoscopes and endoscopic accessories Part 3: Determination of field of view and direction of view of endoscopes with optics, which focuses on rigid and flexible endoscopes whose entrance pupil is located at the distal window. This calculation method is not appropriate for capsule systems as it exaggerates the FOV in capsules where the transparent cover (dome) is located further away from the entrance pupil. The sponsor reassessed FOV by measuring from the entrance pupil. The re-calculated FOV was calculated to be 170° from the entrance pupil.

- **Imaging Chain performance and color reproducibility**

The sponsor provided a description and component level test data of each of the components of the imaging chain including the light source (LED), optics (lens), image sensor (camera hardware), in-camera processing (camera software), data transmission (wirelessly from capsule to receiver), file compression/processing/storage (image reconstruction), and local/remote display (review workstation software and hardware). In addition, the sponsor provided system level test data for color reproducibility intended to demonstrate that the images acquired by the device are meaningful to users by comparing the input and output colors of the whole imaging chain.

- **Battery life**

Battery testing was performed to demonstrate that the 10-hour operating time of the capsule is not constrained by the battery. Since battery life is directly related to the illumination intensity and image quality, the sponsor provided optical spectra of the light source at different time points of the battery life period to demonstrate that the 10-hour operation time of the capsule is not constrained by battery life.

MAGNETIC RESONANCE (MR) COMPATIBILITY

No testing has been conducted to demonstrate whether the device is MR compatible. The labeling has included a Caution that the capsule should not be stored near any powerful magnetic fields, and the user should not be exposed to magnetic resonance imaging

(MRI) while the capsule is ingested. A warning has been included in the labeling stating that a patient should not undergo MRI until excretion of the capsule has been verified.

SUMMARY OF CLINICAL INFORMATION

A prospective, multi-center study entitled *Evaluation of Capsule Endoscopy with PillCam COLON 2 in Visualization of the Colon (MA-204)* was conducted to evaluate the clinical effectiveness of the PillCam COLON 2 Capsule (colon capsule endoscopy or CCE). The primary objective of the study was to compare CCE with optical colonoscopy (OC) for agreement on absence or presence of colon polyps (≥ 6 mm or ≥ 10 mm). There were a total of 17 enrollment sites; 11 were located in the US and 6 were located in Israel.

Study Design

CCE was performed on subjects 6 weeks prior to their OC procedure in order for a central reader to interpret the CCE results prior to OC. In the initial phase of the study, colonoscopists were blinded to CCE results when evaluating their OC findings. The data analysis for this phase of the study is reported here.

A total of 884 subjects were enrolled using the following inclusion criteria:

1. Subject is between the ages of 50 and 75 years
2. Subject is classified as average risk per the American Gastroenterological Association (AGA) Guidelines on colorectal cancer (CRC) screening (individuals without a personal or family history of CRC or adenomas, inflammatory bowel disease, or high-risk genetic syndromes)¹.

Among the 884 subjects enrolled, 184 subjects were excluded from the effectiveness analysis. A total of 104 subjects (11.8%) were excluded due to issues related to the performance of the CCE including 77 (8.7%) that were excluded on the basis of an inadequate colon preparation prior to CCE or a rapid transit of the capsule through the colon. It was mutually agreed upon by the FDA and the Sponsor that there would not be sufficient data to compare the efficacy of CCE to colonoscopy if transit times were less than 45 min. A total of 63 subjects withdrew from the study. Two subjects were excluded because of OC procedure violations. One site was terminated due to major protocol violations, accounting for 15 excluded subjects. The samples included in the study were average risk asymptomatic, first time screening patients undergoing colonoscopy. The use of CCE has not been evaluated in other populations.

A total of 700 subjects successfully completed an investigation with both CCE and OC and were included in the effectiveness analysis. The data analysis of the effectiveness of CCE was undertaken on a per subject basis. The comparison of CCE with OC was based on the presence or absence of at least one finding of a polyp of size in diameter (≥ 6 mm or ≥ 10 mm) identified on OC.

