Cross Disciplinary Team Leader (CDTL) Review

Date	23 July 2012
From	Lucie Yang, Division of Medical Imaging Products (DMIP)
NDA	017858
Applicant	Pharmalucence Inc.
Date of Submission	21 October 2011, received same day
PDUFA Goal Date	21 August 2012
Established Name	Technetium Tc 99m Sulfur Colloid Injection
Proposed Dosage and Administration	3.7 to 37 MBq (0.1 to 1 mCi in 0.1 to 1 mL) by subcutaneous injection
Proposed Indication	In adults to assist in the localization lf lymph nodes draining a primary tumor in patients with **malignant melanoma** when used with a hand-held gamma counter (this indication for breast cancer was approved 22 July 2011)
Recommendation:	***Approval***

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Introduction

The subject of this Cross Discipline Team Leader (CDTL) review is the Efficacy Supplement submitted by Pharmalucence as a 505 (b)(2) application for Technetium Tc 99m Sulfur Colloid Injection (SCI) (NDA 017858). SCI is a radioactive diagnostic agent approved nearly 35 years ago for a number of different indications in adults and pediatric patients via intravenous, intraperitoneal, or oral administration.

In July 2011, SCI was approved for localizing lymph nodes draining a primary tumor using a hand-held gamma counter in adults with breast cancer injected subcutaneously. On 21 October 2011, Pharmalucence, Inc. submitted an efficacy supplement to support a similar indication for melanoma.

The reviewer has examined the relevant excerpts from the supplemental NDA submission and subsequent submissions by the sponsor, as well as reviews and consult responses listed the table below.

Reviews and consult responses included in this review

Material Reviewed / Consulted	Name of Discipline Reviewers
Clinical Review	Phillip Davis
Statistical Review	Satish Misra, Jyoti Zalkikar, Thomas Gwise
Pharmacology Toxicology Review	Yanli Ouyang
OPDP	James Dvorsky
Project Manager	Alberta Davis-Warren

OPDP=Office of Prescription Drug Promotion;

Background

Lymph node localization has become important for managing the care of patients with cutaneous melanoma because removal of lymph nodes helps with assessing the spread of disease [1;2]. As for the breast cancer-related indication, the sponsor's proposed indication for melanoma is also for the non-specific structural claim of lymph node localization rather than for a specific claim of localizing the sentinel lymph node (which, if negative for cancer, implies that other lymph nodes do not need to be excised).

Following subcutaneous injection, SCI enters lymphatic capillaries and is transported with lymph to lymph nodes. The endothelial cells lining the walls of initial lymphatic capillaries are separated by a 10 to 25 nm gap, allowing small radiocolloids such as SCI (100 nm filter, particle size 5-100 nm) to freely enter the lumen of the lymphatic [3].

The decay of Tc 99m emits a photon which can be detected by imaging or a hand-held gamma counter.

To date, no imaging agent has a specific indication for lymph node localization in melanoma patients. However, isosulfan blue (Lymphazurin 1%, referred to here as "blue dye" or BD) is approved for a broad indication: "delineates the lymphatic vessels draining the region of injection." Thus, blue dye was used as a comparator in certain literature reports used by the sponsor in support of this application.

According to the supplement, the literature included in the systematic review for lymph node localization in patients with melanoma also described lymphoscintigraphy (using a gamma camera or similar equipment) *pre-operatively* to facilitate surgical planning. However, only the *intra-operative* procedures involved simultaneous use of BD and SCI (detected using hand-held gamma counter) in the same patient. Thus, only intra-operative lymph node localization procedures were included in the meta-analysis performed to support SCI efficacy.

In Supporting Document 131, the sponsor explicitly states that Pharmalucence is not requesting an indication for use of SCI in lymphoscintigraphy with a gamma camera.

Chemistry, Manufacturing and Controls (CMC)

No information was submitted in this supplement.

Clinical Microbiology

No information was submitted in this supplement.

