CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211580Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2)
Application Number(s)	NDA 211580
Priority or Standard	Standard
Submit Date(s)	1/23/2018
Received Date(s)	1/23/2018
PDUFA Goal Date	11/23/2018
Division/Office	DMIP/ODE IV
Review Completion Date	11/09/2018
Established Name	Indocyanine green
(Proposed) Trade Name	SPY AGENT Green
Pharmacologic Class	Contrast agent
Code name	IC2000
Applicant	Novadaq Technologies
Formulation(s)	25 mg powder for injection
Dosing Regimen	Reconstituted with 10 mL sterile water and injected intravenously for visualization of vessels, blood flow, and tissue perfusion and for visualization of extrahepatic biliary ducts Reconstituted with 20 ml sterile water and injected interstitially into the cervix as four injections of 1 ml each for visualization of lymph nodes and lymphatic vessels
Applicant Proposed Indication(s)/Population(s)	(b) (4) SPY AGENT Green is indicated for fluorescence imaging of lymph nodes and delineation of lymphatic vessels in the cervix and uterus in patients with solid tumors during lymphatic mapping, (b) (4) a component of intraoperative management. (b) (4) SPY AGENT Green is indicated for (b) (4) fluorescence imaging of biliary ducts (b) (4) (b) (4) SPY AGENT Green is indicated for fluorescence imaging of blood flow and tissue perfusion during: vascular, gastrointestinal, organ transplant, and plastic, micro- and reconstructive surgeries, including general minimally invasive surgical procedures.
Regulatory Action	Approval
Recommended Indications/Populations	**Visualization of Vessels, Blood Flow and Tissue Perfusion** Indicated in adults and pediatric patients one month of age and older for fluorescence imaging of micro- and macro-vasculature, blood flow and tissue perfusion before, during and

	after vascular, gastrointestinal, organ transplant, and plastic, micro- and reconstructive surgeries, including general minimally invasive surgical procedures. **Visualization of Extrahepatic Biliary Ducts** Indicated in adults and pediatric patients age 12 to 17 for fluorescence imaging of extrahepatic biliary ducts. **Visualization of Lymph Nodes and Lymphatic Vessels During Lymphatic Mapping for Cervical and Uterine Tumors** Indicated for fluorescence imaging of lymph nodes and delineation of lymphatic vessels in the cervix and uterus during lymphatic mapping in patients with solid tumors for which this procedure is a component of intraoperative management.

Table of Contents

Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DPMH=Division of Pediatric and Maternal Health

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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BD	blue dye
BLA	biologics license application
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CSF	color segmented fluorescence
FA	fluorescent angiography
FDA	Food and Drug Administration
FILM	Fluorescence Imaging for Lymphatic Mapping
FL	fluorescence
IB	Isosulfan blue dye
ICG	indocyanine green
IDE	Investigational Device Exemption
IND	Investigational New Drug application
LN	lymph node
mITT	modified intent to treat
NDA	new drug application
NIR	near-infrared
NIRF	near-infrared fluorescence
OCP	Office of Combination Products
PC	percentage of controls
PP	per protocol
PT	percentage tested
RSSC	robotic single-site cholecystectomy
SAP	statistical analysis plan
SLN	sentinel lymph node
TTF	transit-time ultrasound flow

1. Executive Summary

1.1. Product Introduction

NDA 211580 for indocyanine green (ICG) is a 505(b)(2) application with multiple proposed indications for the use of ICG (initial approval 1959) near infrared fluorescence (NIRF) imaging including lymphatic mapping in patients with solid tumors of the cervix and uterus, visualization of extrahepatic biliary ducts , and visualization of vessels, blood flow and tissue perfusion before, during and after vascular, gastrointestinal, organ transplant, and plastic, micro- and reconstructive surgeries, including general minimally invasive surgical procedures. The Applicant currently markets various fluorescent imaging systems cleared (510(k)) by the Center for Devices and Radiological Health (CDRH) for NIRF imaging with ICG for intraoperative visualization of biliary ducts as well as visualization of blood vessels and tissue perfusion; these 510(k) cleared device indications are proposed in this ICG NDA

The active ingredient in ICG is a tricarbocyanine dye that has been in clinical use for 60 years. When administered intravenously, ICG binds to plasma proteins and circulates throughout the body. Upon exposure to the appropriate wavelengths, ICG will emit fluorescence which can be detected with devices designed to image in the near-infrared spectrum. ICG is excreted into the bile allowing imaging of the biliary tree during cholecystectomy. When injected interstitially, ICG is taken up by the lymphatics allowing visualization of these structures during surgery.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The approval action for this NDA is based upon the totality of the data submitted, which included a completed clinical trial and literature to support the safe and effective use of ICG for the indications sought. In addition, the historical safe use of ICG dating back to 1959 and the existing CDRH cleared indications for ICG NIRF provided additional supportive evidence of safety and effectiveness.

For the lymphatic mapping claim, the sponsor's clinical trial demonstrated significant improvement for ICG over the comparator blue dye for visualization of lymph nodes (LNs) and lymphatic vessels during lymphatic mapping for cervical and uterine tumors. Equally important, was the demonstration that ICG could identify nodes bilaterally in the pelvis more often than blue dye. The biliary ducts and blood vessel and tissue perfusion indications were previously cleared by CDRH under co-packaging and are well established in clinical practice. The sponsor submitted additional literature publications that provided further evidence for the safe and effective use of ICG in these defined clinical settings. The newly sought indication for LN mapping has also been used in clinical practice as an off-label use for ICG.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

New Lymph Node Mapping Indication:
The randomized study done by the Applicant and supported by published literature demonstrates that ICG can identify draining LNs in the pelvis better than the use of blue dye. It is expected that the product will be able to facilitate visualization of LNs intra-operatively on both sides of the pelvis to better stage patients with early stage uterine and cervical cancers.

CDRH Cleared Indications:
The literature submitted by the Applicant in support of the visualization of vessels, blood flow, tissue perfusion, and extrahepatic biliary ducts, in combination with the known safety of ICG at the Applicant's proposed dosing, provide evidence that ICG can be safely used in these populations to enhance the intraoperative visualization of these anatomic structures. It should be noted that reliable evidence of improved surgical and other clinical outcomes by NIR imaging is not available due to the study designs of literature reports. Nevertheless, the totality of submitted evidence and lack of safety signals show that the intraoperative use of ICG can successfully delineate referenced anatomic structures and provide a useful intraoperative adjunctive imaging tool.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Visualization of Lymph Nodes and Lymphatic Vessels:** • 10% to15% of women undergoing surgical procedures to treat uterine and cervical cancers will be upstaged by routine lymphadenectomy. However, only 30% of women undergo lymph node staging at the time of surgery. • There is no evidence that routine lymphadenectomy results in improved survival. • The morbidity associated with lymphadenectomy limits its use. Lymphadenectomy can lead to lymphedema, injury to major nerves and vessels and development of lymphocysts.	• The ability of the surgeon to identify in real-time the possible routes of lymphatic spread, without resorting to en-bloc resection, could lead to more women having staging and reduce surgical morbidity. Improving staging by including a lymph node evaluation could reduce the number of women who are overtreated based on features of the uterine tumor without information on the status of the lymph nodes, and tailor treatment to the individual.

	• An important limitation of design of the efficacy study is the lack of information on false negative rate for tumor detection in the nodes identified by the lymphatic mapping procedure. **Visualization of Extrahepatic Biliary Ducts**: • In the U.S., laparoscopic cholecystectomy is a common surgical procedure. The standard of care for visualizing biliary duct anatomy during this procedure is intraoperative cholangiography, which requires catheter placement into the cystic duct, contrast injection, and radiography. It is not clear that this invasive procedure decreases the risk of surgical complications. **Visualization of Vessels, Blood Flow, Tissue Perfusion:** • Intraoperative radiologic assessment of micro and macro vasculature patency and tissue perfusions after vascular-, organ- and other grafting and reconstructive surgery is not standard practice. Early graft failure related to technical problems at the anastomosis site might be corrected if identified during the procedure.	• Indocyanine green has been in long-term clinical use for assessment of liver function and has a well-characterized safety profile. NIRF imaging systems for use with ICG are CDRH-cleared for intraoperative visualization of biliary ducts, micro and macro-vasculature, and tissue perfusion in grafts and other reconstructive procedures

Current Treatment Options	**Visualization of Lymph Nodes and Lymphatic Vessels in Patients with Uterine and Cervical Tumors:** • Surgical staging with or without lymphadenectomy. • Off-label use of blue dye or technetium-99 labeled pharmacophores for lymph node identification. **Biliary and Visualization of Vessels, Blood Flow, Tissue Perfusion:** • The standard of care for imaging biliary ducts is intraoperative cholangiography. • There is no standard of care for intraoperative assessment of micro and macro vascular graft patency.	• In the absence of lymph node histology, post-operative treatment is based only on histologic findings in the uterine tumor. • Imaging options that enhance visualization of anatomic structure with acceptable safety profiles are needed in these defined surgical settings.
Benefit	**Visualization of Lymph Nodes and Lymphatic Vessels:** • Performing a sentinel node procedure in patients with uterine and cervical tumors is feasible and is anticipated to lead to fewer surgical complications compared to full	• Failure to perform lymphadenectomy can result in overtreatment and understaging. Not all

	lymphadenectomy. The mapping procedure also allows for ultra-staging of nodes to detect low-volume disease. One limitation of the study is the lack of information on false negative tumor detection rates with the lymphatic mapping procedure. • Practice guidelines recommend performing a side-specific nodal dissection in cases of failed lymphatic mapping. Lymph nodes on both sides of the pelvis were identified in 74% of women in this study. It is anticipated that the majority of women undergoing mapping will not need additional pelvic dissection. • Ability to visualize nodes that might not be part of the routine dissection. In this study, 2% of women had para-aortic nodes found, and in one of these women, it was the only node found. **Visualization of Extrahepatic Biliary Ducts, Vessels, Blood Flow, Tissue Perfusion:** See above comments.	surgeons routinely perform lymphadenectomy in women with early stage uterine or cervical cancers. Use of this product could reduce potential surgical complications while improving staging in these low risk patients who might otherwise not have lymph node staging done as part of their surgery. • This study and the literature support the use of ICG over blue dyes for lymphatic mapping. • The literature submitted, history of clinical safe use and totality of evidence support the ability of ICG to be safely used and improve visualization when used with NIRF systems cleared by CDRH for the same indications for use proposed in the present NDA. Data demonstrating improved clinical outcomes with the use of ICG NIRF imaging is not available in the literature.

Risk and Risk Management	**Visualization of Lymph Nodes and Lymphatic Vessels in Patients with Uterine and Cervical Tumors:** • The value of lymphatic mapping to identify sentinel node has not been validated in uterine and cervical cancers. Therefore, further studies need to be conducted to determine cancer detection rates in sentinel nodes compared to a truth standard of full nodal dissection. Long term clinical outcome studies would also be valuable.	• The use of ICG is for lymph node identification would expand the patient population undergoing staging and might allow for a patient-tailored approach to adjuvant therapies. However, the value of sentinel node procedure needs to be verified in the context of a full regional nodal dissection in patients with uterine and cervical cancers before adoption of sentinel node detection alone for these patients
	Visualization of Extrahepatic Biliary Ducts, Vessels, Blood Flow, Tissue Perfusion:	• No risk management activity required.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X☐	**Patient experience data were not submitted as part of this application, and were not considered in this review.**			

2. Therapeutic Context

2.1. Analysis of Condition

ICG was developed by Kodak as an imaging agent. It was first approved for clinical use in 1957. The characteristics that made the drug accepted include its absorption maximum around 800nm, confinement to the vascular compartment by binding with plasma proteins, low toxicity, and the rapid excretion into bile. The long history of clinical use has established its safety profile for the doses used clinically. ICG is effective for angiographic use through its binding to lipoproteins in the blood, allowing it to be retained in the vessels. ICG can be given for repeated injections; and it provides a good signal-to-noise ratio as there is little near-infrared (NIR) autofluorescence in tissues.

Uterine cancer is the most common gynecologic cancer in women is the U.S. and represents 3.6% of all new cancers diagnosed. There will be an estimated 63,230 new cases in 2018, with 11,350 deaths from the disease. The rates for new uterine cancer cases have been rising on average 1.3% each year over the last 10 years [1].

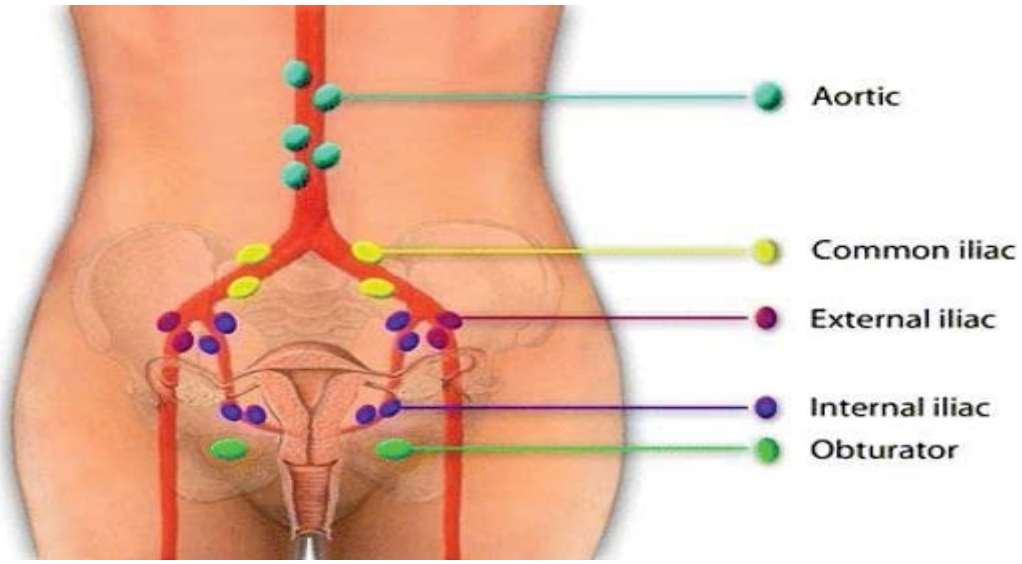
For cervical cancer, there will be an estimated 13,240 new cases diagnosed this year, with an estimated 4,170 deaths. When confined to the primary site, the 5-year survival is 92% [2].

The Federation of International Gynecology and Obstetrics adopted surgical staging for uterine cancers in 1988, with pathology that includes information about the primary tumor as well as LN status, and this staging has guided assessment of prognosis and use of adjuvant therapies. The staging system includes information regarding tumor grade, depth of myometrial invasion, local and regional spread, LN metastasis, and distant metastasis. The initial management of endometrial cancer should include comprehensive surgical staging to include total hysterectomy, BSO, pelvic and para-aortic lymphadenectomy, and peritoneal washings.

Three quarters of women diagnosed with uterine cancer will have disease limited to the body of the uterus at the time of diagnosis, and will survive at least 10 years after diagnosis. Therapy is based on pathological features of the surgical specimen when the LN status is unknown. Approximately 10% to 15% of women will be upstaged after surgery, but there is a tradeoff between systematic lymphadenectomy and no dissection at all, as complications are higher for women undergoing lymphadenectomy. The most recent Cochrane review [2] states that performance of lymphadenectomy in early-stage endometrial cancer is not associated with a reduction in death or relapse compared to omission of the procedure. Routine performance of lymphadenectomy adds operative time, cost, and complications such as injury to nerves or major vessels, cellulitis, lymphedema, and formation of lymphocysts. These findings have led to the questioning of the value of lymphadenectomy in patients with early-stage endometrial cancers. Nevertheless, surgical staging does reduce the use of external beam radiation, which is associated with more frequent and severe comorbidities than lymphadenectomy.

The cervix and uterus are midline structures, and their lymphatic drainage is found on one or both sides of the pelvis (**Figure 1**). Imaging methods for determining the presence of LN metastases that are widely accepted include CT and MRI, but their diagnostic performances are low and do not replace surgical staging [3]. During the surgical procedures, identification of nodes on both sides is critical to adequate staging. With current methods, the rate of bilateral identification of nodes is about 65% to 80% when LN mapping is done [4, 5]. The NCCN guidelines [6, 7] for both uterine and cervical cancers shown below (**Figure 2**) require a side-specific completion lymphadenectomy if a sentinel node is not found.

Figure 1: Lymph Node Drainage Patterns

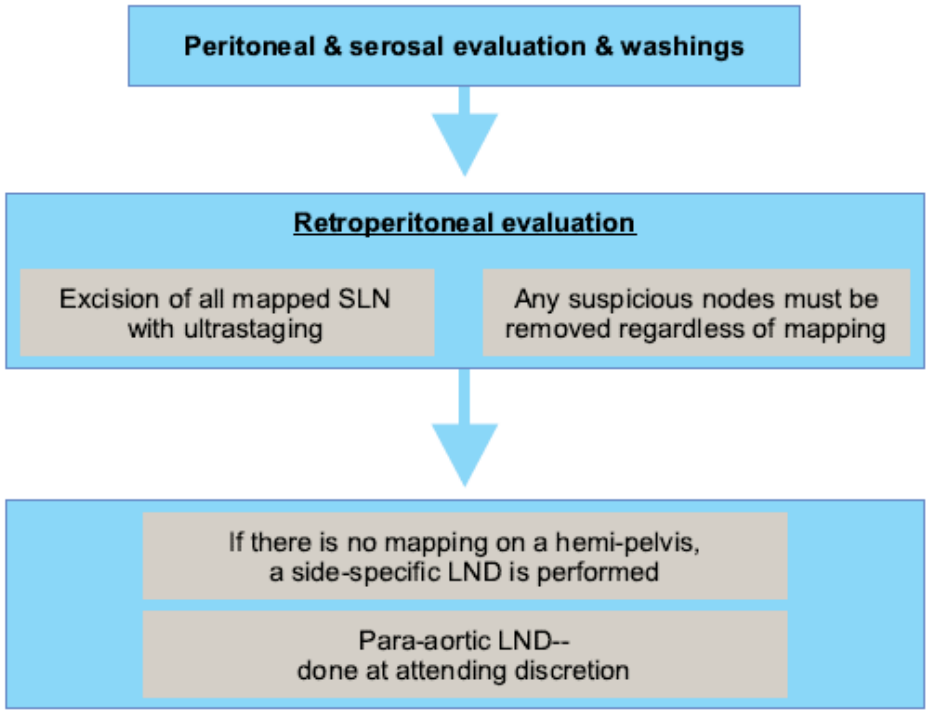


Source: Crane et al. *Multispectral Fluorescence Imaging for the Detection of the Sentinel Lymph Node in Cervical Cancer: A Novel Concept*. Mol Imaging Biol. 2011.13(5):1043–1049.