¹ AGA Guidelines: *Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline From the American Cancer Society, the US Multi-Society Task Force on Colorectal and the American College of Radiology; Gastroenterology 2008;134:1570-1595*

Descriptive Analysis

Sizes of the largest colon polyp identified in a subject by OC and CCE were compared regardless of segmental location. The non-segmental analysis was performed to provide an ‘all-or-none’ per subject view of the data, which is clinically valuable information for clinicians to consider in discussing the pros and cons of undergoing this study with a patient. The results outlined in Table 4 below show that among 115 subjects with a polyp identified on OC that was greater than 6 mm but less than 10 mm in diameter, CCE also identified 55 (47.8%) subjects with a polyp greater than 6 mm but less than 10 mm in diameter anywhere in the colon, and 19 (16.5%) subjects with a 10 mm in diameter sized polyp, for a total of 74 subjects (64.3%) with a CCE detected polyp of 6 mm or greater.

Among 77 subjects with a polyp identified on OC that was greater than 10 mm in diameter, CCE identified a polyp anywhere in the colon less than 6 mm in diameter in 12 (15.6%) subjects, a polyp greater than 6 mm but less than 10 mm in diameter in 18 (23.4%) subjects, and a polyp measuring at least 10 mm in diameter in 37 (48.1%) subjects. Thus, CCE identified a total of 55 subjects (71.4%) with a polyp of 6 mm or greater. CCE failed to identify any polyp that was found on colonoscopy of 6 mm or greater in 22 (28.6%) subjects and any polyp of 10 mm or greater in 40 (51.9%) subjects.

TABLE 4: Comparison of the polyp with the largest diameter (mm) identified by OC and CCE in a subject, regardless of segmental location.

Max CCE (mm)	Max OC (mm)				Total
	0	0<OC<6	6≤OC<10	10≤OC	
0	168	84	20	10	282
0<CCE<6	90	71	21	12	194
6≤CCE<10	18	52	55	18	143
10≤CCE	13	12	19	37	81
Total	289	219	115	77	700

Analysis of Agreement

Location-based and size-based analyses of the agreement of CCE with OC were conducted. Two polyp size thresholds, 6 mm and 10 mm, were considered for defining a subject as positive for a polyp. Publications regarding the cancer risks for polyps as well as the US Multi-Society Task Force on Colorectal Cancer use a 6 mm and a 10 mm threshold for colonoscopy surveillance decision-making. If one or more polyps were identified on OC, the polyp with the largest estimated diameter was used for comparison purposes and is referred to as the ‘reference’ polyp. The colon segment location of the reference OC polyp was determined and recorded as the cecum, ascending colon, transverse colon, descending-sigmoid colon or rectum. The largest

polyp identified on CCE within the same or an adjacent segment location of the “reference OC” polyp was used to determine agreement with OC based on a size-matching algorithm. If there were two polyps of equal size that were “the largest” and located in different segments of the colon, then the location and size-matching algorithm was repeated on each of these reference OC polyps to determine agreement of CCE with OC. In such instances, the reference OC polyp chosen for the final determination was the one that was in favor of the device. For each subject, the CCE evaluation was classified into one of four categories of agreement with OC: true positive (TP) agreement, false negative (FN) disagreement, false positive (FP) disagreement, or true negative (TN) agreement.

Using the 6 mm or greater sized polyp threshold, the positive and negative percent agreements of CCE with OC were, respectively, 68.8% (132/192, 95% CI 61.7-75.2%) and 81.3% (413/508, 95% CI 77.6- 84.6%). Using the 10 mm or greater sized polyp threshold, the positive and negative percent agreements were 64.9% (50/77, 95% CI 53.2-75.5%) and 92.9% (579/623, 95% CI 90.6-94.8%).

Following the completion of a colonoscopy when the polyp detected on CCE was not identified, the results of the CCE evaluation were unblinded and the colonoscopy was repeated in a second attempt to identify the polyp identified on CCE. The unblinded colonoscopy results for the ≥ 6 mm threshold showed a 1% and 3% increase in the positive and negative percent agreement values, respectively. The unblinded colonoscopy results for the ≥ 10 mm threshold showed a 1% increase in the positive and negative percent agreements

Safety:

Only one (0.1%) case (out of 884 cases) was reported within this study as a serious adverse event (abdominal pain related to OC procedure). The event was resolved the following day.

A total of 142 non-serious adverse events related to the study, occurred in 101(11%) out of 884 subjects.