Nonclinical Pharmacology / Toxicology

Dr. Ouyang's review recommended approval and indicated that no nonclinical information was submitted.

Clinical Pharmacology / Biopharmaceutics

No information was submitted in this supplement.

Clinical / Statistical – Efficacy

Dr. Phillip Davis (clinical) and Dr. Satish Misra (statistics) support approval for the reasons described below. I concur.

The sponsor performed a systematic review of published literature. Of the eight studies which met pre-specified search criteria (Davis, finalized 16 July 2012, section 6.1.1, page 23; Misra, finalized 16 July 2012, Appendix, page 23) for melanoma, only four studies (Davis, finalized 16 July 2012, section 5.3, page 14) described paired outcome data for both SCI and BD during intra-operative procedures and were included in the meta-analysis. Only one of these four articles was prospectively designed.

As for the breast node localization indication, the pre-specified statistical analyses involved an odds ratio approach for melanoma. The random effects meta-analysis met its primary non-inferiority endpoint: the odds ratio (95% CI [1]) for comparing BD to SCI was 5.25 (2.08, 13.24), with the lower limit of the 95% CI being greater than the non-inferiority threshold of 0.85. The superiority endpoint was also met: the odds ratio (95% CI) for successful lymph node localization using SCI and BD in combination (SCI + BD) compared to that of BD alone was 15.14 (3.89, 58.92), with the lower limit of the 95% CI being greater than 1.0.

As for the breast node localization indication, the statistical team questioned the meaningfulness of the odds ratio approach and requested a direct, patient level comparison of SCI versus BD as an alternative approach for melanoma (Misra, finalized 16 July 2012, section 3.3.5, page 16). As seen in the table below, SCI localized at least one lymph node in 96% of patients, and this was superior to BD. As for breast, SCI and BD can both fail to localize a lymph node for melanoma (1.6%).

Tracer localization by patient* for melanoma

Number of Clinical Studies	Number of Patients	BD Present (%)	SCI Present (%)	Only BD Present (%)	Only SCI Present (%)	Neither SCI nor BD Present (%)
4	249	83.6	96.4	3.2	15.5	1.6
95% CI		73.4, 90.4	92.0, 98.5	1.4, 6.9	9.6, 24.1	0.4, 6.5

*Percent of patients in which at least one lymph node contained the specific tracer

Weaknesses of the studies submitted to support SCI efficacy include availability of only study-level data and the possible introduction of bias due to a variety of factors, including the lack of blinding, randomization, parallel study groups, and protocols stating whether the same surgeon determined and recorded if BD, SCI, both, or neither localized a node. That the protocols for these studies are not available also limits the ability to assess whether patient level data are comparable across studies (Misra, finalized 16 July 2012, section 2.2, page 8).

[1] Confidence Interval

Safety

No new safety data was included in the supplement. The published literature did not describe any adverse reactions to SCI. The safety reports contained in the annual report submitted in June 2012 (Davis, finalized 16 July 2012, section 7.7, page 30) did not change the known safety profile for the drug. No changes to the Adverse Reactions section of the label were made.

Advisory Committee Meeting

None.

Pediatrics

The applicant requests a waiver for pediatric studies for malignant melanoma based on the orphan designation for the melanoma lymph node localization indication and on the *Food, Drug and Cosmetic Act* which states that PREA requirements do not apply to drugs with an orphan designation. The reviewer has no objection.

Other Relevant Regulatory Issues

The sponsor also requests an application fee waiver and seven years of exclusivity based on the orphan designation for the melanoma lymph node localization indication.

No inspections were performed. No financial disclosure information is needed for a published literature-based submission.

Labeling

Major updates to the label were applied to the indication statement and the clinical studies section to include lymph node localization in patients with malignant melanoma. Specifically, the indication statement was revised to the following:

> Technetium Tc 99m Sulfur Colloid Injection is a radioactive diagnostic agent indicated in adults to assist in the localization of lymph nodes draining a primary tumor in patients with breast cancer or malignant melanoma when used with a hand-held gamma counter.