Figure 2: NCCN Guidelines for Sentinel Lymph Node (SLN) Staging

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 4: The SLN algorithm for surgical staging of endometrial cancer*



The risk for isolated para-aortic nodal metastases is approximately 3%. Failure to identify para-aortic metastases potentially results in failure to prescribe appropriate adjuvant therapy. In early stage cancers, para-aortic LNs are not routinely excised, but done at the surgeon's discretion, resulting in the potential for under staging these patients. A method for detection of these nodes without the need for the usual extensive dissection would improve cancer staging.

This is further supported by the SGO consensus guidelines that recommend sentinel lymph node (SLN) mapping in lieu of routine pelvic lymphadenectomy for patients with low-grade endometroid carcinomas [8].

2.2. Analysis of Current Treatment Options for Gynecologic Malignancies

Surgical staging is the standard of care for patients with uterine and cervical cancers. The key elements are dissection of the pelvic and periaortic nodes and the dissection of the parametrium from the pelvic sidewall to allow en bloc removal. In practice, only about 30% of women with these early stage cancers are undergoing LN staging of any kind resulting in incomplete staging for most women.

Lymphatic mapping might be used off-label to identify the lymph nodes most proximal to the primary uterine or cervical tumor. Isosulfan blue, and Tc99 m labelled pharmacophores are indicated for use in lymphatic mapping in various tumor types.

2.3. Analysis of Current Treatment Options for Visualization of Biliary Extrahepatic Ducts and Visualization of Vessels, Blood Flow, and Tissue Perfusion.

For these ICG indications, the Applicant markets NIRF imaging systems that are CDRH cleared for use with ICG (Table 10). The literature indicates a lack of standard of care intraoperative imaging for various settings including: assessment of graft patency during coronary artery bypass surgery, assessment of micro-perfusion at the time of anastomosis in colorectal surgery, and assessment of skin flap viability (micro-perfusion) during breast reconstruction post mastectomy. In these settings, clinicians rely on visual assessment without a reliable imaging test to aid in the performance of these procedures. However, in the case of laparoscopic cholecystectomy, the standard of care imaging to visualize the biliary anatomy and extrahepatic biliary ducts is intraoperative cholangiography. Nevertheless, there is continued debate about whether intraoperative cholangiography reduces the frequency or severity of bile duct injury during cholecystectomy. Imaging aids the intraoperative visualization of blood vessels, tissue perfusion, and, in the case of laparoscopic cholecystectomy, biliary anatomy identification.

3. U.S. Regulatory Actions and Marketing History

3.1. Regulatory Background

ICG has been used in humans since 1957and gained FDA approval in 1959. Originally indicated for hepatic function testing, it was then approved for use in cardiac output determination in cardiology. In 1975, Akorn, the holder of the ICG NDA, was granted a new indication for ophthalmic angiography. In 2007, Pulsion Medical Systems was granted approval for an abbreviated new drug application (ANDA) for a generic ICG drug product.

The development of new cameras and imaging systems led to the expansion of the indications of ICG for visualization of vessels, blood perfusion and visualization of biliary anatomy under several 510(k)submissions. Several modifications of the Applicant's NIR imaging systems were cleared by CDRH for the specific use of the Novadaq NIR platform of devices with ICG marketed by a different manufacturer provided as co-packaging.

3.2. Summary of Presubmission/Submission Regulatory Activity

This is a combination product. Throughout the regulatory history, both Center for Drug Evaluation and Research (CDER) and CDRH have worked collaboratively to evaluate each step.

2004: Novadaq filed a request for designation for the SPY Intra-Operative Imaging System for the combination of its imaging device and IC-Green (from Akorn, Inc). The Lead Center was determined to be CDRH by the Office of Combination Products. This allowed ICG to be approved for additional indications when used with specified Novadaq Imaging Systems and the co-package kit. The devices include:

- SPY Elite Fluorescence Imaging System (SPY Elite; K042961, K060867, K063345, K071037, K071619, K072222, K073130, K073088, K100371)
- PINPOINT Endoscopic Fluorescence Imaging System (PINPOINT; K091515, K150956, K161792)

2013: IND submission (b) (4) plan to label ICG, the listed drug, to include visualization claims in multiple areas and expand the indication of ICG to include lymphatic claims, using the marketed SPY platform of devices under a 505(b)(2) submission. Pre-NDA meeting held 9/17/2013. Consults obtained from CDRH, Office of Combination Products (OCP), and Cardio-Renal (CDER).

- The Applicant stated it planned to manufacture its own ICG using the USP monograph without making any manufacturing or processing changes, which was acceptable to the Agency.
- The Applicant planned to support the indications with literature summaries. The Applicant was advised to consider studies that were well-controlled and statistically sound that could be considered confirmatory. FDA agreed that a 505(b)(2) application would be reasonable.
- The Applicant planned to include expansion of indication to lymphatic identification. The Agency recommended that clinical trials would be needed for this new route of administration (interstitial rather than intravenous).

2014: Type B/pre-NDA meeting was requested and held 12/14/2014 to review two proposed clinical trials for lymphatic indication (Fluorescence Imaging for Lymphatic Mapping (FILM) trial using the PINPOINT system) (b) (4)

(b) (4)

2015: Protocol amendment submitted. Meeting request submitted 10/12/2015. In November after several interactive rounds with the Applicant, OCP advised that the lead center would be CDRH, and the Applicant would need to submit the clinical trial to CDRH for its review. **IND** (b) (4) **was withdrawn**. Development was done under IDE G150254 for the lymphatic claim.

- **G150254** submitted to the Division of Surgical Devices for the lymphatic mapping indication in gynecologic surgeries. It was jointly reviewed by CDER and CDRH staff from the Division of Surgical Devices and the Obstetrics/Gynecology Branch in the Division of Reproductive, Gastro-Renal and Urology Devices.
    - Received a conditional approval letter for the FILM study on 12/23/2016.
    - Conditions to be addressed included:
        - Asked to clarify whether Stage IA endometrial and cervical cancer patients would be enrolled in this study. It should be noted that American College of Obstetricians and Gynecologists Practice Bulletin 149, published in April 2015, states "no randomized controlled trials have demonstrated a benefit of lymphadenectomy in apparent early-stage endometrial cancer (disease confined to the uterine corpus or cervix [stage I and stage II])". If you intend to include these patients, please provide justification preferably in the form of SGO guidelines that recommends lymphadenectomy in these early stage cancers.
        - Changes to the informed consent were requested to correctly inform the patients of the intent of the surgery and use of confidential information handling and storing.

2016:

- **G150254/A1:** submitted 2/4/2016, was the Applicant's responses to the conditional approval.
- **G150254/A002**: submitted 3/1/2016 with the revised protocol (PP LNM 01 V3.0) for the modifications to the inclusion and exclusion criteria.
    - second conditional approval letter issued on 3/4/2016.
- **Q160207** was submitted to CDRH for pre-submission feedback. Meeting was held 9/16/2016.
    - The Applicant agreed to discuss with the FDA any changes to the FILM clinical trial prior to submitting a protocol amendment.
    - Agreed to submit the statistical analysis plan (SAP) for the FILM study.
- Teleconference between OCP and the Applicant to address the Applicant's concerns regarding changing center assignments and reviewers over the course of the product development. The recommendations were:
    - To submit the SAP to CDRH,
    - To submit another Q-submission to discuss the multiple indications and to identify the clinical trials and identify at least one piece of literature on which the Applicant would rely to establish the indication,
    - To establish a contact at FDA to facilitate the communications.

2017:

- **Q160207/S1** received 4/5/2017 for the company to provide background information to continue IC2000 product development pathways and indications with both CDRH and CDER with a teleconference held 6/20/2017
    - Suggestion was made for a concomitant submission as a co-package.
    - Difficulties finding a predicate device with similar intended use.
    - FDA stated that either a general indication for the devices or a specific cross-labeling for the drug and device was needed.
    - Agreed that the Applicant could seek the biliary indication for IC2000 based on literature.
- **IND 135996** submitted 6/28/2017 as a pre-NDA meeting, and meeting held 11/14/2017
    - Confirmed that both CDRH and CDER have reviewed IDE G150254 and contributed to the Agency's advice.
    - Agreed to provide histopathology for the FILM trial and confirmed that their systemic summary supported lymphatic mapping claim for uterine and cervical cancers.
    - Confirmed that the NDA would include the existing angiographic indications for the SPY systems through literature review.
    - Would include summary safety data from all ICG manufacturers.
    - Acknowledged that a full manufacturing data inspection would be required.
    - Acknowledged the need for a bridge from their formulation to the one used in the published studies to justify using different sources of ICG. This could be done with meta-analyses to leverage previous submissions to develop cross-conforming labeling for devices(s) and drug.
- [redacted] (b) (4)

2018:

[redacted] (b) (4)

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

N/A

4.2. Product Quality

N/A

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

The devices that will be affected by the drug labeling have all been cleared through the 510(k) process. They are the SPY family of NIR imaging systems including hand-held and the PINPOINT family of laparoscopic devices. They have all the indications sought by this Applicant except for lymphatic mapping. In this NDA, lymphatic mapping is a new indication with the drug being delivered through a new route of administration. The Applicant plans to submit 510(k)s to update the device indications to match the drug indications.

The cleared devices include:

K042961 SPY Intra-Operative Imaging System
K060867 SPY Intra-Operative Imaging System
K063345 Spy Imaging System
K073130 SPY Fluorescent Imaging System
K091515 SPY scope Intra-Operative Imaging System
K100371 SPY Intra-Operative Imaging System
K150956 PINPOINT Endoscopic Fluorescence Imaging System
K161792 PINPOINT Endoscopic Fluorescence Imaging System
K162885 SPI Phi Open Field Handheld Fluorescence Imaging System

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Animal efficacy studies were conducted by the Applicant to demonstrate visualization of biliary anatomy, visualization of blood flow and tissue perfusion by endoscopic fluorescence imaging with the optical imaging agent ICG. However, nonclinical pharmacology,

pharmacokinetics/ADME, toxicology studies were not conducted with SPY AGENT Green (indocyanine green). ICG has been available for more than 50 years, and findings of safety for SPY AGENT Green were based on relevant published nonclinical literature and available clinical data for ICG by the intravenous and interstitial routes of administration.

Animal Proof of Concept Studies
To support visualization of biliary anatomy including the major extra-hepatic bile ducts (the cystic duct, common bile duct, and common hepatic duct), ICG (0.5 mL – 2 mL bolus of 2.5 mg/mL solution) was intravenously administered to Yorkshire pigs, and biliary anatomy was imaged by white-light, PINPOINT mode, SPY mode or color segmented fluorescence (CSF) mode by use of several laparoscope models. Full visualization (86% to 100%) of biliary anatomy was enabled through ICG administration and PINPOINT 5 mm and 10 mm standard length fluorescence laparoscopes compared to white-light alone (14% - 43%).

To support visualization of blood flow and tissue perfusion, ICG was administered to pigs that had undergone surgical intervention to produce an ischemic region within the small bowel. Image quality was similar between the PINPOINT 5 mm and 10 mm standard length fluorescence laparoscope systems.

Toxicology Studies
Toxicity studies were not conducted on SPY AGENT Green or ICG by the Applicant. The Applicant provided literature data to support the nonclinical toxicology portion of the submission. In an extended, single-dose toxicity study, Sprague Dawley rats received a single intravenous administration of 20 mg/kg ICG [9]. No systemic or local toxicity was observed either 1 day or 14 days following intravenous administration of ICG at 20 mg/kg, the only dose tested. LD_{50} for ICG was 60 mg/kg in male Swiss-Webster mice, and no toxicity findings (histopathology, injection site reactions, or observations) were reported at a dose level of 35 mg/kg [10]. An intravenous LD_{50} of 60 to 80 mg/kg for ICG was reported in a study by Warner, G.S. [11].

Reproductive and Developmental Toxicity Studies
Reproductive and developmental toxicity studies were not conducted on SPY AGENT Green or indocyanine green.

Other Toxicity Studies
Photochemical toxicity studies were not conducted on SPY AGENT Green or ICG by the Applicant. In a published study by Ho J.D. et al. [12], prolonged exposure of ICG to human retinal epithelial cells, resulted in dose- and time-dependent cytotoxicity. In a published study by Gandorfer et al., [13] 0.05% ICG was found to be phototoxic to the retina following short-term irradiation by visible light.

5.2. Referenced NDAs, BLAs, DMFs

NDA-011,525 for IC-Green (held by Akorn) and ANDA-040,811 for indocyanine green (held by Diagnostic Green GMBH).

5.3. Pharmacology

5.3.1. Primary Pharmacology

ICG is a water soluble, tricarbocyanine dye. ICG absorbs light at around 800 nm, and fluorescence emission occurs in the near-infrared region (800 to 850 nm) [14]. ICG is rapidly bound to plasma protein following intravenous administration, resulting in a shift in fluorescence emission by 25 nm to longer wavelengths. Extensive binding to plasma proteins limits dye diffusion and leakage from the vasculature into the interstitium.

When administered by interstitial or intradermal injection, ICG is taken up by the lymphatic system and cleared through the subclavian veins into the circulatory system. ICG is poorly metabolized following administration by intravenous or interstitial routes of administration and undergoes rapid elimination through the hepatobiliary system and excretion in the bile salts, unchanged. Near-infrared fluorescence emission, extensive protein binding, and rapid elimination with poor metabolism contribute to the continued use of ICG in fluorescence imaging of blood flow, tissue perfusion, delineation of structural anatomy, and lymphatic mapping.

The Applicant conducted three imaging studies in Yorkshire pigs (**Table 1**, **Table 2**, **Table 3**) with ICG and PINPOINT to demonstrate visualization of biliary anatomy, including the major extra-hepatic ducts (cystic, common bile, and common hepatic ducts), blood flow, and tissue perfusion.

Table 1: Study Title: Visual Assessment of Biliary Anatomy with PINPOINT

Study Number	Report P283 VR01
Conducting Laboratory	(b) (4)
Date of Study Initiation	30 November 2015
GLP compliance	Yes
QA statement	Yes
Drug	Indocyanine green, 2 mL of a 2.5 mg/mL bolus intravenous injection

Methods
For imaging of biliary anatomy, Yorkshire pigs were anesthetized, and laparoscopic ports were placed for imaging. A 2 mL bolus injection of ICG (2.5 mg/mL) was delivered by intravenous administration. ICG was present in the bile by 40 min post-injection. Dissection of Calot's triangle was not required for visualization of biliary anatomy. Success criteria of the study was

"NIR visualization of at least one of the extra-hepatic bile ducts with the PINPOINT NIR. Inability to locate any of the specified ducts would be recorded as a study failure."

Results
Major extra-hepatic bile ducts were visualized through use of all PINPOINT laparoscopes tested using each of the PINPOINT display modes (white light, SPY, PINPOINT, and CSF mode). The Applicant stated that the PINPOINT System met the success criteria of the study with visualization of the extra-hepatic bile ducts with the PINPOINT NIR system.

Conclusions
The study demonstrated that the major extra-hepatic ducts could be visualized through use of the PINPOINT laparoscope in all four display modes. ICG did not interfere with biliary tract identification.

Table 2: Study Title: Visual Assessment of Biliary Anatomy with 10 mm VIS-NIR Endoscope

Study Number	Report P283 VR02
Conducting Laboratory	(b) (4)
Date of Study Initiation	11 April 2016
GLP compliance	Yes
QA statement	Yes
Drug	Indocyanine green, 0.5 mL of a 2.5 mg/mL bolus intravenous injection

Methods
For imaging of biliary anatomy, Yorkshire pigs were anesthetized, and laparoscopic ports placed for imaging. A 0.5 mL bolus injection of ICG (2.5 mg/mL) was delivered by intravenous administration by the ear. ICG was administered 40 minutes prior to insertion of the laparoscopic ports, and appearance of ICG fluorescence was assessed 45 minutes following ICG administration. Pigs were euthanized under general anesthesia by intravenous injection of sodium barbital solution. Success criteria of the study was "NIR visualization of at least one of the extra-hepatic bile ducts with the PINPOINT NIR. Inability to locate any of the specified ducts would be recorded as a study failure." Two pigs were evaluated as part of the study and visualization determined independently by three surgeons.

Results
Major extra-hepatic bile ducts were visualized through use of all PINPOINT laparoscopes tested using white light, SPY, PINOINT, and CSF display modes. One surgeon was not able to visualize the cystic duct under PINPOINT mode with any of the laparoscopes under evaluation. The cystic duct of pig No. 1 was visualized by two of three surgeons in white-light mode. All extra-hepatic ducts were visualized by all three surgeons through all fluorescence PINPOINT display modes in pig No. 2. Extra-hepatic ducts could not be visualized by surgeons under white-light mode. The

Applicant stated that the PINPOINT System met the success criteria of the study with visualization of the extra-hepatic bile ducts with the PINPOINT NIR system.

Conclusions
Visualization of biliary anatomy was enhanced through use of the PINPOINT NIR system in conjunction with ICG. The extra-hepatic ducts could not be visualized in two pigs by three surgeons under white light conditions.

Table 3: Study Title: Visual Assessment of Biliary Anatomy and Tissue Perfusion with 5MM VIS-NIR Endoscope and the Endoscopic Fluorescence Imaging Single Sensor Camera

Study Number	Report P298 TR12
Conducting Laboratory	(b) (4)
Date of Study Initiation	11 April 2016
GLP compliance	Yes
QA statement	Yes
Drug	Indocyanine green, 0.5 mL of a 2.5 mg/mL bolus intravenous injection

Objectives
The study objectives were to demonstrate visualization of one or more extra-hepatic bile ducts, permit surgeons to perform minimally invasive surgery using standard endoscope visible light, and permit visual assessment of vessels, blow flow, and related tissue perfusion, through use of ICG-enabled NIR imaging.