- Three adverse events were reported as related to the capsule procedure and resolved within the same day (i.e., severe gagging reflex and mild vomiting and abdominal cramping).
- Eleven adverse events were reported as related to the colonoscopy procedure as follows:
 - 6 moderate adverse events, out of which 5 occurred in the same subject and resolved within the same day (i.e., fever, headache, abdominal pain, bloating and nausea); a second subject suffered from moderate abdominal pain that resolved within 3 days.
 - 5 mild adverse events resolved within 8 days (i.e., abdominal pain / cramping (3 cases), fever and bleeding-old blood).

The remaining 128 adverse events were reported as related to the colon preparation (prior to CE and optical colonoscopy procedures).

LABELING

The labeling is sufficient and satisfies the requirements of 21 CFR § 801.109 for prescription devices. The clinician’s manual includes the Indications for Use, a detailed summary of the device’s technical parameters, and all information related to the safe use of the device such as

patient preparation, instructions for use, contraindications, warnings, and cautions. In addition, the clinician’s manual includes a summary of the clinical study conducted and an analysis of the results.

The patient manual includes a discussion of what the PillCam COLON 2 Capsule is, how it works, and how a patient should prepare for the procedure. The manual also notifies the patient of the risks associated with capsule endoscopy and the colon preparation, and also includes a list of contraindications. Finally, the manual summarizes the clinical trial results, not only highlighting the percentage of patients in which a polyp was correctly identified by capsule endoscopy, but also the percent of patients in which the capsule either missed or falsely identified a polyp with respect to optical colonoscopy.

RISKS TO HEALTH

Table 5 below identifies the risks to health that may be associated with use of colon capsule imaging systems and the measures necessary to mitigate these risks.

TABLE 5: Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measure
Adverse Tissue Reaction	Biocompatibility
Equipment, malfunction leading to injury	Electrical safety, thermal and mechanical safety Software validation, verification and hazard analysis Non-clinical testing Labeling
Interference with other devices and with this device (e.g., interference with image acquisition, patient information compromised);	Electromagnetic compatibility testing Software validation, verification and hazard analysis Non-clinical testing
Poor image acquisitions	Optical imaging performance testing Non-clinical testing Labeling
Failure to excrete	Labeling
Misinterpretation of the captured images	Clinical performance data Non-clinical testing Labeling

Possibility of missing a polyp, or falsely identifying a polyp	Clinical performance data Software validation, verification and hazard analysis Labeling
Abdominal pain, nausea , vomiting, choking	Clinical performance data Labeling

SPECIAL CONTROLS:

The special controls for colon capsule imaging systems, as described in 21 CFR § 876.1330 are described below. The submitter will need to demonstrate that its device addresses the special controls, either by meeting the special controls included within the regulation or by some other means that provides equivalent assurances of safety and effectiveness.

In combination with the general controls of the FD&C Act, the Colon Capsule Imaging System is subject to the following special controls:

1. The capsule must be demonstrated to be biocompatible
2. Non-clinical testing data must demonstrate the mechanical and functional integrity of the device under physically stressed conditions. The following performance characteristics must be tested and detailed protocols must be provided for each test:
 - Bite test to ensure that the capsule can withstand extreme cases of biting.
 - pH Resistance test to evaluate integrity of capsule when exposed to a range of pH values.
 - Battery life test to demonstrate that the capsule’s operating time is not constrained by the battery capacity.
 - Shelf-life testing to demonstrate that the device performs as intended at the proposed shelf-life date.
 - Optical testing to evaluate fundamental image quality characteristics such as resolution, field of view, depth of field, distortion, signal to noise ratio, uniformity, and image artifacts. A test must be performed to evaluate the potential of scratches, caused by travelling through the gastrointestinal tract, on the transparent window of the capsule and their impact on the optical and color performance.
 - An optical safety analysis must be performed based on maximum (worst-case) light exposure to internal gastrointestinal mucosa, and covering ultraviolet, visible and near-infrared ranges, as appropriate. A mitigation analysis must be provided.
 - A color performance test must be provided to compare the color differences between the input scene and output image.
 - The video viewer must clearly present the temporal or spatial relationship between any two frames as a real-time lapse or a travel distance. The video viewer must alert the user when the specific video interval is captured at a frame rate lower than the nominal one due to communication errors.