OPDP had no labeling recommendations at this time.

Post-marketing Studies

None.

Recommendations / Risk Benefit Assessment

Recommendation:
Approval of SCI for localization of lymph nodes draining a primary tumor in patients with malignant melanoma when used with a hand-held gamma (b) (4). This is an intra-operative procedure.

Of note, the efficacy of pre-operative SCI lymphoscintigraphy was not demonstrated.

Risk Benefit Assessment:
SCI used alone to identify lymph nodes draining a melanoma lesion (96% success) is superior to that of BD. SCI and BD may both fail to identify lymph nodes in 1.6% of patients.

As with any radiopharmaceutical, radiation is a concern. However, the exposure from SCI for lymph node localization is lower than that administered for other indications (see section 2.3 of the label).

The adverse reaction experience over nearly 35 years since SCI has been marketed is acceptable. This post-marketing experience includes off-label use for lymph node localization in patients with melanoma.

Reference List

1. American Society of Clinical Oncology and Society of Surgical Oncology Joint Clinical Practice Guideline. Sentinel Lymph Node Biopsy for Melanoma. http://www.asco.org/ASCOv2/Department%20Content/Cancer%20Policy%20and%20Clinical%20Affairs/Downloads/Guideline%20Tools%20and%20Resources/SNB%20Melanoma/SNB%20in%20Melanoma%20Full%20Guideline%207.5.12.pdf . 2012.

Ref Type: Online Source

2. Brady MS: **Advances in sentinel lymph node mapping for patients with melanoma**. *Future Oncol* 2012, **8:**191-203.

3. Uren RF, Howman-Giles RB, Chung D, Thompson JF: **Role of lymphoscintigraphy for selective sentinel lymphadenectomy**. *Cancer Treat.Res.* 2005, **127:**15-38.

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/s/

LUCIE L YANG
07/23/2012

CLINICAL REVIEW

Application Type	NDA [505(b)(2)] Efficacy supplement
Application Number(s)	17858 – S-0035
Priority or Standard	Standard
Submit Date(s)	10/21/2011
Received Date(s)	10/21/2011
PDUFA Goal Date	8/21/2012
Division / Office	Medical Imaging Products/ODEIV
Reviewer Name(s)	Phillip Davis, MD
Review Completion Date	
Established Name	Technetium 99m Sulfur Colloid Injection (SCI)
(Proposed) Trade Name	
Therapeutic Class	Radiopharmaceutical imaging agent
Applicant	Pharmalucence Inc.
Dosage form/Formulation(s)	Lyophilized powder containing sodium thiosulfate and gelatin
Strength	2mg thiosulfate per vial
Route of administration	Subcutaneous
Dosing Regimen	3.7 to 37 MBq (0.1 to 1.0 mCi)

	in 0.1 to 1 ml volume
Indication(s)	Localization of lymph nodes [redacted] draining a primary tumor in patients with breast cancer [redacted] malignant melanoma.
Intended Population(s)	Malignant melanoma

Template Version: March 6, 2009

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No figures included.

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends approval of the 505(b)(2) supplemental NDA for Technetium Tc 99m sulfur colloid injection for the new indication of "localization of lymph nodes draining a primary tumor in patients with breast cancer or malignant melanoma when used with a hand-held gamma counter." This recommendation is based on review of the clinical data contained in the submitted literature publications and previous review of the post marketing safety data.

1.2 Risk Benefit Assessment

This radiopharmaceutical and the proposed new indication and route of administration have an acceptable risk benefit assessment based on the following:

- Acceptable performance of sulfur colloid when used to identify tracer-containing lymph nodes draining a melanoma tumor.
- Acceptable radiation absorbed doses following the single dose by subcutaneous injection; radiation dose for lymph node localization lower than doses for the approved uses
- Acceptable adverse event experience in the clinical studies and in the post-marketing safety database with an estimated number of > (b) (4) patients exposed after initial drug approval; no reports of deaths related to study drug administration during this period.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

None are recommended.