Methods
For imaging of biliary anatomy, Yorkshire pigs were anesthetized, and laparoscopic ports were placed for imaging. A 0.5 mL bolus injection of ICG (2.5 mg/mL) was delivered by intravenous administration by the ear. ICG was administered 40 minutes prior to insertion of the laparoscopic ports, and appearance of ICG fluorescence was assessed 45 minutes following ICG administration. Three pigs were evaluated as part of the study for visualization of major hepatic bile ducts and blood perfusion by three independent surgeons.

An ischemic region in the small bowel was created by a minimally invasive surgical procedure. ICG solution (2 mL of a 2.5 mg/mL solution) was administered intravenously. Visualization of blood flow in healthy and ischemic regions was assessed, and images in real time were recorded in SPY, PINPOINT, and CSF modes. A different scope was used for each pig (n=three pigs for study) following administration of ICG. Success criteria of the study was:

(a) NIR visualization of at least one of the extra-hepatic bile ducts with the PINPOINT NIR using 0°, 30° and 45° 5mm laparoscopes.
(b) Cauterization of blood vessels in the small bowel to create an ischemic portion that can be used to assess blood perfusion.

(c) NIR visualization of blood flow and delineation of ischemic areas induced in the small bowel with PINPOINT near-infrared imaging using 0°, 30° and 45° 5mm laparoscopes.

Results
The Applicant stated that the PINPOINT System enabled visualization of the major extra-hepatic bile ducts through use of the 5mm laparoscope system for NIR imaging. Surgeons were also able to perform minimally invasive surgery under visible light and visually assess vessels, blood flow and tissue perfusion. ICG permitted the delineation between normal and ischemic regions through NIR imaging.

Conclusions
Surgeons could visualize the major extra-hepatic ducts through use of the PINPOINT System and NIR imaging. Surgeons were also able to discriminate between normal and ischemic regions of the small bowel under SPY, PINPOINT, and CSF modes of the laparoscopic system.

5.3.2. Secondary Pharmacology

No secondary pharmacology studies with ICG or SPY AGENT Green were conducted by Novadaq.

5.3.3. Safety Pharmacology

No safety pharmacology studies with ICG or SPY AGENT Green were conducted by Novadaq.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Landsman M.L.J. et al. [14] "Light-absorbing properties, stability, and spectral stabilization of indocyanine green".	Binding to serum plasma proteins contributes to absorption characteristics of ICG and results in a 25nm shift in absorption and emission spectra.
Alander J.T. et al. [15] "A Review of Indocyanine Green Florescent Imaging in Surgery"	ICG is rapidly and extensively bound to serum plasma proteins, with no effect on protein structure. Fast binding limits the extent of dye diffusion from the vasculature and contributes to rapid absorption.
Distribution	
Proulx S.T. et al. [16] "Quantitative Imaging of Lymphatic Function with Liposomal Indocyanine Green".	C57Bl/6 mice were administered ICG either alone or as a liposomal formulation by intradermal injection of the paw. Enhancement of the foot-draining popliteal lymph nodes occurred within 1 hour post injection, demonstrating rapid distribution of ICG to the lymphatic space.

Type of Study	Major Findings
	Partial uptake of ICG by venous capillaries and/or endothelial venules may occur due to accumulation of ICG in the liver by 10 min.
Hammond et al. [17] "Endoscopic Tattooing of the Colon. An Experimental Study"	Mongrel dogs underwent laparotomy and catheter irrigation of the colon followed by a colonoscopy procedure to inject ICG (0.3 -1.5 mL of 1% ICG) into several sites in each dog (tattooing procedure). Adequacy of the tattooing procedure was assessed by the extent of residual dye labeling on the serosal surface of the colon. ICG was present for 7 days, post-injection with no adverse reactions reported.
Lee J.G. et al. [18] "Randomized Comparative Study of Indocyanine Green and India Ink for Colonic Tattooing: An Animal Survival Study"	Mucosal and serosal staining of the colon was present 2 weeks following submucosal injection of ICG by a sclerotherapy needle (colonic tattooing) in pigs (n=8; 17/29 injected sites). Mild histologic reaction that included granuloma (n=2) or inflammation (n=1) was present in pig colon following 1% ICG injection.
Price N. et al. [19] "Safety and efficacy of India ink and indocyanine green as colonic tattooing agents".	Colonic tattooing with ICG was only retained for 1 day in one of 22 New Zealand white rabbits, and injection of concentrated or diluted ICG resulted in mucosal ulceration and moderate to severe inflammation. In contrast, colonic tattooing with India ink was present up to 5 months in rabbits.
Metabolism	
Paumgartner G. [20] "The Handling of Indocyanine Green by the Liver	ICG is not metabolized following intravenous administration and is excreted by the liver. ICG does not undergo enterohepatic circulation or re-uptake from the intestine.
Excretion	
Ott P. et al. [21] "Hepatic Removal of Two Fractions of Indocyanine Green After Bolus Injection in Anesthetized Pigs".	ICG excretion route and elimination kinetics were investigated in anesthetized pigs (offspring of Danish Landrace/Yorkshire sows and

Type of Study	Major Findings
	Duroc/Hampshire boars) following intravenous administration of a single 5 min bolus injection. Plasma clearance of ICG was biphasic with short half-life of 3 to 4 minutes, and longer half-life of more than 1 hour at low concentrations. ICG excretion occurred exclusively through hepatobiliary elimination.
TK data from general toxicology studies *Study not conducted.*	N/A
TK data from reproductive toxicology studies *Study not conducted.*	N/A
TK data from Carcinogenicity studies *Study not conducted.*	N/A

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: Single-Dose Intravenous Toxicity Study of IRDye800CW in Sprague-Dawley Rats* [9]

Key Study Findings

- No toxicity findings (hematology, clinical chemistry, and histopathology) were reported either 1 day or 14 days following intravenous administration of ICG at 20 mg/kg, the no observed adverse effect level.

Conducting laboratory and location: Baylor School of Medicine, Houston TX
GLP compliance: Yes

Methods

Dose and frequency of dosing:	Single dose of 0 (vehicle) and 20 mg/kg once
Route of administration:	Intravenous
Formulation/Vehicle:	Saline
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	6/sex/group main study; 6/sex/group recovery
Age:	N/A
Satellite groups/ unique design:	No
Deviation from study protocol affecting interpretation of results:	No

*The authors conducted toxicity study of both dyes, ICG and IRDye800CW.

Observations and Results: changes from control
No toxicity studies were performed by the Applicant to evaluate the toxicological potential of ICG. The Applicant cited a published study by Marshall et al. [9] that described a GLP extended, single-dose toxicity study of ICG conducted in Sprague Dawley rats. There were no effects of ICG administration on hematology and clinical chemistry parameters or by histological examination. The NOAEL was determined to be 20 mg/kg, the only dose tested.

5.5.2. Genetic Toxicology

No studies have been performed to evaluate the genotoxic potential of ICG.

5.5.3. Carcinogenicity

No animal studies have been performed (or reported in the literature) to evaluate the carcinogenic potential of ICG or potential effects on fertility. ICG is not expected to have carcinogenic potential due to the relatively short half-life of 2.5 to 3 minutes and hepatobiliary excretion of intact dye several minutes following intravenous administration.

5.5.4. Reproductive and Developmental Toxicology

No animal studies have been performed (or reported in the literature) to evaluate reproductive and developmental toxicology of ICG.

5.5.5. Other Toxicology Studies

ICG can undergo decomposition, producing reactive oxygen species (e.g., singlet oxygen) that are potentially cytotoxic, following exposure to light [22]. Nonclinical studies reported in the literature evaluated the potential for phototoxicity following exposure to ICG. Prolonged exposure to ICG has the potential to be phototoxic to the retina as demonstrated by in vitro assays on retinal glial cells [23], retinal pigment epithelial cells [12], and ex vivo on the intact retina and eye [13, 24]

5.6. Clinical Pharmacology Executive Summary

This 505(b)(2) NDA for drug product SPY AGENT™ Green (indocyanine green for Injection, USP, also known as ICG or IC2000), is intended for use in combination with Novadaq premarket notification (510(k)) cleared devices. These devices include the PINPOINT Endoscopic Fluorescence Imaging System (PINPOINT) and the SPY Fluorescence Imaging System (SPY Elite).

ICG contains the active ingredient indocyanine green, a water soluble, tricarbocyanine dye.

No new clinical pharmacology studies have been conducted by the Applicant in support of this application. The clinical pharmacology review focused on the appropriateness of the proposed

doses of ICG for a) visualization of vessels, blood flow, and tissue perfusion before, during, and after surgery , including general minimally invasive surgical procedures in adult and pediatric patients 1 month of age and older; b) visualization of extrahepatic biliary ducts in adult patients; and c) for visualization of LNs and lymphatic vessels during lymphatic mapping in women with cervical and uterine tumors.

Three related meta-analyses provide data to support the effectiveness and safety of ICG for the fluorescence angiography and related biliary anatomy indication, studies Macro-IAM-01, Micro-IAM-01 and Biliary IAM-01. The pooled study results for visualization success rate from all three meta-analysis studies showed that overall success rate for the visualization for all three studies ranged from 97% to 99.9%.

Based upon the literature in meta-analysis, the recommended single intravenous dose in adults and pediatric patients 1 month and older for a surgical procedure is 1.25 mg to 5 mg. The recommended intravenous dose in adults for visualization of perfusion in extremities through the skin for plastic, micro, and reconstructive surgeries is 3.75 to 10 mg. Additional doses may be administered to obtain additional imaging sequences during the procedure, however, do not exceed a total dose of 2 mg/kg.

Use of ICG for visualization of vessels, blood flow and tissue perfusion has been established in pediatric patients 1 month and older. Pediatric use is supported by published data in 49 pediatric patients who received ICG for assessment of blood flow and tissue perfusion in cardiovascular/vascular and plastic, micro and reconstructive procedures, and clinical trials in adults. Adverse reactions in pediatric patients were similar to those reported in adults. The dose range was also similar to the effective dose range in adults.

Clinical data to support the use of ICG with Novadaq devices in lymphatic mapping is provided from the Novadaq FILM clinical study in subjects with cervical and uterine cancer. Additional data to support the lymphatic mapping indication is provided from a systematic review of published literature in this patient population. The dosage used in the FILM study was a total of 4 x 1 ml of a 1.25 mg/ml solution of ICG injected into the cervix as superficial (1 mm to 3 mm) and deep (1 cm to 3 cm) injection at each of the 3 o'clock and 9 o'clock positions.

5.7. Summary of Clinical Pharmacology Assessment

No new clinical pharmacology studies have been conducted by the Applicant in support of this application. The Applicant provided clinical pharmacology data from the literature. The clinical pharmacology review focused on the appropriateness of the proposed doses of SPY AGENT™ Green for various indications sought by the Applicant.

5.7.1. Pharmacology and Clinical Pharmacokinetics

A summary review of relevant published literature is given below:

The SPY fluorescence imaging systems are intended for intraoperative use. When injected intravenously, ICG rapidly binds to blood proteins, and thus is confined to the vascular space (i.e., does not leak from the circulation). Binding to blood proteins shifts the absorption peak for ICG from 780 nm to approximately 806 nm. SPY Elite or PINPOINT illuminate the surgical field/area of interest with an 806 nm laser light. Absorption of the laser light causes fluorescence excitation of the ICG, followed by emission of near-infrared light at a longer wavelength, peaking at approximately 830 nm. The NIR light used both in excitation and fluorescence penetrates tissue several millimeters. SPY Elite or PINPOINT capture the NIR images of the ICG fluorescence emission, process these images, and display them on a video monitor to enable the physician to evaluate blood flow within the vessels and tissue perfusion, or to visualize biliary anatomy.

ICG green undergoes no significant extrahepatic or enterohepatic circulation; simultaneous arterial and venous blood estimations have shown negligible renal, peripheral, lung or cerebrospinal uptake of the dye. ICG is taken up from the plasma almost exclusively by the hepatic parenchymal cells and is secreted entirely into the bile. After biliary obstruction, the dye appears in the hepatic lymph, independently of the bile, suggesting that the biliary mucosa is sufficiently intact to prevent diffusion of the dye, though allowing diffusion of bilirubin.

Following interstitial injection in humans, the protein binding properties of ICG cause it to be taken up by the lymph from which it enters the circulatory system and follows the same excretory pathway as intravenous administration.

The plasma fractional disappearance rate at a 0.5 mg/kg dose has been reported to be significantly greater in women than in men, although there was no significant difference in the calculated value for clearance.

No chemical or metabolic action of the ICG is required, and the ICG has no pharmacologic effect on the patient. ICG fluorescence emission is simply utilized to enable the capture of blood flow, tissue perfusion, or biliary anatomy images.

5.7.2. General Dosing and Therapeutic Individualization

General Dosing
The recommended dosing regimen is as follows:

Visualization of Vessels, Blood Flow and Tissue Perfusion:

- The recommended dose for a single image sequence is 1.25 mg to 5 mg ICG (b) (4) in adult and pediatric patients one month and older. For visualization of perfusion in extremities through the skin, the recommended dose is 3.75 to 10 mg (b) (4) Additional doses (b) (4) may be administered to obtain additional imaging sequences during the procedure.

Visualization of Extrahepatic Biliary Ducts:

- The recommended dose for a single image sequence is 2.5 mg ICG (b) (4) ICG should be injected intravenously approximately 45 minutes prior to surgery to allow ICG to collect into the biliary anatomy. (b) (4)

Visualization of Lymph Nodes and Lymphatic Vessels During Lymphatic Mapping for Cervical and Uterine Tumors:

- The recommended dose is four 1.25 mg injections (four 1 ml injections) for a total dose of 5 mg (4 ml). ICG should be injected at the 3 o'clock and 9 o'clock positions of the cervix with a superficial (1 to 3 mm) and deep (1 to (b) (4) cm) injection at each position.

Justification of Doses:
To support dosing for blood flow, tissue perfusion and biliary duct visualization, the Applicant conducted meta-analyses (Macro-IAM-01 (ICG Angiography Meta-analysis-01), Micro-IAM-01 and Biliary-IAM-01) from published literature citing the use of commercial ICG with Novadaq fluorescence imaging systems. The meta-analysis also supported the safety and effectiveness of ICG for fluorescence angiography (blood flow in vessels and microvascular perfusion) and related extrahepatic biliary anatomy visualization indications. Three different meta-analyses included the following searches:

Macro-IAM-01 - for intraoperative visualization of blood flow in arteries, veins and bypass grafts (macrovascular blood flow in vessels) including but not limited to: coronary bypass surgery, organ transplant procedures, plastic reconstructive surgery utilizing autologous flaps, renal cancer surgery, and vascular surgery.

Micro-IAM-01: for intraoperative visualization of tissue perfusion (microvascular blood flow) including but not limited to: myocardial perfusion in cardiac and cardiovascular surgeries, tissue flap perfusion in plastic reconstructive surgery, perfusion in vascular surgeries such as wound, amputation and coronary procedures, GI tract perfusion during surgery of the colon, stomach or esophagus, and parathyroid perfusion during endocrine surgery.

Biliary-IAM-01: for intraoperative visualization of extrahepatic biliary anatomy including at least one of the major extrahepatic bile ducts (cystic duct, common bile duct or common hepatic duct). Following protocol-specified criteria, 4 published studies were identified as containing unique (not duplicate reporting) patients having visualization success rates using ICG fluorescence.

Table 4 describes the key features, objectives, design and doses used for three metanalyses.

Table 4: Summary of Key Study Features Across Three Meta-Analysis Studies

Report or Study No.	Main study objective	Design	Number of patients / published studies	Location in NDA
Macro-IAM-01 Meta-analysis	To demonstrate the effectiveness of ICG fluorescence imaging using Novadaq's systems (including the da Vinci) in the intraoperative visualization of blood flow in arteries, veins and bypass grafts (macrovascular blood flow) during procedures such as: • Coronary bypass surgery • Organ transplant procedures • Plastic reconstructive surgery utilizing autologous flaps • Renal cancer surgery • Vascular surgery	Overall systematic summary review in the form of a meta-analysis of published clinical studies	1184 / 13 studies	Module 5.3.5.3.3
Micro-IAM-01 Meta-analysis	To demonstrate the effectiveness of ICG fluorescence imaging using Novadaq's systems (including the da Vinci) in the intraoperative visualization of blood flow in tissues (microvascular blood flow) during procedures such as: • Myocardial perfusion in cardiac and cardiovascular surgeries • Tissue flap perfusion in plastic reconstructive surgery • Perfusion in vascular surgeries such as wound, amputation and coronary procedures • GI tract perfusion during surgery of the colon, stomach or esophagus • Parathyroid perfusion during endocrine surgery	Overall systematic summary review in the form of a meta-analysis of published clinical studies	2055 / 33 studies	Module 5.3.5.3.4
Biliary-IAM-01 Meta-analysis	For intraoperative visualization of extrahepatic biliary anatomy including at least one of the major extrahepatic bile ducts (cystic duct, common bile duct or common hepatic duct)	Overall systematic summary review in the form of a meta-analysis of published clinical studies	314 / 4 studies	Module 5.3.5.3.5

NA = Not applicable
* Some of the publications identified in this category will also include data for tissue viability during plastic reconstruction surgeries.