- A performance test evaluating the latency caused by any adaptive algorithm such as adjustable frame rate must be provided.
 - If the capsule includes a localization module, a localization performance test must be performed to verify the accuracy and precision of locating the capsule position within the colon.
 - A data transmission test must be performed to verify the robustness of the data transmission between the capsule and the recorder. Controlled signal attenuation should be included for simulating a non-ideal environment.
 - Software validation, verification and hazards analysis must be provided.
 - Electrical equipment safety, including thermal and mechanical safety and electromagnetic compatibility (EMC) testing must be performed. If the environments of intended use include locations outside of hospitals and clinics, appropriate higher immunity test levels must be used. Labeling must include appropriate EMC information.
 - Information demonstrating immunity from wireless hazards.
3. The clinical performance characteristics of the device for the detection of colon polyps must be established. Demonstration of the performance characteristics must include assessment of positive percent agreement and negative percent agreement compared to a clinically-acceptable alternative structural imaging method.
4. Clinician labeling must include:
- Specific instructions and the clinical and technical expertise needed for the safe use of the device.
 - A detailed summary of the clinical testing pertinent to use of the device, including the percentage of patients in which a polyp was correctly identified by capsule endoscopy, but also the percent of patients in which the capsule either missed or falsely identified a polyp with respect to the clinically-acceptable alternative structural imaging method.
 - The colon cleansing procedure.
 - A detailed summary of the device technical parameters.
 - A detailed summary of the device- and procedure-related complications pertinent to use of the device.
 - An expiration date/shelf life.
5. Patient labeling must include:
- An explanation of the device and the mechanism of operation.
 - Patient preparation procedure.
 - A brief summary of the clinical study. The summary should not only include the percentage of patients in which a polyp was correctly identified by capsule endoscopy, but also the percent of patients in which the capsule either missed or falsely identified a polyp with respect to the clinically-acceptable alternative structural imaging method. .
 - A summary of the device- and procedure-related complications pertinent to use of the device.

BENEFIT/RISK DETERMINATION

The benefits and risks of the device are based on the data collected in the clinical study described above.

1. Risk Assessment

Patient Safety

Based on the clinical trial results, the primary concern associated with the PillCam COLON 2 Capsule Endoscopy System is that a normal or negative CCE examination does not exclude the possibility of colon polyps or colon cancer. Patients with a false negative CCE result would not be identified as having a colon polyp or cancer, and would have possible histologic progression of the lesion or the development of a cancer is possible during the surveillance period.

Second to the risk of a false negative result, is the possibility of a false positive determination as these patients may be advised to undergo unnecessary additional evaluation.

Procedure-Related Concerns

The probability of a harmful event is very low. Capsule retention is a very uncommon event especially when patients with known or suspected gastrointestinal obstructions, strictures or fistulas, Crohn's disease or chronic use NSAIDs are carefully screened. The contraindications associated with this patient population have been incorporated in the labeling. In a worst case scenario of a capsule device resulting in an intestinal obstruction, attempts at endoscopic or colonoscopic capsule retrieval are preferable.

2. Benefit Assessment

The benefits of CCE with the Given PillCam COLON 2 Capsule Endoscopy System in a selected population of patients after an incomplete optical colonoscopy with adequate preparation, and a complete evaluation of the colon was not technically possible, outweigh the potential risks of false positive and negative results. Both clinicians and patients involved with CCE evaluations will need to understand the limitations of this technology, and make informed decisions regarding the implications of the study results. The options available to patients with an incomplete colonoscopy would be Computed Tomography Colonoscopy (CTC) or CCE. Both have limitations and advantages, which need to be discussed with the patient in reaching a decision for further therapy.

In conclusion, given the available information summarized, the data support that for the detection of colon polyps in patients after an incomplete optical colonoscopy with adequate preparation, and a complete evaluation of the colon was not technically possible, the probable benefits outweigh the probable risks for the PillCam COLON 2 Capsule Endoscopy System. The device provides substantial benefits and the risks can be mitigated by the use of the identified special controls.

CONCLUSION

The de novo for the PillCam COLON 2 Capsule Endoscopy System is granted and the device is classified under the following:

Product Code: PGA
Device Type: Colon Capsule Imaging System
Class: II
Regulation: 21 CFR 876.1330