1.4 Recommendations for Post-market Requirements and Commitments

None are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Technetium Tc 99m Sulfur Colloid Injection (Tc 99m-SCI) is a diagnostic radiopharmaceutical initially approved by FDA on April 17, 1978 (NDA 17-858). The formulation used for subcutaneous administration is the same as used for the approved indications. Each 10 mL multi-dose vial of Tc 99m-SCI contains, in lyophilized form, 2.0 mg sodium thiosulfate anhydrous, 2.3 mg edetate sodium and 18.1 mg bovine gelatin; a Solution A vial with 1.8 mL of 0.148 N hydrochloric acid solution and a Solution B vial with 1.8 mL aqueous solution of 24.6 mg/mL sodium biphosphate anhydrous and 7.9 mg/mL sodium hydroxide. When a solution of sterile and non-pyrogenic Sodium Pertechnetate Tc 99m in isotonic saline is mixed with these components, following instructions provided with the kit, Tc 99m SCI Injection is formed.

Approved Tc 99m-SCI indications and usage are:

- localization of lymph nodes draining a primary tumor in patients with breast cancer when used with a hand-held gamma counter.
- in adults and children for imaging areas of functioning reticuloendothelial cells in the liver, spleen, and bone marrow;
- orally in adults and children for esophageal transit studies, gastroesophageal reflux scintigraphy, and for the detection of pulmonary aspiration of gastric contents; and
- in adults as an imaging agent to aid in the evaluation of peritono-venous (LeVeen) shunt patency.

The sponsor's proposed new indication is (in blue font):

"Technetium Tc 99m sulfur colloid injection is indicated for the localization of lymph nodes (b) (4) draining a primary tumor in patients with breast cancer (b) (4) malignant melanoma."

Lymph node localization

Tc 99m-SCI has been used since the 1990s for identifying lymphatic pathways and lymph nodes (LN) in certain cancer patients. Lymphatic mapping combined with lymph node biopsy is usually performed before or during surgical removal of primary tumors. The purpose of a LN biopsy is to identify and remove lymph nodes that receive lymphatic drainage from the patient's primary tumor. Resected lymph nodes are submitted for microscopic evaluation to determine if cancer cells are present. This information (cancer positive or cancer negative) provides valuable prognostic information, and the status of regional lymph nodes is used to stage disease and plan therapy. A LN biopsy revealing absence of cancer usually results in no further removal of lymphatic tissue. This allows patients to avoid the more invasive complete lymph

node dissection, where all lymphatic tissue in a region is removed when one of the biopsied lymph nodes is found to contain cancer cells.

The current standard of care for patients diagnosed with melanoma is excision of the primary lesion. Since melanoma spreads through the lymphatic channels to regional lymph nodes, accurate staging at the time of diagnosis is important in order to plan additional therapies that may be available to patients. Tc-99m-SCI (with a hand-held gamma counter) is routinely used in combination with blue dye (BD) for lymphatic mapping to guide surgeons performing LN biopsy procedures in patients with clinically node negative melanoma. Lymph node mapping with Tc 99m-SCI can provide clarity to ambiguous and multidirectional lymphatic flow patterns that are sometimes encountered in melanoma and its use is supported by published literature as a prognostic tool. Survival benefits imparted by this procedure are still being debated and investigated in clinical trials. Nonetheless, it has become the standard approach for management of melanoma patients who are at higher risk of having regional nodal metastases, including: those with tumors ≥ 1 mm thick, lesion ulceration, and high mitotic rates. Patients with regional lymph nodes confirmed by pathology as positive for cancer generally have complete regional lymphadenectomies, which may be curative. As with other cancers, melanoma patients with LN biopsy procedures revealing all sampled nodes negative for cancer typically have no further lymphatic tissue removed. [1]

Regulatory considerations

As with the breast cancer indication, the sponsor's new proposed addition of malignant melanoma to the indication statement is consistent with a structural delineation claim as described in the FDA guidance for industry titled: "Developing Medical Imaging Drug and Biological Products Part 2: Clinical Indications." For imaging agents seeking a structural delineation indication, an acceptable efficacy endpoint is the number of test procedures that result in the localization of the tracer in at least one histologically confirmed lymph node.