Study Feature	Macro-IAM-01 N= 13 studies	Micro-IAM-01 N=33 studies	Biliary-IMA-01 N=4 studies
Clinical Sites	Single center: 12 Multicenter: 1 (2 sites) Countries US: 4 Japan: 4 Canada: 2 Finland: 1 Siwtzerland: 1 UK: 1	Single center: 29 Multicenter: 4 Countries: US: 27 Germany: 2 Denmark: 1 Hong Kong, China: 1 Switzerland: 1 UK:1	Single center: 4 Multicenter: 0 Countries: US: 2 Italy: 1 Switzerland: 1
Study Design types	Prospective: 5 Retrospective: 1 Longitudinal: 1 Pilot and feasibility: 3 Design not reported: 3	Prospective: 12 Retrospective:15 Prospective & retrospective: 1 Feasibility/preliminary: 1 Cohort: 1 Randomized: 1. Design not reported: 2	Prospective: 3 Retrospective:1
Drug Doses and Injection Techniques	ICG doses ranged from 0.0125 – 25 mg. ICG was administered by intravenous injection in all except two studies. One study did not report the injection technique and one study reported low dose (0.0125 mg) direct graft injection in addition to intravenous injection via the central line.	ICG doses ranged between 2.5 and 17.5 mg. The intravenous injection mode was reported for most of the studies either via a peripheral or central venous catheter (25/33, 76%). One (1) study reported injection into the antecubital fossa. Seven (7) studies did not report the injection technique.	Three studies reported administration of a 2.5 mg dose of ICG. The ICG dose in the 1 study ranged between 0.02 mg/kg to 0.25 mg/kg. Intravenous injections of ICG were reported for three studies. One study did not report the injection technique but likely it was intravenous injection of ICG as this is the usual route of ICG administration for cholangiography.
Imaging devices	SPY System: 12 da Vinci System: 1	SPY System: 25 PINPOINT System: 6 da Vinci system: 2	PINPOINT System: 1 da Vinci system: 3

All three meta-analyses provide data supporting the clinical utility of ICG with PINPOINT/ SPY fluorescence imaging systems. The pooled study results for visualization success rate from all three meta-analysis studies are presented in **Table 5**.

Table 5: Pooled Study Results for Visualization Success Rate for Intraoperative Visualization of Macrovascular Blood Flow in Vessels, Microvascular Tissue Perfusion and Extrahepatic Biliary Anatomy

Study	No. Visualizations Attempted	No. Visualizations Succeeded	Overall Success Rate (%)	95% CI
Macro-IAM-01	2854	2768	97.0	(96.3, 97.6)
Micro-IAM-01	2696	2693	99.9	(99.7, 100.0)
Biliary-IAM-01	286	284	99.3	(97.3, 100.0)

Reference: Studies Macro-IAM-01, Micro-IAM-01 and Biliary-IAM-01, Appendix C, Tables 3, provided in Modules 5.3.5.3.3 *Report Macro-IAM-01*, 5.3.5.3.4 *Report Micro-IAM-01* and 5.3.5.3.5 *Report Biliary-IAM-01*

To support the lymphatic mapping indication, the Applicant conducted one phase 3 clinical study with ICG and a systematic summary review, in the form of a meta-analysis, of published literature with commercially available ICG. The efficacy and safety of ICG was assessed in a randomized, open-label, multicenter, single-arm, within subject, lymphatic mapping study in patients with uterine and cervical cancer (FILM study; PP LNM 01).

A total of 176 patients were randomized to receive either ICG followed by 1% blued dye (BD) or BD followed by ICG. A total of 4 x 1 ml of a 1.25 mg/ml solution of ICG was injected into the cervix of each subject as a combination of a superficial and deep injection at each of the 3 o'clock and 9 o'clock positions.

The results of this study showed that 93% of nodes were identified with ICG with PINPOINT and 43% of nodes were identified with BD. Therefore, recommended interstitial dose in women is four 1.25-mg injections for a total dose of 5 mg. This dosing is also supported by 11 studies that were identified as containing unique (not duplicate reporting) patients having LN detection rates using ICG fluorescence. Five studies compared ICG to BDs, and six studies reported only ICG detection rates.

Pediatric Dosing:
The Applicant evaluated ICG dosing in pediatric patients by conducting a literature search that included publications from January 1, 1959 to June 8, 2018. According to the Applicant, 95 published articles were identified as containing unique (not duplicate reporting) of use of ICG in pediatric patients. Of these, nine articles contained data relating to the use of ICG with Novadaq/Stryker Fluorescence Imaging Technology Systems (Novadaq imaging articles; including the da Vinci). Thirty-eight articles contained data relating to the use of ICG with other (non-Novadaq) fluorescence imaging devices. Forty-eight articles contained data examining non-fluorescence imaging uses of ICG.

Of 1,185 pediatric patients in 95 articles, only 57 pediatric patients in nine Novadaq imaging articles were reported; whereas 133 pediatric patients in 38 non-Novadaq imaging articles and 995 pediatric patients in 48 non-imaging articles were reported.

The intravenous ICG doses ranged from 0.2 mg to 35 mg in publications with pediatric patients, except for one study where investigator injected 168 mg ICG intravenously (3 mg/kg) in a 15-year-old male adolescent with asymptomatic primary sclerosing cholangitis (non-Novadaq imaging article). The higher doses included cumulative amounts of multiple doses.

The pediatric recommended dose is based on data in the 49 pediatric patients who received ICG for assessment of blood flow and tissue perfusion in cardiovascular/vascular and plastic, micro and reconstructive procedures and achieved adequate visualization. The dose range was also similar to the effective dose range in adults. As shown in **Table 6**, a majority of pediatric subjects (41 of 49) received a dose of 1.25 mg to 5 mg. Therefore, a dose of 1.25 mg to 5 mg is recommended in children 1 month and older.

Table 6: Summary ICG Doses Pooled by the Pediatric Sub-Population (Data from Novadaq Angiographic Articles)

Patient Population	Number of Patients	Doses (mg)
Infants (1 mo-2 years)	3*	4.4
Children (>2-12 years)	1	5.0
Adolescents (13-21 years)	4	10.0
Infants to Adolescents (1 mo-21 years)	41	1.25-5.0
Total	49	1.25-10.0

*Includes conjoined twins, from an abstract that was obtained from a manual search after the literature search was performed on

Therapeutic Individualization

There is no therapeutic dose individualization.

Outstanding Issues

None

5.8. Comprehensive Clinical Pharmacology Review

The Applicant did not conduct any new clinical pharmacology studies. The clinical pharmacology described below is provided by the Applicant from the literature.

5.8.1. General Pharmacology and Pharmacokinetic Characteristics

Following intravenous injection in humans, ICG is rapidly bound to plasma proteins, primarily lipoproteins with a lesser and variable binding to albumin (2% to 30% of total) and is confined to the intravascular compartment with minimal leakage into the interstitium. Simultaneous arterial and venous blood estimations have shown negligible renal, peripheral, lung, or cerebrospinal uptake of the ICG. ICG is taken up from the plasma almost exclusively by the hepatic parenchymal cells and is secreted entirely into the bile. ICG does not undergo significant enterohepatic recirculation. After biliary obstruction, the dye appears in the hepatic lymph, independently of the bile, suggesting that the biliary mucosa is sufficiently intact to prevent diffusion of the dye, though allowing diffusion of bilirubin ICG has an initial biological half-life of 3 to 4 minutes with a slower secondary elimination phase of about an hour or more at lower concentrations.

In humans, after endoscopic injection of 1 ml to 2 ml of a 1% ICG solution into the colon wall, ICG stain was easily visualized for at least 36 hours in one study and for 8 days after endoscopic injection of 1 ml of a 12.5 mg/ml solution in a second study. When injected interstitially, the protein binding properties of ICG cause it to be rapidly taken up by the lymph. Since lymph fluid flows into the venous blood stream through the subclavian veins, the ICG drains with lymph fluid into the circulatory system. Then then it is cleared by the hepatic system in the same manner as following intravenous administration.

NIR light has tissue penetration of approximately 5 mm.

5.8.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Efficacy is not based on a biomarker or a pharmacokinetic (exposure-response/imaging). Clinical pharmacology information provides limited supportive evidence of effectiveness.

Based on a systematic summary review of published literature, three meta-analysis studies (Macrovascular ICG Visualization, Microvascular ICG Visualization, and Biliary Duct ICG Visualization) were conducted to assess vascular and related anatomical applications of ICG fluorescence imaging with Novadaq imaging systems.

All three meta-analysis studies provide data supporting the use of ICG with fluorescence imaging systems for visualization of the specified anatomy. The pooled study results for visualization success rate from all 3 meta-analysis studies are presented in **Table 5**.

The FILM study succeeded in demonstrating the effectiveness of intraoperative PINPOINT when used with ICG for the identification of LNs (confirmed to be lymphoid tissue) in subjects with uterine and cervical malignancies who were undergoing LN mapping. LNs visualization is supported by the literature data as well.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general patient population for which the indication is being sought. See **Section 5.7.2** for details on dosing.

Use of ICG for visualization of vessels, blood flow, and tissue perfusion has been established in pediatric patients 1 month and older. Pediatric use is supported by published data for 49 pediatric patients who received ICG for assessment of blood flow and tissue perfusion in cardiovascular/vascular and plastic, micro and reconstructive procedures, and clinical trials in adults (See **Section 5.7.2** for details).

The safety and efficacy of ICG for visualization of extrahepatic biliary ducts and LNs and lymphatic vessels during lymphatic mapping for cervical and uterine tumors have not been evaluated in pediatric patients.

The recommended single intravenous dose in adults and pediatric patients 1 month and older for a surgical procedure is 1.25 mg to 5 mg. Also, use of ICG for visualization of vessels, blood flow, and tissue perfusion has been established in pediatric patients 1 month and older. Pediatric use is supported by published data for 49 pediatric patients. Adverse reactions in pediatric patients were similar to those reported in adults. The dose range was also similar to the effective dose range in adults.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No; no intrinsic factors were identified to affect the performance of the product.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The product will be administered IV, therefore no effect of food is expected.

6. Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Table 7: Clinical Studies Relevant to Lymphatic Mapping

Trial Identity	NCT No.	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers & Countries
		Controlled Studies to Support Efficacy and Safety						
FILM-PPLNM 01	NCT 0220 9532	Phase 3 Non-Inferiority with-in patient comparison, randomized to receive either study drug or blue dye first	The cervix was injected 4 times with a 1 ml solution of a 1% of IB (10 mg/ml) for a total dose of 40 mg IB and 4 times with 1 ml of a 1.25 mg/ml solution of IC2000 for a total dose of 5 mg IC2000. The injections comprised a combination of a superficial (1 mm to 3 mm) and deep (1 cm to 3 cm) at the 3 and 9 o'clock positions of the cervix.	The ability of IC2000 and PINPOINT to identify Lymphatic tissue as non-inferior to blue dye and white light in PP population defined as the proportion of LNs identified by IC2000 & PINPOINT & IB respectively, (confirmed as lymphoid tissue by histology) divided by the total number of LNs identified & excised. If non-inferiority met, then comparison as superiority testing in mITT population	Single series of Injections at time of surgery Follow-up at 30 days	N=181 enrolled N=180 randomized N=176 completers PP=163 mITT=176 Safety=176	Age>18 years FIGO: Clinical Stage 1 Endometrial or Cervical Cancers Clinical Stage 1A Cervical Cancer<2 cm Negative nodal status and negative metastatic disease at randomization	6 U.S. sites (including Puerto Rico) 2 Canada
		Other studies pertinent to the review of efficacy or safety						
LNM-UC01	N/A	**Meta-Analysis:** 11 studies identified: • 5 with a	Dose of 0.1 to 10.0 mg ICG injected interstitially into the cervix	To assess the effectiveness of ICG fluorescence imaging using Novadaq's systems (including the da Vinci) for LN identification during lymphatic	Single injections given interstitially	N=1512	Early stage uterine and cervical cancers	

		comparator of blue dye and 6 with ICG only • 6 prospective • 4 retrospective		mapping in subjects with uterine and cervical malignancies Secondary: • per subject bilateral LN identification rate including both comparative and noncomparative studies • per subject bilateral LN identification rate in a comparison with radiotracer	at 2 sites in the cervix at time of surgery			

Table 8: Clinical Studies in Support of Visualization of Vessels, Blood Flow, Tissue Perfusion, and Biliary Duct Imaging

Study Author, Year	Population	Design, N	Dosing	Endpoints	Findings	Clinical & Statistical Comments
Biliary Duct Imaging						
Zarrinpar, 2016	Laparoscopic biliary and hepatic operations	Open label, single center, prospective study of different ICG doses and different injection to imaging times for NIRF imaging; N=37	Dose: 0.02 mg/kg to 0.25 mg/kg I.V. 10 min, 45 min, and 3 hours prior to surgery	Qualitative visualization scores (surgeons performing assessment were blinded to dose and injection time)	Visualization of biliary tract improved with 0.25 mg/kg dose and 0.08 mg/kg vs. 0.02 mg/kg ($p<.01$) and with increasing time (45 min vs. 10 min) from ICG injection to imaging	**Clinical:** Controlled single center dose and injection time study (limited info on image interpretation methods); Strong supportive data for proposed dosing and administration of ICG in this patient population **Statistical:** This appears to be a study aimed at evaluating the quality of visualization of the extrahepatic biliary duct with

Study Author, Year	Population	Design, N	Dosing	Endpoints	Findings	Clinical & Statistical Comments
						systematic variation of dosing and timing from injection of ICG to visualization. Visualization of the extrahepatic biliary tract is quantitatively improved with increasing doses of ICG and with increased time after ICG administration. The value of the finding would be more credible if it can be confirmed in at least another site.
Boogerd, 2017	Laparoscopic cholecystectomy	Open label, non-randomized, single center, prospective study of different ICG doses (2) and different injection timepoints (5) prior to surgery for NIRF imaging; N=28	Dose: =5 or 10 mg I.V.	Bile duct to liver ratios using GraphPad Prism Software	BLRs in the 5 mg group were highest 3 to 6 hours post dosing and 5 to 23 hours post dosing in the 10 mg group	**Clinical:** Observational dose and injection time study; supportive data for ICG use in the proposed population **Statistical:** This was a single-center, observational study with no primary endpoints specified. The study provides supportive information of the use of FI in this population.
Schols; 2013	Elective laparoscopic cholecystectomy	Open label, single center, prospective study of vascular and	Dose: 2.5 mg I.V. immediately after induction of anesthesia; 50%	Identification timepoints for biliary ducts and cystic artery with	Common bile duct and cystic duct identified earlier with NIRF; No ICG	**Clinical:** Observational study, supportive data

Study Author, Year	Population	Design, N	Dosing	Endpoints	Findings	Clinical & Statistical Comments
		biliary NIRF imaging for "early" biliary tract identification; N=30	pts required second 2.5 mg dose	fluorescence and conventional white light camera modes	associated complications	**Statistical:** This was a single-center, observational study with no primary endpoints specified. The study provides supportive information about the use of ICG for early biliary tract identification.
Buchs, 2013.	Patients undergoing robotic single-site cholecystectomy (RSSC)	Open label, single center, prospective study comparing indocyanine green near-infrared fluorescent imaging during RSSC to standard RSSC; N=44 (23 ICG pts, 21 standard RSSC)	Dose: 2.5 mg IV (30 to 45 min prior to surgery)	Perioperative outcomes	Shorter operative time for ICG group in pts with BMI <25. No differences in conversions, complications or LOS.	**Clinical:** Observational study, supportive data **Statistical:** This study was conducted to report authors' experience with ICG RSSC and compare the outcomes to standard RSSC. This was a single-center, exploratory study with no primary endpoints specified.
Spinoglio, 2013	Patients undergoing RSSC	Open label, single center, prospective study of ICG guided near-infrared	Dose: 2.5 mg IV (30 to 45 min prior to surgery)	Visualization rates for biliary anatomy	All procedures completed with at least 1 structure visualized per patient; no complications	**Clinical:** Observational study; Supportive data **Statistical:** This single-center study was conducted to report the safety and performance of

Study Author, Year	Population	Design, N	Dosing	Endpoints	Findings	Clinical & Statistical Comments
		(NIR) fluorescent imaging; N=45				the da Vinci Fluorescent Imaging Vision System in detecting biliary anatomy. Comparative information was with respect to historical data without affirming that the two populations were compatible.
Macro-Perfusion						
Desai, 2006	Patients undergoing coronary bypass surgery	Single center, prospective within-patient randomized trial comparing transit-time ultrasound flow (TTF) measurement vs ICG graft imaging with post-operative x-ray angiography as a reference standard. Patients (all examined grafts) were evaluated with	Dose =2.5, 1.25 mg or 0.125 mg (depending on anastomosis and graft to be assessed)	"Sensitivity" and "Specificity" to detect >50% stenosis or occlusion with X-ray angiography post-op day 4 as gold standard	Sensitivity of ICG reported as 83% vs. 25% for TTF; Specificity of ICG 100% vs. 98.4% for TTF; 12 (8%) grafts found to have >50% occlusion.	**Clinical:** Controlled single center study with exception of image interpretation methods; strong supportive data **Statistical:** This was a within-patient randomized, well-controlled, prospective, single-center clinical study with prespecified primary endpoint. The statistical methods were valid. The paper reports statistically significant results indicating that ICG imaging had a higher sensitivity than the TTF measurement in detecting greater than 50% stenosis or graft occlusion in the graft or perianastomotic area.

Study Author, Year	Population	Design, N	Dosing	Endpoints	Findings	Clinical & Statistical Comments
		both imaging modalities. N=106 patients (139 grafts)				
Desai, 2005	Patients undergoing coronary bypass surgery	Single center, prospective, open label, evaluation of intraoperative ICG imaging of coronary bypass grafts; N=120 pts (348 grafts).	Dose =2.5, 1.25 mg or 0.125 mg (depending on anastomosis and graft to be assessed)	Number of patients requiring graft revisions and agreement with X-ray angiography (subset of 6 pts, 22 grafts)	4.2% of pts needed graft revision using ICG visualization; 100% agreement with X-ray in small subset	**Clinical:** Observational prospective study; supportive data **Statistical:** This was a single-arm, single-center observational study to evaluate the quality of visualization underwent coronary bypass surgery. No primary endpoints were prespecified. The differences of the visualization quality between different types of conduits are difficult to interpret without rigorous study design.
Balacumaraswam, 2004	Patients undergoing coronary bypass surgery	Single center, prospective open label study of intraoperative ICG fluorescence imaging (Novadaq SPY system) of	Dose =0.03 mg/kg	Graft perfusion, patency rate	ICG fluorescence imaging identified graft failure in 4% of patients	**Clinical:** Observational prospective study supporting the feasibility of ICG NIRF imaging to assess CABG graft patency (one surgeon performed all procedures)

Study Author, Year	Population	Design, N	Dosing	Endpoints	Findings	Clinical & Statistical Comments
		graft patency in CABG procedures; N=200 patients (533 graft conduits).				**Statistical:** This was a single-center, observational study with no primary endpoints specified.
Micro-Perfusion						
Wormer, 2016	Patients undergoing abdominal wall reconstructive surgery	Prospective, randomized, multicenter (2) blinded controlled study of ICG imaging in abdominal wall reconstructive surgeries. N=95	Dose =5 mg via I.V. injection	Perioperative outcomes (complication rates): modification rate of flaps, rates of flap and skin necrosis, reoperation, wound infection and wound complications	Hypo-perfusion on ICG imaging associated with wound infection	**Clinical:** Multi-center, randomized, controlled study; strong supportive data **Statistical:** This was a randomized, double-blinded, multi-center, well-controlled study to evaluate the use of ICG-imaging in reducing wound complications in complex abdominal wall reconstruction. The study population was well defined. The report of the ICG imaging effect on wound infection provides supportive information.
Jafari, 2015	L sided anterior colon resection	Multi-center (11), prospective, open label clinical trial evaluating ICG fluorescent	Dose =3.75 to 7.5 mg via I.V. injection	Perioperative outcomes: ICG FA success rate, change in resection plan,	No anastomotic leaks in pts with change in resection plan based on ICG	**Clinical:** Multi-center study; Supportive data **Statistical:** This study was conducted to report authors'

Study Author, Year	Population	Design, N	Dosing	Endpoints	Findings	Clinical & Statistical Comments
		imaging for assessing colon and rectal perfusion. N=139		anastomotic leak rate	imaging; overall leak rate 1.4%.	experience with the feasibility and safety of ICG imaging during low anterior resection and left colectomy. There was no control group and no primary endpoint was prespecified. The success rate of 99% for ICG imaging was difficult to interpret without a reference group for comparison.
Hellan, 2014	Patients undergoing robotic colorectal resections	Multi-center, prospective study evaluating the impact of ICG fluorescence imaging on resection sites in L sided colon and rectal resections. N=40	Dose =2 mg/kg via I.V. injection	Perioperative outcomes: change in transection location base d on ICG	ICG imaging resulted in change of transection point in 40% of pts; 2 of these pts (5%) developed postoperative leak.	**Clinical:** Multi-center study; Supportive data **Statistical:** This study was conducted to report authors' experience with ICG in proximal visualization and distal visualization. The primary endpoints were not prespecified. The report of ICG effect on the mean time of decisions and the change of transection location provides supportive information on visualization of perfusion and determination of transection location in robotic colorectal resections.

Study Author, Year	Population	Design, N	Dosing	Endpoints	Findings	Clinical & Statistical Comments
Ris, 2014	Colorectal surgery	Single center, prospective, open label Study of NIRF (PinPoint System) ICG imaging to guide laparoscopic colorectal anastomosis. N=30 (25 cancer patients, 5 benign disease)	Dose =2.5 mg via I.V. injection	Peri-operative outcomes	Intraoperative ICG imaging successful in 29 of 30 patients; no complications and no post-operative anastomotic leaks	**Clinical:** Single-center observational study; Supportive data **Statistical:** This observational clinical study assessed the feasibility of real-time NIR fluorescence imaging using ICG during laparoscopic colorectal surgery. No primary endpoints were prespecified. The assessment results were purely descriptive.
Sherwinter, 2013	Low anterior resection for benign and malignant disease	Prospective, open label feasibility study using ICG imaging for assessing anastomotic micro-circulation; N=20	Dose =2.5 mg via I.V. injection	NIRF ICG imaging success rates	ICG imaging was successfully performed in all patients	**Clinical:** Supportive observational data **Statistical:** This was a single-center, open-label feasibility study observing the use of near infrared imaging to evaluate transanally anastomotic tissue perfusion following low anterior resection.
Phillips, 2012	Breast reconstructive surgery post	Single center, prospective, open label study of ICG	Dose =17.5 mg via I.V. injection	Intraoperative assessment for future skin	ICG imaging “predicted” flap failure in 19 of 21	**Clinical:** Supportive observational data for ICG NIRF

Study Author, Year	Population	Design, N	Dosing	Endpoints	Findings	Clinical & Statistical Comments
	mastectomy	imaging compared to clinical assessment to predict skin flap necrosis; N=32 pts (51 reconstructions)		necrosis using ICG (pos/neg) mapping with 4-week post-operative visit as reference standard	cases where clinical assessment did not.	**Statistical:** This was a single-center, observational study with a clearly defined primary endpoint. The study provides supportive information to assess if ICG can better predict skin flap necrosis compared to fluorescein dye and clinical judgment.
Munabi, 2013	Breast reconstructive surgery post mastectomy	Single center, open label study using perfusion scores on ICG imaging to predict flap outcomes; N=42 pts	Dose =5 mg via I.V. injection	Perfusion values of flaps and skin zones	Spy Elite value of ≤7 (SPY-Q Software) was reported to predict flap necrosis	**Clinical:** Supportive observational data for ICG NIRF **Statistical:** This was a single-center, observational study evaluating the use of ICG imaging as an assessment tool in breast reconstruction.
Losken, 2012	Breast reconstructive surgery post mastectomy	Single center, prospective study using intraoperative ICG imaging (Spy Q) to compare perfusion of different lower	Dose =5 mg via I.V. injection	Perfusion of flaps and skin zones (absolute flow values)	Perfusion of all flaps was successfully measured with ICG; differences in perfusion of different flaps &	**Clinical:** Supportive observational data for ICG NIRF **Statistical:** This was a single-center, observational study with a clearly defined primary endpoint. The study provides supportive information to

Study Author, Year	Population	Design, N	Dosing	Endpoints	Findings	Clinical & Statistical Comments
		abdominal flaps; N=77 pts			zones was observed	compare perfusion of different lower abdominal flaps.
Mattison, 2016	Breast reconstructive surgery	Single center, prospective study comparing ICG imaging (SPY Elite) to surgeon's assessment of flap viability; N=31 pts (55 breasts)	Not stated	Estimation of tissue viability by surgeon and ICG NIRF (using SPY-Q software) absolute perfusion values	5 of 31 pts (8 breasts) developed necrosis; 2 of 5 pts needed only debridement; the remaining 3 required replacement. Resection area was less based on surgeon's judgement compared to ICG NIRF; high false positive rate observed	**Clinical:** Supportive observational data for ICG NIRF *as an adjunct only* to clinical assessment for evaluating tissue perfusion in this population **Statistical**: This was a single-center, prospective study with a clearly defined primary endpoint. The study provides supportive information regarding the use of SPY imaging in the assessment of flap viability following skin-sparing mastectomies.
Venturi, 2017	Breast reconstructive surgery	Prospective, open label, observational study using intraoperative ICG imaging to predict nipple necrosis;	Not stated	Relative perfusion rates (using SPY-Q software) at 90 seconds	ICG imaging revealed decreased perfusion in all 3 (2 pts) cases of nipple necrosis compared to	**Clinical:** Supportive observational data that ICG NIRF may be a useful *adjunct* in evaluating patients at risk for future nipple necrosis **Statistical**: This was a single-

Study Author, Year	Population	Design, N	Dosing	Endpoints	Findings	Clinical & Statistical Comments
		N=20 pts (32 breasts)			normal perfusion in successful cases without necrosis	center, open-label, observational study that revealed impaired perfusion in patients who developed tissue necrosis compared to normal perfusion seen in successful operations without necrosis.

6.2. Review Strategy

Lymphatic Mapping

In a 2014 meta-analysis for ICG-guided lymphatic mapping for sentinel node biopsy procedures, the pooled detection rate was 96%, the sensitivity was 87%, with the specificity at 100%. The authors stated that this technique was safe, but ICG concentration and volume still needed assessment. **Table 9** reflects this use across multiple solid tumors evaluated [25]. The Applicant is seeking a LN mapping claim for uterine and cervical cancers based on the clinical trial they completed. (b) (4)

Table 9: Literature Summary

Author	Year	Country	Sample size	Mean age	Tumor	Stage	QUADAS
T. Kitai	2005	Japan	18	56.9	Breast cancer	12 T1, 6 T2	9
K. Nagata	2006	Japan	48	e	Colorectal cancer	25 pT1, 4 pT2	11
K. Ishikawa	2007	Japan	16	57.0	Gastric cancer	14 pT1, 2 pT2.	11
N. Furukawa	2010	Japan	12	e	Cervical cancer	e	11
Y. Tajima	2010	Japan	77	57.2	Gastric cancer	52 pT1, 21 pT2, 4 pT3	11
S. Yamashita	2011	Japan	31	63.0	Lung cancer	27 pT1, 4 pT2	9
I. Miyashiro	2011	Japan	10	68.0	Gastric cancer	10 pT1	11
K. Yano	2012	Japan	130	e	Gastric cancer	109 pT1, 21 pT2	11
S. Jeschke	2012	Austria	26	62.0	Prostate cancer	13 pT2, 13 pT3	11
E. Rossi	2012	USA	20	61.0	4 cervical cancer 16 endometrial cancer	e	12
R. Holloway	2012	USA	35	63.4	Endometrial cancer	13 I ,4 II ,8 III	11
C. Hirche	2012	Germany	34	e	Breast cancer	21 pT1, 24 pT2, 2 pT3/4	9
C. Hirche	2012	Germany	26	e	Colon cancer	6 pT1, 5 pT2, 15 pT3/4	11
Y. Yuasa	2012	Japan	20	65.3	Esophageal cancer	20 T1	9
J. Van der Vorst	2013	Netherlands	10	60.5	Oral cancer	e	11

Patient characteristics and qualities of included studies.
QUADAS: Quality Assessment tool for Diagnostic Accuracy in Systemic reviews.

Assessment of Blood Flow, Tissue Perfusion, and Biliary Duct Imaging

The NDA review approach was rooted in the long-term ICG clinical use and a well-understood safety profile along with several CDRH 510(k)clearances of the Applicant's various NIR imaging systems (**Table 10**) for use with ICG for the same indications proposed under the NDA. Given the history of clinical safe use and cleared indications, the studies submitted to extend the ICG drug label to include visualization of vessels, blood flow, tissue perfusion and extrahepatic biliary ducts were considered supportive. The clinical review team's objective was to determine if the totality of evidence (literature submitted, history of safe use, CDRH cleared indications) provides adequate support for the efficacy and safety of the proposed ICG indications.

A meta-analysis of the literature for each CDRH cleared indication, including biliary duct imaging and blood flow assessment (macro-perfusion and micro-perfusion), was submitted by the Applicant, but the review team did not find all the studies of acceptable quality for inclusion in the assessment of the performance of ICG imaging (b) (4) We selected prospective studies that provided useful clinical data in support of the proposed indication for further review; these studies are listed and summarized in **Table 7**. FDA reviewers conducted their own

literature search and identified additional studies for inclusion in FDA independent review of the literature.

Table 10: Applicant's Cleared Devices Using Indocyanine Green

Device	Indication for Use
K042961	For use in intra-operative visual assessment of the coronary vasculature and bypass grafts during CABG surgery
K060867	Intended for non-invasive intra-operative visual assessment of the coronary vasculature and bypass grafts during CABG
K063345	Used in capturing and viewing fluorescent images for the visual assessment of blood flow as an adjunctive method for the evaluation of tissue perfusion and related tissue-transfer circulation in tissue-free flaps used in plastic, micro-, and reconstructive surgical procedures
K073130	Intended to intra-operatively enable surgeons to visually assess blood flow and related tissue perfusion during organ transplant procedures
K091515	To provide real-time endoscopic visible and near infra-red fluorescence imaging. Enables surgeons to perform routine visible light procedures as well as further assess vessels, blood flow, and related tissue perfusion with near infra-red imaging during minimally invasive surgery
K100371	Intended to provide fluorescence images for the visual assessment of blood flow in vessels and related tissue perfusion during gastrointestinal surgical procedures
K150956	Indicated to provide real time endoscopic visible and near infra-red fluorescence imaging. Enables surgeons to perform minimally invasive surgery using standard endoscopic light as well as visual assessment of vessels, blood flow and related tissue perfusion and at least one of the major extra-hepatic ducts and when indicated intra-operative cholangiography
K161792	Same as K150956 above
K162885	visual assessment of blood flow to evaluate tissue perfusion and related tissue-transfer circulation in tissue and free flaps used in plastic and micro- and reconstructive surgeries visual assessment of blood flow in vessels and related tissues perfusion during gastrointestinal surgical procedures

7. Statistical and Clinical and Evaluation

7.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant performed one clinical trial to evaluate the safety and efficacy for the lymphatic mapping claim and provided published literature to support the claim as part of this 505(b)(2) application.

7.1.1. A Study Assessing the Safety and Utility of PINPOINT Near Infrared Fluorescence Imaging in the Identification of Lymph Nodes in Patients with Uterine and Cervical Malignancies Who Are Undergoing Lymph Node Mapping (FILM)

Trial Design
This was a phase 3, randomized, prospective, open-label, multicenter clinical study evaluating the efficacy and safety of using ICG with PINPOINT Near Infrared Fluorescence Imaging to identify LNs in subjects with uterine and cervical malignancies who were undergoing LN mapping. FILM was designed as a non-inferiority, within-patient comparison to determine the effectiveness of ICG using PINPOINT in the identification of LNs compared to LNs identified using 1% Blue Dye (BD) with standard-of-care high-definition white light visualization alone. Patients were randomized to receive either BD or ICG first, and evaluated with standard operating room lighting or NIR first (depending on which drug was injected first).

Study Endpoints
Primary Efficacy Endpoint:

1. Effectiveness of intra-operative IVG or BD to identify LNs defined as the proportion of LNs detected by ICG or BD, respectively (and confirmed as lymphatic tissue).

Secondary Endpoints:

1. LN detection rate defined as the proportion of cases in which at least one LN was found with either IICG or BD.
2. Bilateral LN detection rate.
3. Incidence of adverse events (AEs) and adverse device events of ICG and PINPOINT and BD.
4. Proportion of LNs identified by following lymphatic channels.
5. Anatomic distribution of LNs.

Statistical Analysis Plan
Efficacy of intra-operative ICG and PINPOINT with respect to BD was defined as non-inferior as per the following non-inferiority criterion:

Non-Inferiority Criterion
Percentage of LNs detected with ICG is greater than percentage of LNs detected with BD minus a 5% non-inferiority margin

If this primary objective was met, then ICG was tested for superiority by the following criterion:

Superiority Criterion
Percentage of LNs detected with ICG is greater than percentage of LNs detected with BD

Note: The primary endpoint is LN level, not patient level.

The hypotheses for non-inferiority/superiority are as follows, where:
PT=percentage tested
PC=percentage of controls

Non-inferiority: Null: PT≤ PC minus a 5% non-inferiority margin; Alternative: PT > PC minus a 5% non-inferiority margin

Superiority: Null: PT≤ PC; Alternative: PT > PC

Let D = Point Estimate Difference, tested minus control rates
Let LL = Lower Limit of Two-Sided 95% CI for D

The rejection of the non-inferiority null requires: LL> minus a 5% non-inferiority margin
The rejection of the "non-superiority" requires: LL>0%

As shown in **Table 17**, superiority was easily achieved.

Several secondary endpoints were evaluated. The results for two of these will be presented in this review:

Principal Secondary Endpoints:

1. Patient-level LN detection rate: Defined as the percentage of patients in which at least one LN was found

2. Bilateral LN detection rate: Defined as the percentage of patients in which a LN was found on both sides of the uterus

The bilateral endpoint is clinically significant since it impacts the extent of surgery.

The supportive study [27] (How et al., 2015, hereafter "How study") focused on these two principal secondary endpoints. The results from that study will be presented for comparison with the FILM Study.

Protocol Amendments

PP LNM 01 Version 1.0 June 24th, 2015

1. PP LNM 01 Version 2.0 January 18, 2016
    a. A new principal investigator was added (Fidel Valea, MD)
    b. Removed the secondary objective of intra-operative identification of lymphatic channels
    c. Updated the potential risk section to include the device license in Canada (one of the investigative sites)
    d. Randomization would occur on the day of surgery rather than during anesthesia
    e. Defined Group A as using blue dye first and Group B as using ICG first
    f. The concentration (10 mg/ml) and total dose (40 mg) of BD and the total dose of ICG (5 mg; 1.25 mg/ml x 4 ml) were added for clarification of the drug dose
    g. Changed the surgical procedure to allow the surgeon's judgement on what lymph nodes would be removed after identification of lymphatic channels and nodes with either blue dye or ICG rather requiring the removal of "all" nodes
    h. clarified that the area scanned after identification of lymph nodes is within the abdominal cavity (a full 360-degree scan), not just the area surrounding the injection site.
    i. Changed to exclude patients with locally advanced cervical or uterine cancer
    j. Redefined hepatic dysfunction as MELD Score >12, added laboratory testing requirements pre-operatively and defined which MELD calculator to use
    k. Defined what would constitute each PINPOINT LN mapping kit
    l. Specified which surgical procedures would be appropriate for inclusion
    m. Changed day 30 follow-up to telephone call
    n. Stated that post-operative nausea or vomiting in the first 24 to 48 hours, and post-operative pain related to the surgical procedure would not be considered AEs
    o. Agreed to a 95% two-sided confidence interval with a claim of non-inferiority if the lower bound of the interval was greater than -0.05; if the lower bound was greater than 0, the claim would be superiority
    p. Justified the sample size calculation of 300 lymph nodes or 150 patients (assuming at least two nodes per patient)
    q. Defined the safety population as all randomized patients who receive at least one injection of ICG or blue dye

2. PP LNM 01 Version 3.0 March 1, 2016
    a. Revised inclusion/exclusion criteria to match NCCN Clinical Practice Guideline to exclude patients with clinical Stage 1A1 cervical cancer without lymph-vascular pace involvement and negative margins on cone biopsy

3. PP LNM 01 Version 4.0 April 14, 2016
    a. To avoid spillage of the dye, mapping will be done by both techniques before excising the identified nodes

b. Required all nodes identified by either or both dyes to be removed
c. Allowed for inclusion those patients with Federation of International Gynecology and Obstetrics Clinical Stage IA cervical cancer ≤2 cm in size undergoing minimally invasive hysterectomy, trachelectomy, or conization with lymph node mapping
d. Changed study variables to determine the proportion of LNs identified from following lymphatic channels, removed the rate of positive LN detection and rate of negative LN detection
e. Increased the sample LN size in the study from 300 to 525LN (assumes at least three to four nodes per patients will be excised rather than two)
f. Defined SNL identification and mapping as the tumor draining lymph nodes rather that "first nodes" and added the goal of lymphadenectomy is to remove the LNs that are at high risk for local spread of the cancer
g. Changed secondary objective to conform with FDA recommendations, including the need for histologic confirmation of lymphatic tissue, the anatomic distribution of LNs, and the proportion of LNs found following lymphatic channels
h. Will use the per-protocol (PP) population for the non-inferiority endpoint and modified intent-to-treat (mITT) for the superiority testing
i. Method for handling missing data by a sensitivity analyses of the primary and secondary endpoints will be conducted using a best-case and a worst-case scenario. The best-case scenario will consider nodes with missing histology as lymphoid tissue for PINPOINT and as non-lymphoid tissue for blue dye. The worst-case scenario will consider nodes with missing histology as non-lymphoid tissue for PINPOINT and as lymphoid tissue for blue dye

4. PP LNM 01 Version 5.0 November 14th, 2016
    a. Hypothesis clarification of the discrepancy in the definitions of p_t and p_c
    b. Will perform sensitivity analysis on the non-inferiority rest using the mITT
    c. Addressed the details of the statistical method that will be used and appropriately account for the within-cluster correlation for primary hypothesis testing.