In the case of isosulfan blue dye, the product label states the drug, upon subcutaneous administration, delineates the lymphatic vessels draining the region of injection. Isosulfan blue uses include an indication as an adjunct to lymphography in lymph node involvement by primary or secondary neoplasms. This indication statement is consistent with a structural delineation claim.

The sponsor provides no data analyses to support the usefulness of Technetium 99m Sulfur Colloid Injection for staging melanoma patients and proposes no such label claims. For a diagnostic/disease detection claim it would be necessary to demonstrate the presence/absence of tumor in lymph node(s) (defined as nodes containing the tracer) is predictive of the presence/absence of tumor in the remaining axillary lymph nodes. The truth standard would be pathologic examination of the regional lymph nodes surgically removed along with the cancer.

2.2 Tables of Currently Available Treatments for Proposed Indications

The only currently approved drug for identifying lymphatic tissues is Lymphazurin 1% (isosulfan blue dye), which has the following indication:

Lymphazurin 1% (isosulfan blue dye) upon subcutaneous administration delineates the lymphatic vessels draining the region of injection. It is an adjunct to lymphography in: primary and secondary lymphedema of the extremities; chyluria, chylous ascites or chylothorax; lymph node involvement by primary or secondary neoplasm; lymph node response to therapeutic modalities.

2.3 Availability of Proposed Active Ingredient in the United States

Tc 99m-SCI is currently marketed by the sponsor in the U.S. The formulation used for subcutaneous administration is the same approved formulation used for all other routes of administration.

2.4 Important Safety Issues With Consideration to Related Drugs

Severe hypersensitivity reactions requiring treatment are cited in the package insert for isosulfan blue.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Tc 99m SCI (NDA 17-858) was initially approved by the FDA April 17, 1978. A supplement was approved 7/22/2011 extending the indicated population for Tc 99m SCI use to include patients with breast cancer.

For the new proposed indication, there was no pre-submission regulatory activity to describe.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This application relies solely on literature publications.

3.2 Compliance with Good Clinical Practices

The applicant states that “it did not and will not use the services, in any Capacity, of any person debarred under section 306 of the Federal Food,

Drug and Cosmetic Act in connection with this 505(b)(2) supplement." The clinical reviewer acknowledges the submitted literature publications appear to have been conducted according to good clinical practices with informed consent of study subjects and local IRB approvals.

3.3 Financial Disclosures

Financial disclosure statements are not necessary for literature publications submitted in this 505(b)(2) application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No CMC data was submitted with this 505(b)(2) sNDA application.

4.2 Clinical Microbiology

No new data are needed and none were provided.

4.3 Preclinical Pharmacology/Toxicology

No new data are needed and none were provided.

4.4 Clinical Pharmacology

No clinical pharmacology data was submitted in the initial sNDA.

The below information is based on the currently approved drug label for Tc 99m-SCI:

4.4.1 Mechanism of Action

Technetium Tc 99m decays by isomeric transition and emits a photon that can be detected for imaging purposes.

Following subcutaneous injection, Tc 99m Sulfur Colloid enters the lymphatic capillaries and is transported with lymph to lymph nodes. When there is massive nodal metastatic involvement, the normal transport to lymph nodes is lost because few normal cells remain in the node.

Following intravenous injection, Technetium Tc 99m Sulfur Colloid is taken up by the reticuloendothelial system (RES), allowing RES rich structures to be imaged.

Following intraperitoneal injection, Technetium Tc 99m Sulfur Colloid mixes with the peritoneal fluid; rate of clearance from the cavity allows assessment of the patency of the peritoneovenous shunt. Clearance varies from insignificant, which may occur with complete shunt blockage, to very rapid clearance with subsequent transfer into the systemic circulation when the shunt is patent.