5. PP LNM 01 Version 6.0 August 25th, 2017
    a. Revisions to SAP as recommended by FDA implemented prior to database lock

7.1.2. Study Results

Compliance with Good Clinical Practices
The clinical trial was conducted in accordance with the International Conference on Harmonization Good Clinical Practice.

Financial Disclosure
Information was requested, and the response received was satisfactory. No conflicts of interest identified.

Patient Disposition
The mITT population was used for primary analyses. This population consisted of all subjects who received at least one injection of ICG or BD. A total of 176 subjects qualified as mITT, with 87 in the B-P Arm (BD first, then ICG) and 89 in the P-B Arm (ICG first, then BD). The results in these two arms were identical and are not reported separately. Inclusion in the PP population required that patients were evaluable for the primary endpoint. This population included 163 patients. A total of 545 nodes were detected in the mITT population; 517 in the PP population.

It should be noted that there were 32 excisions that were not validated as lymph nodes. Removal of these nodes from the analyses reduced the two principal populations as follows: mITT: 513 lymph nodes; PP: 485 nodes. The Applicant's tables indicate that all nodes entered into the calculations. However, as stated in the SAP (p11 of SAP): "the denominator (for node statistics) will include excised nodes confirmed as lymphoid tissue." Therefore, the Reviewer supplemented the Applicant's statistics with statistics confined to validated lymph nodes. This modification did not impact the statistical outcome.

The Statistical Reviewer did not find any clear statements regarding differences between the PP population other than that the PP lost 13 subjects due to protocol violations. The Reviewer's concern would be that the 13 subjects retained in the mITT had excisions where the lymph node status was "imputed", but no statement to this effect was found. In the text below FL or Test refers to ICG, while Control refers to BD.

There were eight study centers: two in Canada, six in the U.S. The patients disposition is summarized below.

Planned: n=150. Number Screened: n=199. Screen failures: n=18.Enrolled: n=181
Ineligible not randomized: n=1. Randomized but later ineligible (no study drugs given): n=4.
Final Randomized: n=176. Study Completers: n=176
Lost-to-Follow Up: None. Withdrew consent: None. Withdrawn for Adverse Event: None
PP Population: n=163
mITT: n=176; 134 distributed among 6 USA centers; 42 among 2 Canadian centers
Randomization by arm: 87 randomized to B-P Arm (BD then ICG); 89 to P-B Arm (ICG then BD)

Protocol Violations/Deviations
There were 18 major deviations from the protocol (**Table 11**). In one case, a patient received the wrong dose; 3 mL of each drug was used rather than 4 mL. In another case, the surgeon spilled the vial containing the blue dye requiring the blue dye to be replaced from pharmacy stock rather than from the study stock. However, both these patients underwent mapping and were included in the safety and mITT populations but not the PP population.

Table 11: Major Protocol Deviations

Descriptive Category	N
Enrollment (inclusion/exclusion criteria)	6
Consent Issues	2
Missing Labs	4
Pregnancy Test Missing	3
Device Malfunction	2
Spilled Study Drug	1
Wrong dose given	1
Aborted Procedures	5
Negative cone biopsy margins	1
Adhesions causing failure to map	1
Unsuspected Metastatic Disease	2
Excessive Bleeding precluding injections	1

There were 37 minor protocol deviations (**Table 12**). At one site, urine bilirubin rather than serum bilirubin was used. The pathology deviation was due to using slices of the node that were not of the same thickness as specified in the protocol but still allowed for tissue identification.

Table 12: Minor Protocol Deviations

Descriptive Category	**N**
Enrollment	17
Consent out of window	5
Alternative labs	8
ASA not known	3
Randomization done too early	1
Procedural	20
Video did not record	4
H&E slides not processed per protocol	2
Follow-up outside 30-day window	11
Vital signs not recorded at time of injection	1
Labs obtained outside window	2

Table 13 and Table 14 summarize the study patient demography and other baseline characteristics.

Table 13: Demographics

Demographic Parameters	Total (N=199) n (%)
Sex	
Female	180
Age	
Mean years (years)	62
Min, max (years)	31, 88
Age Group	
<65 years	111
≥65 years	70
Not recorded	18
Race	
White	140
Black or African American	8
Asian	7
American Indian or Alaska Native	
Native Hawaiian or Other Pacific Islander	
Other[1]	2
Ethnicity	
Hispanic or Latino	23
Not Hispanic or Latino	
Region (optional)	
United States	134
Canada	42
BMI	
<25	35
25 to <30	43
>30	98

Other Baseline Characteristics

Table 14: Cancer Characteristics for Study Population*

Characteristic	No.
Pre-op diagnosis	
Clinical stage 1 endometrial cancer	169
Clinical stage 1 cervical cancer	2
Clinical stage 1a cervical cancer	5
Final endometrial cancer histology	
Adenocarcinoma	146

Characteristic	No.
Serous carcinoma	13
Clear cell carcinoma	4
Carcinosarcoma	3
Other	3
Final cervical cancer histology	
Squamous cell	3
Adenocarcinoma	4

*Extracted from Table 14 of Applicant Study Report

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
The treatment protocol called for randomization of patients eligible into one of two cohorts using blue dye and white light first followed by ICG and NIR, or the opposite. Once the abdomen was entered and insufflated, the lymphatic mapping was done per the randomized assignment. All patients received both dyes and had mapping completed with both white light and NIR imaging.

All nodes identified, regardless of identification method, were to be removed and sent for frozen section confirmation that the specimen was indeed lymphatic tissue. Completion lymphadenectomy was not required by the protocol.

Efficacy Results – Primary Endpoint
To assess the effectiveness of ICG compared to blue dye in the identification of LNs, non-inferiority testing was performed. If successful, a superiority testing would be performed.

Table 15 summarizes the numbers of lymph nodes identified by various methods of visual inspection.

Table 15: Method of Node Identification

Sentinel Lymph Node Identification Method[a]	No. Nodes
Appearance (No dye present in node)	9
Blue dye only	6
Both blue and fluorescent dye	231
Fluorescent dye only	274
Following duct with both dyes/both dyes in node	1
Following duct with both dyes/fluorescent dye in node	1
Following duct with both dyes/no dye in node	4
Following blue duct/fluorescent dye in node	11
Following blue duct/no dye in node	3
Following fluorescent duct/no dye in node	5

[a] by following an identified channel an additional detection=25 nodes

The results for the primary endpoint of lymph node detections for both the mITT and for the PP populations are shown in **Table 16.** ICG is significantly superior to BD. In fact, ICG detects twice as many lymph nodes as does BD. The Control (BD) is not a strong comparator.

Table 16: Primary Endpoint Results (FILM Study)

Subjects/Nodes	Mean Nodes	Mean Detection/Subject			% Nodes Detected (LL of 95% CI)		
		FL	BD	Diff	FL	BD	Diff (*)
Applicant Results mITT (176/545) PP (163/517)	 3.1 3.2	 3.0 3.1	 1.4 1.5	 1.5 1.5	 97% 97%	 46% 47%	 50% LL=39% 50% LL=39%
Reviewer Results mITT (172/513) PP (162/485)	 3.0 3.0	 2.8 2.8	 1.3 1.3	 1.5 1.5	 93% 93%	 43% 43%	 51% LL =45% 51% LL =45%

*FL refers to ICG; * means statistically significant at the level of 5%*

Table 16 includes mean number of Detections per Subject and mean number of detections per subject stratified by ICG and BD. These mean values again indicate that ICG made virtually all lymph node detections, and BD approximately half of all these detections.

The CIs for the primary endpoint need to consider the possible correlations among "within-patient" detections. The Applicant used the ZO Statistic described by Nam and Kwon (Statistics in Medicine 2009 (28) 1668-1679). The Reviewer used the more straightforward Delta Method, which provided a tighter CI: With LL = lower limit of the two-sided 95% CI for the difference in lymph node detection percentages, ICG minus BD, the results were: (LL=45% using Delta versus LL=39% using Nam/Kwon. Since superiority requires only that the LL exceed zero, the method utilized is not critical.

Data Quality and Integrity
No issues identified with data quality or integrity.

Efficacy Results – Secondary and Other Relevant Endpoints
The first secondary outcome was the ability of ICG and blue dye to detect at least one lymph node in a patient. Another secondary outcome was the bilateral lymph node detection rate. Results from the are shown in **Table 17**.

Table 17: Secondary Endpoint Results (FILM Study)

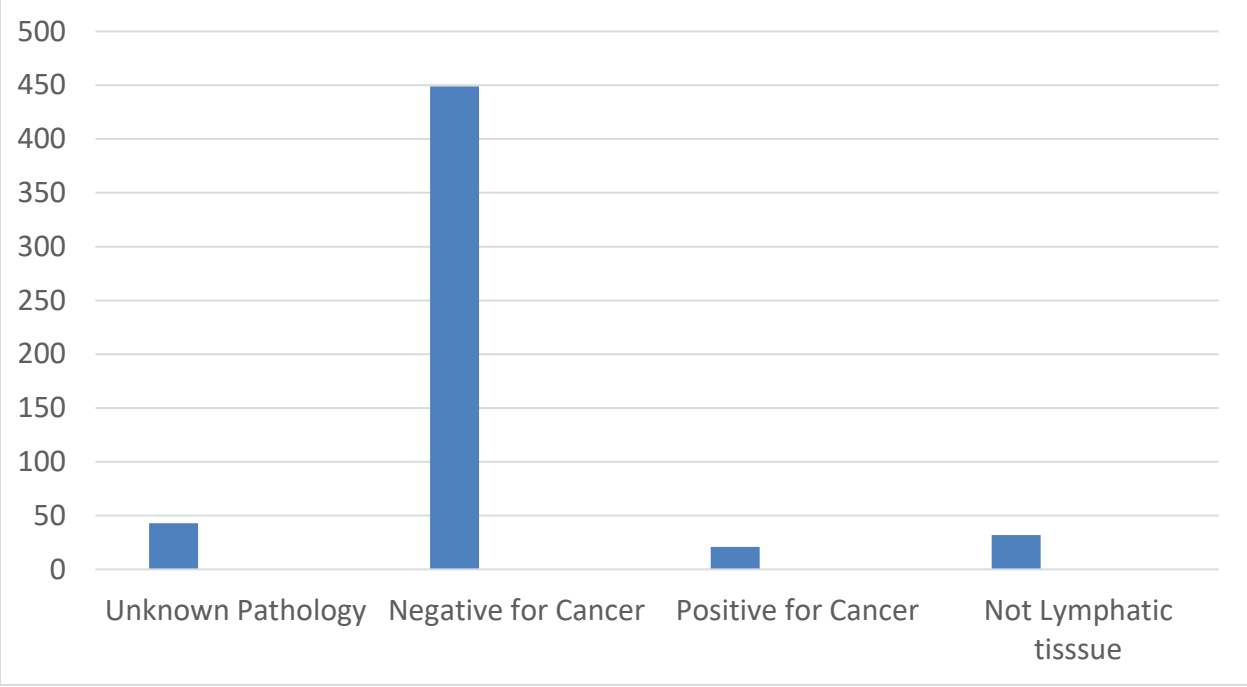
Detection Method	Percentage of Patients With at Least One Lymph Node Detected		Percentage of Patients With Lateral Lymph Node Detection	
	mITT	PP	mITT	PP
FL Alone	30%	29%	46%	45%
FL & BD	67%	69%	27%	30%
BD Alone	2%	1%	1%	1%
Neither	1%	1%	26%	24%

Abbreviations: BD, blue dye; FL, fluorescence; mITT, modified intent-to-treat; PP, per protocol

Clearly, BD alone is inferior to ICG, both in detecting at least one lymph node in a patient and, more significantly, in detecting lymph nodes bilaterally.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
Final pathology of the excised nodes, where the information was available, was reviewed. Because the study did not require collecting the final histopathology, but only the confirmation that the tissue removed was indeed lymphatic, there is missing data on 32 nodes.

Figure 3: Final Histopathology of Excised Nodes



As expected, only a small number of nodes identified were positive for metastatic disease. Twenty-one nodes were found to contain cancer, which upstaged 13 patients with otherwise unsuspected metastatic disease (8% PP, 7% mITT).

When looking at the location of nodes, there were 10 nodes in eight patients with a para-aortic location. All these nodes were identified with ICG while two were also found with blue dye. All nodes were negative for cancer. It could not be determined whether these patients would have undergone para-aortic dissection had the results of the dye not been available.

Eighteen patients had an omental biopsy or resection as part of their procedure. None of these patients had positive node pathology.

Additional Analyses Conducted on the Individual Trial
When using fluorescing dyes, the depth of the overlying tissue can limit the ability to see a signal. In practice, this generally means that patients with a higher BMIs may have limited use of the drug. For this review, the patients were divided into three classes based on BMI to compare the ability of both dyes to detect nodes.

Table 18: BMI and Detection

Node ID Method	Body Mass Index		
	<25	25 to <30	>30
No Dye Present	0	0	2
Blue Dye Only	0	3	2
Fluorescent Only	13	18	46
Both Dyes Present	21	20	36

For patients with the greatest BMI, ICG outperformed blue dye. This may be due to the need to dissect more thoroughly through fatty tissue to see the blue dye, while the fluorescence would be visible through several millimeters of tissue.

Since one of the characteristics of patients at risk for uterine cancer is obesity, the ability to use ICG to identify nodes in this population allows for a more targeted surgical procedure with less dissection of the tissue planes.

Integrated Review of Effectiveness

7.1.3. Assessment of Efficacy Across Trials

The Applicant's review of the literature consisted of 11 articles. They were selected based on a systematic and pre-specified method. The Applicant's stated objective of this meta-analysis was to assess the effectiveness of ICG fluorescence imaging using Novadaq's systems for LN identification during lymphatic mapping in subjects with uterine and cervical malignancies.

Table 19: Summary of Literature from Applicant

Author	Study Design	No. Patients	Comparator	ICG Dose	BD Dose	Comment
Holloway 2012 [26]	Retrospective	35	ICG & BD	0.5ml **(1.25 mg/ml)**	1 ml	
How 2015 [27]	Prospective	100	ICG, Tc99, BD	0.1ml **(0.25 mg/ml)**	0.8ml	**Tc99 0.1ml**
Tanner 2015 [28]	Prospective	111	ICG or BD	4ml	40 mg	
Ehrsiman 2016 [29]	Retrospective	36	ICG or BD	4ml	40 mg	
Eriksson 2017 [30]	Retrospective	472	ICG or BD	4ml	Not stated	
Rossi 2012 [31]	Prospective	20	ICG only	0.5ml **(500 µg/ml)**		
Plante 2015 [32]	Prospective	50	ICG Only	4ml		
Paley 2015 [33]	Prospective	123	ICG Only	2ml		
Hagen 2016 [34]	Prospective	108	ICG only	2ml **(5 mg/ml)**		
Rossi 2017 [35]	Prospective Cohort	385	ICG Only	2ml **(0.5 mg/ml)**		Multi-Center **FIRES Trial**
Perrson 2017 [36]	Prospective	102	ICG Only	1ml **(2.5 mg/ml)**		

Of the studies selected, five were comparative using ICG and blue dye. All five had a higher bilateral detection rate for ICG over blue dye. Four of the five also showed a higher LN detection rate.

When these papers were reviewed, only the How study met the trial design quality that would be consistent with the Applicant's trial. Therefore, the How study is the only study reviewed in depth. The focus is on the lymphatic mapping aspects of the study.

How Study
How et al. [27] was designed as an open-label, controlled, prospective, single-center clinical trial consisting of 100 patients diagnosed with clinical Stage 1 endometrial cancers. All patients received four injections of a mixture containing ICG (0.1 ml, 0.25 mg/ml), blue dye (0.8 ml) and technetium-99 sulfur colloid (0.1 ml) into the cervix, superficial and deep, at 3 o'clock and 9 o'clock.

The regional locations of the LNs were documented as well as the identification method.

Endpoints for the How Study
Detection rate was calculated as the number of patients with at least one detected LN divided by the total number of patients who underwent lymphatic mapping. Subgroup analysis for detection rates was done for each tracer method.
Results:
The two endpoints from the How study **Table 20** in are the two principal secondary endpoints listed above for the FILM Study: 1) Percentage of patients with at least one LN detection; and 2) Percentage of patients with bilateral LN detections. The How study generally supports the results of the FILM study.

Table 20: Indocyanine Green Versus Blue Dye for Overall and Bilateral Detection of Lymph Nodes in Patients with Uterine or Cervical Cancer

Detection Method	FILM Study	How Study	FILM Study	How Study
FL alone	30%	20%	46%	25%
FL and BD	67%	67%	27%	40%
BD alone	2%	3%	1%	3%
Neither	1%	10%	26%	32%

Source: FILM study statistics derived from Statistical Reviewer's mITT data.
Abbreviations: BD, blue dye; FL, fluorescence

7.1.4. Additional Efficacy Considerations

Literature submissions in support of visualization of vessels, blood flow, tissue perfusion, and biliary duct imaging are summarized below

Visualization of Vessels, Blood Flow and Tissue Perfusion

Study 1: Desai et al, 2006. A randomized comparison of intraoperative ICG imaging and transit-time ultrasound flow (TTF) flow measurement to detect technical errors in coronary bypass grafts.

Population: Patients (N= 106) undergoing isolated coronary artery bypass grafting (46 patients underwent x-ray angiography, 139 grafts total).

Objectives: Compare ICG NIRF imaging to transit-time ultrasound for assessment of graft patency.

Study Design: Single-center, prospective within-patient randomized clinical trial comparing TTF measurement versus ICG imaging with post-operative x-ray angiography as a reference standard.

Endpoints: "Sensitivity and Specificity" to detect >50% stenosis or occlusion with x-ray angiography post-op day 4 as gold standard.

Statistical Analysis: Comparisons between the two imaging tests were performed using the extended McNemar test for paired data; sample size calculation was performed based on 80% power to demonstrate a 40% difference in sensitivity between the two imaging modalities.

Results
This prospective, randomized, controlled single-center study reported statistically significant differences between ICG angiography and TTF for detecting greater than 50% stenosis or graft occlusion in patients undergoing coronary bypass grafting in whom surgeons used both imaging modalities to assess graft patency (with x-ray angiography as reference standard). Sensitivity of ICG was reported as 83% versus 25% for TTF; Specificity of ICG 100% versus 98.4% for TTF; PPV of ICG 100% versus 60% for TTF; NPV of ICG 98.4% versus 93.2% for TTF. Given there is no standard of care for intraoperative graft assessment, these results support the use of ICG NIRF as an intraoperative tool for aiding surgeons in their assessment of graft patency. There were both ICG false negatives (two) and false positives (two) when compared to the x-ray angiography. Thus, ICG NIRF should be thought of as an adjunctive imaging tool.

Study 2: Wormer et al, 2016. A prospective randomized double-blinded controlled trial evaluating ICG fluorescence angiography on reducing wound complications in complex abdominal wall reconstruction.

Population: Patients undergoing abdominal wall reconstructive surgery for hernia repair.

Objectives: Evaluation of effect of ICG NIRF imaging on surgical complications.

Study Design: Prospective, two-center, randomized, double blinded, controlled study of ICG imaging in abdominal wall reconstructive surgeries **(**N=95).

Endpoints: Complication events: modification rate of flaps, rates of flap and skin necrosis, reoperation, wound infection, and wound complications.

Statistical Analysis: No hypothesis testing was performed; descriptive statistics were used to compare the experimental group (surgeons informed of ICG image results) with control group (surgeons unaware of ICG image findings).

Results
Forty-nine patients were randomized into the control group versus 46 for the experimental group; patient demographics (e.g., age, BMI, medical history) and operative characteristics were reported as similar. In the experimental group, advancement flaps were modified by the surgeon 37% of the time versus 4% in the control group. There were no statistically significant differences between groups for skin necrosis rates, fat necrosis, reoperation rates, wound infection or wound complication rates. Patients identified as having hypoperfusion by ICG imaging had a higher rate (28.1% versus 9.4%) of wound infection. However, flap modification after viewing images in these patients *did not* help prevent wound related complications (15.6% versus 12.5%,).

Other studies
An additional 11 studies were reviewed in which ICG was administered via IV injection at doses ranging from 0.125 mg to 17.5 mg preoperatively or intraoperatively (and may have included a repeat administration during surgery) in patients undergoing coronary artery bypass grafting, abdominal and breast reconstructive surgeries where NIRF was performed. Although each of these studies contained design inadequacies, the literature data provides supportive evidence for the use of ICG for intraoperative visualization of vessels and assessment of blood flow and tissue perfusion.

Visualization of Extrahepatic Biliary Ducts
Study 1: Zarrinpar, A. et al. Intraoperative Laparoscopic Near-Infrared Fluorescence Cholangiography to Facilitate Anatomical Identification: When to Give Indocyanine Green and How Much. Surgical Innovation, 23(4); 8/01/2016.

Population: Adult patients undergoing laparoscopic biliary and hepatic operations; N=34.

Objectives: Explore optimal dosing and timing from ICG injection to ICG visualization.

Study Design: Prospective, non-randomized, single-center study in patients undergoing biliary and hepatic surgery evaluating different ICG doses and timing from ICG injection to imaging the biliary tree.

Endpoints: Qualitative and quantitative image scores for each dose and injection time.

Statistical Analysis: No pre-specified statistical plan; Student's t-test was used to compare data across groups.

Results
This single-center prospective, non-randomized clinical study provides supportive data for the proposed dosing and administration of ICG for visualization of extra-hepatic biliary ducts in minimally invasive biliary (16 patients) and hepatic (17 patients) surgeries. Patients were assigned to groups based on dose and timing of ICG injection relative to surgery and imaging. Group 1 patients were given ICG via intravenous administration 10 minutes prior to visualization and included three different doses (0.02 mg/kg, 0.04 mg/kg, 0,08 mg/kg); group 2

received ICG injections 45 minutes prior to visualization and included four doses (0.02 mg/kg, 0.04 mg/kg, 0,08 mg/kg, 0.025 mg/kg); group 3 received ICG 3 hours prior to visualization with two different doses (0.08 mg/kg, 0.025 mg/kg). The Novadaq PINPOINT endoscopic imaging system was used intraoperatively and surgeries were conducted according to standard of care.

Qualitative assessments were performed by the operating surgeon (blinded to dose and timing of injection) at the completion of each case and rated on a scale of 1 to 5 (1=no improvement, 2=marginally improved, 3=sufficiently improved, 4=well improved, 5=greatly improved) for ability to visualize the extrahepatic biliary tree (distinguishing common bile duct, common hepatic duct, and cystic duct from surrounding tissue). Quantitative fluorescence assessments were performed and calculated as a ratio of the fluorescence signal of the common bile duct to surrounding tissue (fat or liver). Statistical analysis consisted of using the Student's t-test to compare data across the groups and p values < .05 were considered significant.

While there were study design limitations (single site, single rater for qualitative scores, no hypothesis testing), both the qualitative and quantitative assessments were reasonably consistent. The highest duct to fat quantitative scores were seen for the 180 minutes post injection (10.9±8.1 vs. 3.5±3.0 at 15 minute), and there was a trend for higher duct to fat ratios at higher doses (0.08 mg/kg and 0.25 mg/kg). The qualitative assessments also showed higher visualization scores for visualization procedures beginning either 45 minutes or 180 minutes post injection compared to the shorter 15-minute post injection interval. There was also a trend toward higher visualization scores for higher doses for 0.25 mg/kg vs 0.02 mg/kg). This study provides reasonable support for the Applicant's proposed indication of imaging extrahepatic biliary ducts at an initial dose of 2.5 mg (total dose not to exceed 2 mg/kg).

Other studies Five additional literature publications were reviewed that studied the use of ICG for extrahepatic biliary visualization in patients undergoing cholecystectomies at doses between 2.5 mg and 10 mg. Endpoints evaluated included bile duct to liver fluorescence ratios at different doses and timepoints post ICG injection as well as timepoints for identifying ducts with ICG vs standard light, operative times for ICG vs standard procedure and duct visualization rates. All studies reviewed support the claim that ICG can be used as an adjunctive tool for visualization of the extrahepatic biliary ducts. There were no adverse events related to ICG administration reported in any study described above.

In summary, the literature reviewed supports the use of ICG NIRF as an adjunct imaging tool to identify extrahepatic biliary ducts in patients during biliary and hepatic operations. Due to study design limitations, the performance characteristics in terms of sensitivity and specificity for identifying extrahepatic ducts is not available.

7.1.5. Integrated Assessment of Effectiveness

The Applicant's FILM Study demonstrated that ICG is superior to blue dye for visualization of lymph nodes in the lymphatic mapping procedure studied. Virtually all nodes were visualized by ICG and about half of these were by blue dye (97% versus 47%).

The performance in the clinically important endpoint of bilateral node detection also favored ICG:
73% versus 28% (ICG vs BD) for FILM Study
65% versus 43% (ICG vs BD) for the How study

7.2. Review of Safety

ICG has been in use in the United States for nearly 60 years. It has a well-established safety profile after intravenous administration. Hypersensitivity reactions have been reported with use of ICG, as have urticarial reactions, anaphylaxis and death. The risk of anaphylaxis for ICG is reported to be about 1 per 42,000 [37,38].

The current ICG label contains a warning regarding anaphylactic deaths following drug administration during cardiac catherization. The label also includes warnings of (b) (4) Other adverse reactions on the label include urticaria, pruritus, flushing, (b) (4) and skin discoloration.

7.2.1. Safety Review Approach

For the intravenous route of administration, the Applicant conducted a review of the published literature for the commercially available product used with their devices, for the years 2001 to 2017.

The route of administration used for lymphatic mapping in gynecologic cancer is new, as it is given interstitially into the cervix. Much of the safety review will therefore focus on this new method of administration.

7.2.2. Review of the Safety Database

Overall Exposure
The Applicant identified 445 articles that included more than 21,000 patients who underwent ICG image-guided procedures using the SPY systems. The indications in studies and reports for ICG image-guided procedures included visualization of blood circulation and related tissue perfusion, lymphatic flow, and biliary anatomy during a variety of surgical procedures such as plastic, micro- and reconstructive surgeries, cardiovascular surgeries, tumor detection, organ tattooing, biliary duct visualization, lymphography, and lymphatic mapping.

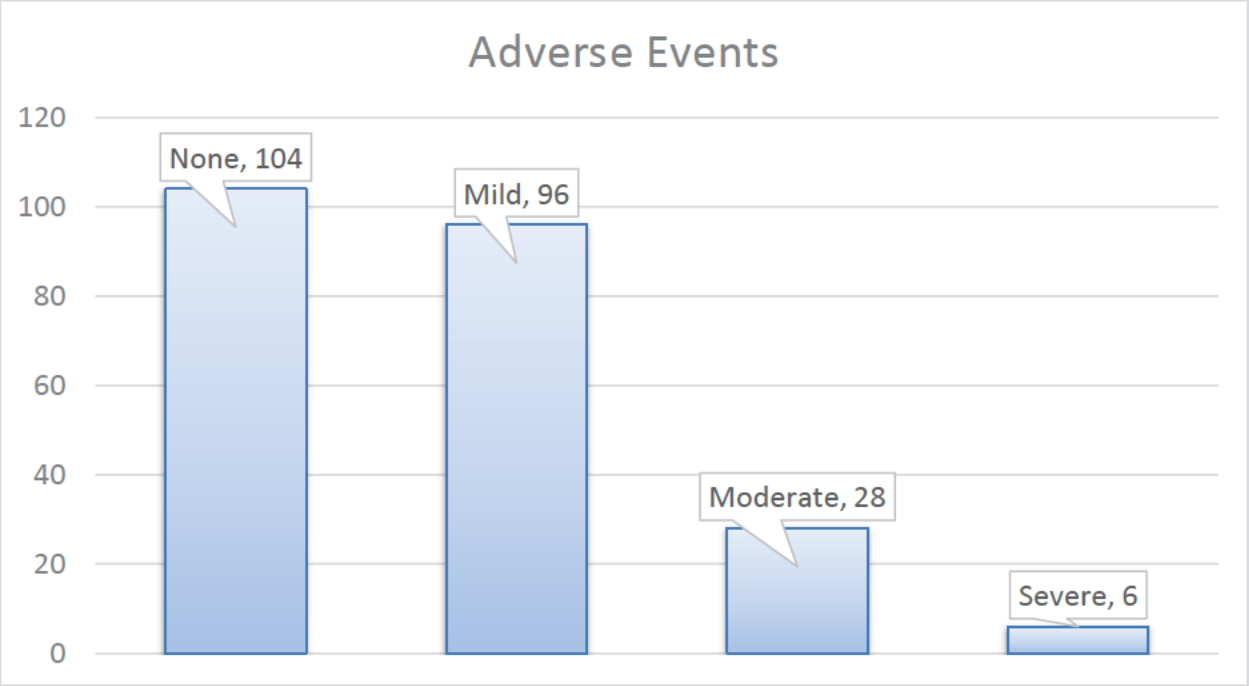
ICG has been marketed for almost 60 years and has a well-established safety profile. For visualization of vessels and perfusion, ICG has been used for more than 30 years. Additionally, ICG has been used for lymphatic mapping for 20 years with a strong safety profile as well. Overall, it is estimated that the risk of allergic reactions from ICG is 1 per 42,000 uses [37,38].

7.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
Many, if not all, adverse events seen in the FILM trial can be attributed to the surgical procedures rather than to the drug.

Categorization of Adverse Events
Safety data from the clinical trial conducted by the Applicant is presented below (**Figure 4**, **Table 21**). Both study arms received ICG and blue dye, therefore, it is not possible to determine whether any adverse events were related to the study drug alone.

Figure 4: Adverse Events Severity



Only six severe adverse events in five patients were noted in the trial. They required hospitalization, and all resolved without sequelae.

Table 21: Adverse Events by Organ System

Organ System	No. Events
Cardiac disorders	4
Ear and labyrinth disorders	2
Gastrointestinal disorders	22
General disorders and administration site conditions	6
Immune system disorders	1
Infections and infestations	15
Injury, poisoning and procedural complications	39

Musculoskeletal and connective tissue disorders	7
Nervous system disorders	8
Psychiatric disorders	7
Renal and urinary disorders	7
Reproductive system and breast disorders	2
Respiratory, thoracic and mediastinal disorders	5
Surgical and medical procedures	1
Vascular disorders	4

7.2.4. Safety Results

Deaths
There were no deaths seen in the clinical trial or reported in the literature reviewed.

Serious Adverse Events
Six serious adverse events in three patients requiring hospitalization were recorded for the trial. None were attributed to the study drug.

There were two patients with dizziness, vertigo and/or headache. One patient had atelectasis and a trace pleural effusion, a not uncommon occurrence after abdominal/pelvic surgical procedures. One patient had what was classified as a partial bowel obstruction (grade 3), which resolved within 7 days, and was most likely a post-operative ileus.

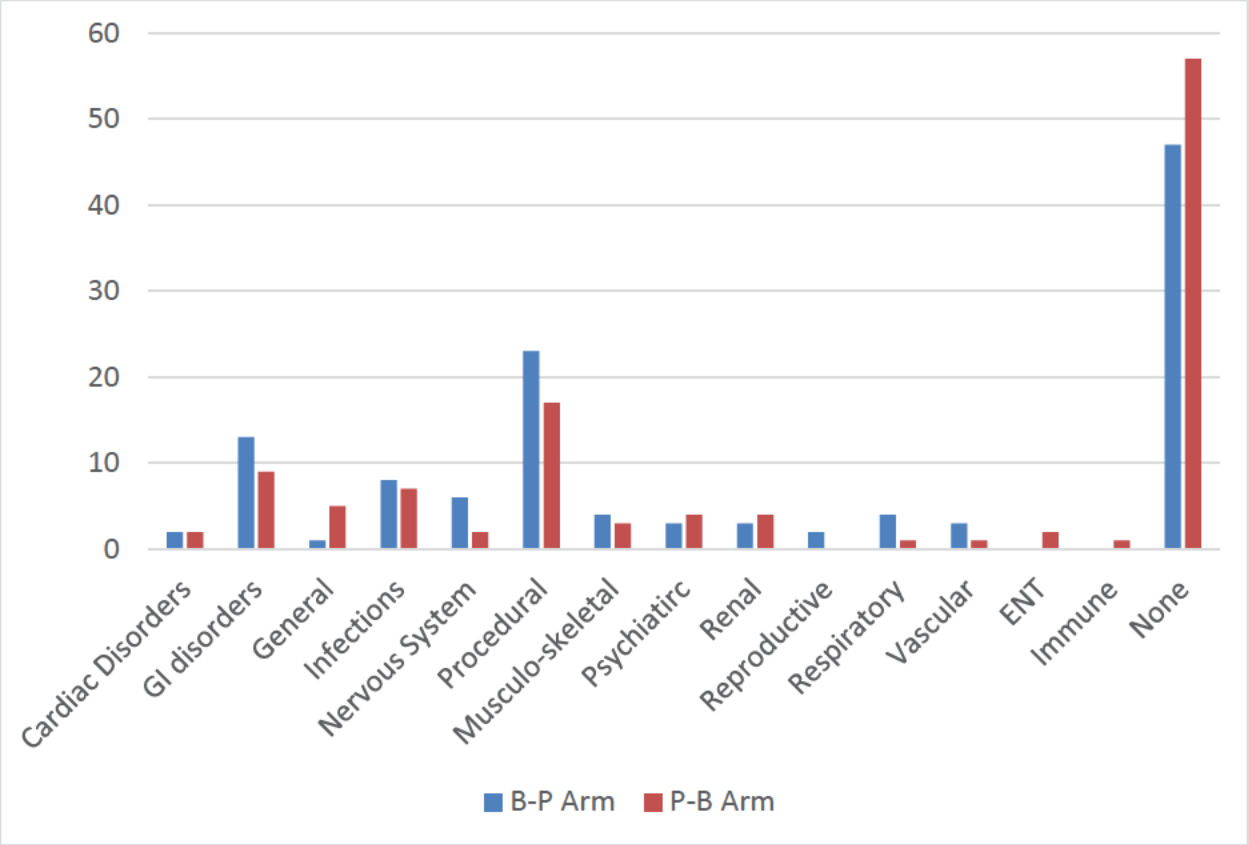
Also reported were excessive drowsiness not felt to be related to anesthesia and a corneal abrasion treated with medication. Neither are attributable to the study drug.

There were no serious adverse events related to ICG administration in the literature studies reviewed for either the biliary or blood vessel and tissue perfusion indications.

Dropouts and/or Discontinuations Due to Adverse Effects
There were no dropouts due to adverse events.

Frequent Adverse Events
Among the adverse events seen in the trial, the highest numbers were classified as procedural, followed by GI disorders (**Figure 5**).

Figure 5: Number of Adverse Events by Organ System



When broken down, as shown below, they would be expected as part of the surgical procedures.

Figure 6: Number of Procedural Events

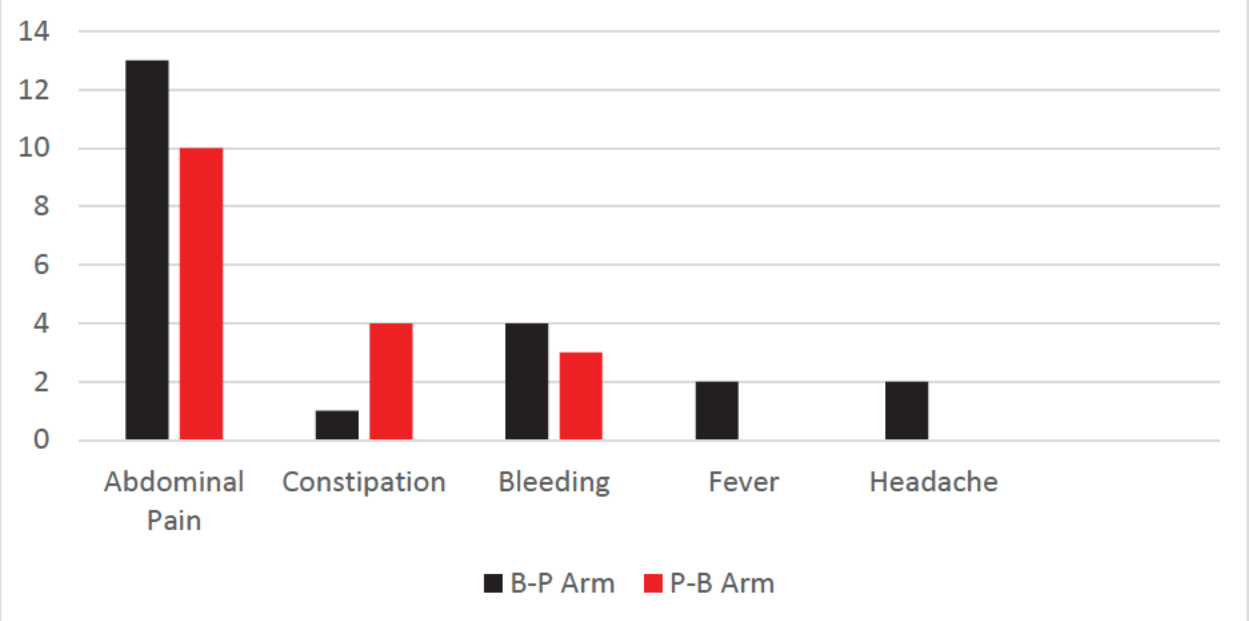
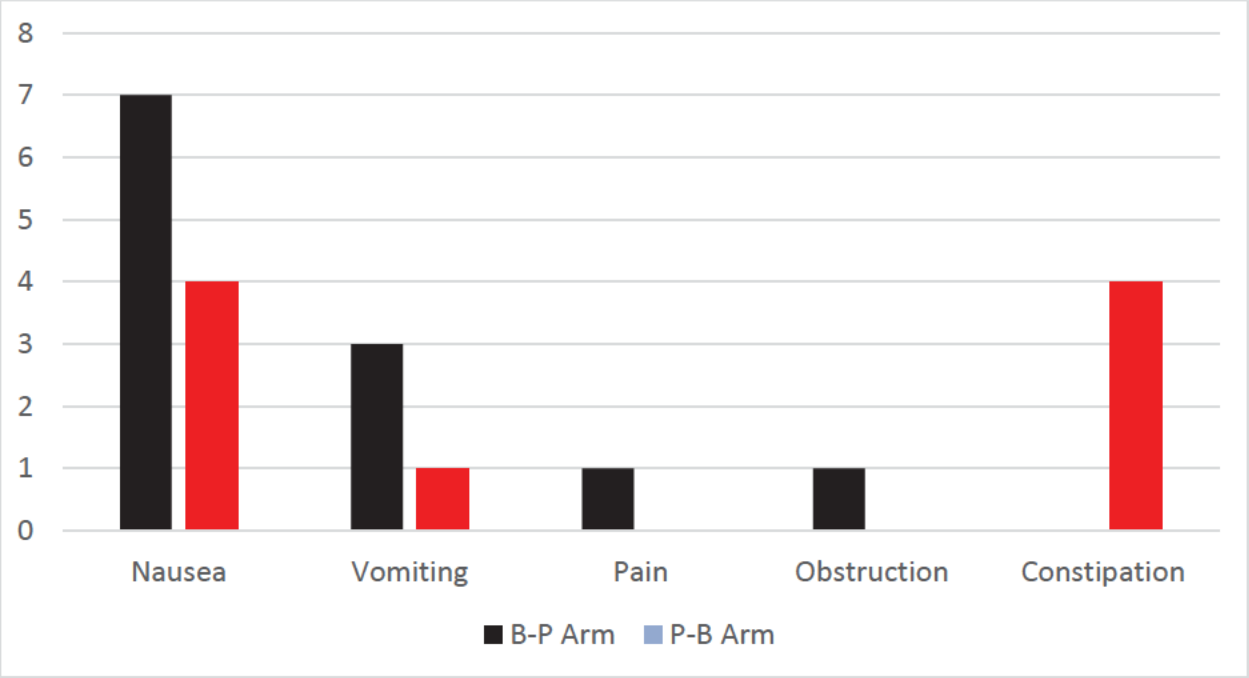


Figure 7: Number of GI Events



Treatment Emergent Adverse Events and Adverse Reactions
There were no treatment emergent adverse events or reactions in the trial.

Laboratory Findings
All patients had pre-operative laboratory testing conducted per institutional standards. Only baseline values were reported. Follow-up laboratory data was not a requirement for the protocol. ICG is a drug that has been used for over 50 years with a well-established safety profile.

Vital Signs
No clinically significant changes in vital signs were noted. These patients were being monitored by anesthesia as part of the surgery during the immediate post-administration period.

Electrocardiograms
EKG's were not performed as part of the study protocol. However, all these patients had continuous cardiac monitoring as part of the standard anesthesia practice and no adverse events classified as abnormal ECG findings were reported.

QT
This was not evaluated during the trial as there is a long history of use of the drug and it was not needed.

Immunogenicity
N/A Immunogenicity evaluation was not needed as there is a long history of clinical use of the

study drug.

7.2.5. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
The Applicant reviewed both the drug safety reports and device safety reports through MAUDE and MedWatch databases. There was one report of anaphylactic shock related to ICG, a known reaction for ICG.

Expectations on Safety in the Postmarket Setting
Since there exists an extensive safety database for all the indications sought, no new safety signals are expected to arise even with the new route of administration.

7.2.6. Integrated Assessment of Safety

The Applicant provided literature supporting the safety for ICG across all the proposed indications. The numbers below represent the number of publications found for each .and the numbers of AEs reported

- Cardiovascular: n=12, no AEs reported
- Plastic, micro- and reconstructive: n=63; 36 reported AEs
- Transplant surgery: n=4, no AEs reported
- Tumor detection: n=23, no AEs reported
- Pre-operative tattooing: n=3, no AEs reported
- Biliary visualization: n=25, no AEs reported
- Lymphography: n=5, 1 report of skin color change
- Lymphedema: n=6, no AEs reported

Overall, the submitted literature supports the drug safety profile and does not raise any new safety signals. The results of the clinical trial and related literature also support the safe use of this drug when administered interstitially.

SUMMARY AND CONCLUSIONS

7.3. Visualization of Extrahepatic Biliary Anatomy and Visualization of Vessels, Blood Flow and Tissue Perfusion

The clinical literature contains several studies examining ICG for imaging extrahepatic biliary anatomy and blood flow and tissue perfusion. ICG was administered as a single administration pre- or intraoperatively and may have included a repeated administration during surgery. Across studies, ICG doses ranged from 0.0125 mg to 25 mg. These studies, in totality, provide evidence of efficacy for ICG for visualization.

7.4. Imaging of Lymph Nodes and Lymphatic Vessels During Lymphatic Mapping

The FILM study was a randomized, prospective, multi-center, open-label within patient comparative study in patients with early stage uterine or cervical cancers, with no known regional nodal or metastatic disease by standard clinical evaluation. ICG and the blue dye comparator were injected into the cervix of patients at the beginning of the operative procedure. A total of 176 patients were randomized to receive either ICG followed by blue dye or blue dye followed by ICG. A total of four 1 ml injections of a 1.25 mg/ml solution of ICG were administered into the cervix at the 3 and 9 o'clock positions with a superficial (1 to 3 mm) and a deep (1 to 3 cm) injection at each position for a total dose of 5 mg per patient. Lymphatic mapping was performed intraoperatively using the PINPOINT Fluorescence Imaging System and standard light, followed by excision of tissues identified by ICG, blue dye, or the surgeon's visual and palpation examination. The resected tissues were evaluated by histopathology as lymph nodes. This study, lacked blinding, and attempted to minimize bias through randomized sequence of ICG and blue dye administration. The efficacy of ICG in the detection of lymphatic vessels and lymph nodes during lymphatic mapping procedures was determined by the number of histology-confirmed lymph nodes detected by ICG and/or the blue dye comparator.

Table 22 shows the distribution of resected, confirmed lymph nodes by the presence or absence of ICG or blue dye. Of the confirmed lymph nodes identified, 96% were identified using ICG, and 46% were identified using blue dye, a difference of 50% with 95% confidence interval 39% to 60% providing statistically significant evidence of efficacy of ICG for the lymphatic mapping indication.

Table 22: Distribution of Resected Confirmed Lymph Nodes Detected by ICG and/or BD

Analysis Population	Nodes (n)	% Detected With Both BD and ICG	% Detected With ICG Only	% Detected With BD Only	% Detected With Neither
Node level	513	44%	52%	2%	2%

7.5. Conclusions and Recommendations

For the indication in LN mapping in gynecologic surgery, the drug performed effectively with a good safety profile. The demonstration of visualization in the patients with high BMI is important given the likely population in whom the drug will be used. The ability to identify bilateral nodes may also reduce the need for hemi-pelvic lymphadenectomy, a procedure recommended when nodes are not found.

The reviewers recommend approval of ICG for the visualization of extrahepatic biliary ducts, the visualization of vessels, blood flow and tissue perfusion, and the visualization of lymph nodes and lymph vessels during lymphatic mapping for cervical and uterine tumors.

8. Advisory Committee Meeting and Other External Consultations

The Division did not obtain the advice of the Medical Imaging Advisory Committee (MIDAC) for this application as there were no public health issues raised that would benefit from a public discussion or that required the expert opinions of the Committee. In addition, the safety profile of the drug is deemed acceptable for the indicated population of patients.

9. Pediatrics

Use of ICG for visualization of vessels, blood flow and tissue perfusion has been established in pediatric patients one month and older. Pediatric use is supported by published data in 49 pediatric patients who received ICG for assessment of blood flow and tissue perfusion in cardiovascular, vascular and plastic, micro and reconstructive procedures, and by clinical trials in adults. Adverse reactions in pediatric patients were similar to those reported in adults. The dose range was similar to the effective dose range in adults. The use of ICG for visualization of vessels, blood flow and tissue perfusion has not been established in pediatric patients less than one month of age.

Use of ICG for visualization of extrahepatic biliary ducts has been established in pediatric patients 12 years of age and older. Pediatric use is supported by clinical trials in adults in addition to clinical use in pediatric patients. The use of ICG for visualization of extrahepatic biliary ducts has not been established in pediatric patients less than 12 years of age.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The table below summarizes significant changes to the proposed label made by the FDA prior to negotiations. The package insert will include the final prescribing information.

Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
Indications and Usage (1)	The Applicant proposed indications organized by route of administration (intravenous and interstitial)	The indications were organized by use; visualization of: vessels blood flow and tissue perfusion (1), extrahepatic biliary ducts (2) and lymph nodes and lymphatic vessels during lymph node mapping (3).
	The Applicant did not propose pediatric indications. The Applicant submitted data on August 1, 2018 regarding pediatric use.	The indication for visualization of: vessels blood flow and tissue perfusion (1.1) was extended to pediatric patients aged 1 month to 17 years. The indication for visualization of extrahepatic biliary ducts (1.2) was extended to pediatric patients age 12 to 17 years. The applicant received a waiver for a pediatric study requirement for the indication visualization of lymph nodes and lymphatic vessels during lymphatic mapping in women with cervical and uterine tumors (1.3) because necessary studies are impossible or highly impractical.
	Visualization of: vessels blood flow and tissue perfusion (1.1): The efficacy was extrapolated from adults and safety and dosing was leveraged from the literature review provided. Visualization of Extrahepatic Biliary Ducts (1.2): We used a similar approach to extrapolate efficacy from adults. Safety and dosing were leveraged from other indications (data in vascular indication). For both indications, the division relied on the information already available for safety data for other 505(b)(2) ICG products (already approved). Although the PeRC (Pediatric Review Committee) granted extension to birth, the Applicant and the clinical team had concerns about use in certain age groups due to lack of efficacy, lack of demonstrated clinical need, and lack of safety data with a device [the 505(b)(2) reference drugs do not have a companion device]. The biliary indication (1.2) was felt to extend reasonably down to age 12, for example, in a patient with sickle cell disease undergoing a cholecystectomy secondary to chronic stones.	
	The Applicant proposed use with the SPY® Elite and PINPOINT Fluorescence Imaging Systems	The generic device specification was added “or with a FDA cleared or approved imaging device that is

Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
		specifically intended for imaging of indocyanine green" for each indication since IC Green can be visualized with any approved or cleared device with these parameters. This information was moved to section 2, Dosage and Administration.
	(b) (4)	
Dosage and Administration (2)		Revised the titles so the D&A subsection titles correlate with the I&U subsections.
		Revised each section to make instructions less repetitive, more concise, and removed information that was practice of medicine.
		Included pediatric dosing. Added device labeling to this section.
Contraindications (4)	Contraindicated in patients with a history of an (b) (4)	Removed. (b) (4)
		There are serious adverse reactions, including anaphylaxis which has occurred with IC Green administration probably due to a component of the whole agent. We, therefore, added a contraindication in

Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
		patients with a history of hypersensitivity to indocyanine green.
Warnings and Precautions (5)	(b) (4) (5.1)	Changed to "Hypersensitivity" the preferred term.
	(b) (4) (5.2).	Deleted. (b) (4)
	(b) (4)	Renamed to reflect the risk: "Interaction with Radioactive Iodine Uptake Studies."
Adverse Reactions (6)	(b) (4)	
		Only the adverse reactions were listed.
Drug Interactions (7)	(b) (4)	
		Effect on Radioactive Iodine Studies, was added. Drug Interactions described in Warnings and Precautions sections must be discussed in more detail under Drug Interactions section.
Use in Specific Populations (8)	The Applicant stated there was no data and used outdated regulatory language.	Pregnancy (8.1) Reformatted to reflect lack of animal data. Human safety data over several decades has not identified any drug associated risks for major birth

Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
		defects, miscarriage, or adverse maternal or fetal outcomes
	The Applicant stated there was no data and used outdated regulatory language.	Lactation (8.2) Reformatted to reflect the small number of cases with no adverse effect in BF infants and no data on the presence of indocyanine green in human milk or the effects on milk production
	Safety and Effectiveness not established in pediatric patients.	Pediatrics (8.3) Reformatted to include pediatric indications (1.1 and 1.2) with the specific age range in which safety and effectiveness have been established. Also, specified the indication (1.3) for which safety and effectiveness in pediatric patients has not been established.
		(b) (4)
Clinical Studies (14)	Studies from 3 uses included in the proposed labeling.	Only the FILM study (for lymphatic mapping) was included for labeling as this is the only adequate and well-controlled study without limitations or bias. The other submitted studies / meta-analyses were reviewed and used in totality to approve the new indications; however, there was no single study (other than the FILM study) adequate for labeling.
Storage and Handling (16)	SPY® Elite Kit PINPOINT Kit PINPOINT Lymphatic Mapping Kit	SPY Elite Kit Kit for use with SPY Elite For visualization of vessels, blood flow, and tissue perfusion SPY Elite Pack (6 SPY Elite Kits) PINPOINT Kit Kit for use with PINPOINT For visualization of vessels, blood flow, and tissue perfusion

Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
		For visualization of extrahepatic biliary ducts: PINPOINT Pack (6 PINPOINT Kits) PINPOINT Lymphatic Mapping Kit Kit for use with PINPOINT (for lymphatic mapping): PINPOINT Lymphatic Mapping Pack (6 PINPOINT Lymphatic Mapping Kits)
Patient Counseling Information.	• Advise patients to seek medical attention for reactions following injection of TRADENAME such as difficulty breathing, swollen tongue or throat, skin reactions including hives, itching and flushed or pale skin, low blood pressure, a weak and rapid pulse and other symptoms of an anaphylactic reaction [*see Warnings and Precautions (5.1)*]. (b) (4) [redacted]	Provided as a heading and included only Hypersensitivity Reactions, as the other counseling information was not actionable.

11. Risk Evaluation and Mitigation Strategies

There is substantial safety information concerning this product. A REMS is not needed.

12. Postmarketing Requirements and Commitment

None needed.

13. Appendices

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13.2. Financial Disclosure

The Applicant's position on financial disclosures was reviewed and no concerns were noted.

Covered Clinical Study (Name and/or Number): FILM Study (PP LNM 01)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 40		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

There are no additional Nonclinical Pharmacology/Toxicology data.

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

N/A

13.5. Additional Clinical Outcome Assessment Analyses

N/A

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LIBERO L MARZELLA
11/20/2018