With oral administration, Technetium Tc 99m Sulfur Colloid is not absorbed accounting for its function in esophageal transit studies, gastroesophageal reflux scintigraphy, and for the detection of pulmonary aspiration of gastric contents.

4.4.2 Pharmacokinetics

Following intravenous administration, Technetium Tc 99m Sulfur Colloid Injection is rapidly cleared from the blood by the reticuloendothelial system with a nominal half-life of approximately 2 1/2 minutes. Uptake of the radioactive colloid by organs of the RES is dependent upon both their relative blood flow rates and the functional capacity of the phagocytic cells. In the average patient 80 to 90% of the injected colloidal particles are phagocytized by the Kupffer cells of the liver, 5 to 10% by the spleen and the balance by the bone marrow.

Following oral ingestion, Tc 99m Sulfur Colloid is distributed primarily through the GI tract with elimination primarily through the feces.

5 Sources of Clinical Data

The applicant has not sponsored any clinical investigations of Tc 99m-SCI for this application, which relies solely on four submitted literature publications.

5.1 Tables of Clinical Studies

The population for all listed studies consists of patients with clinically node negative malignant melanoma who previously underwent a lymph node biopsy procedure before or after removal of their melanoma tumor.

Table 1: Literature publications included in FDA meta-analysis.

Study Author, Year	N patients procedures	Technique and dosing	Design and Objectives	Endpoints
Study 1, James Alex, 1998	23	SCI lymph node mapping (LNM) was performed in all patients, 12 patients also	Single center, prospective, open-label study	Patient level lymph node localization

		received BD for the LNM procedure. Preoperative lymphoscintigraphy (with markings placed on skin) and intraoperative LNM performed for all patients. SCI – approximately 0.25 to 0.9 mCi SCI (in volumes of 0.1 to 1.0 mL) injected equally in 4 parts around the primary tumor or previous biopsy site. BD – 1 to 3 mL of isosulfan BD (1%) injected around the tumor or biopsy site	comparing utility of SCI for LNM procedures (combined with BD) compared to the BD only technique.	rates
Study 2, P. Constantine, 1999	142	Initially, the BD only LNM technique was used for all patients (n=84). Then, more than halfway through the study, the combined BD + SCI technique was used for the remaining (n=58). Preoperative lymphoscintigraphy was performed for all patients. SCI – approximately 0.25 mCi SCI injected equally in 4 parts around the primary tumor or previous biopsy site (total dose = 1mCi). BD – A total of 3 mL of isosulfan BD injected around the tumor or biopsy site	Retrospective review of LNM procedures at a single center performed to evaluate patient level success rates of the combined BD + SCI technique.	Patient level lymph node localization rates
Study 3, Lee Pu, 1999	85	SCI + BD technique used in all patients.	Retrospective database review	Patient level lymph node

		Preoperative lymphoscintigraphy (with markings placed on skin) and intraoperative lymphatic mapping performed for all patients. SCI – approximately 0.5 mCi SCI injected equally in 4 parts around the primary tumor or previous biopsy site. BD – 1to 3 mL of isosulfan BD injected around the tumor or biopsy site	of consecutive patients undergoing lymph node mapping for melanoma treatment to evaluate the validity of lymphatic mapping and sentinel node biopsy as part of the workup and treatment of melanoma patients.	localization rates
Study 4, Michael Sabel, 2000	182	Initially, the BD technique was used for all patients (n=88). Then, approximately halfway through the study, SCI was added to the LNM procedure (n=94). Preoperative lymphoscintigraphy (with markings placed on skin) was performed 2 to 4 hours prior to surgery for all patients. SCI – approximately 0.5 mCi SCI injected at 4 points around the primary tumor or previous biopsy site (total dose = 2mCi) 3-4 hours prior to the LNM procedure. BD – 1 to 3 mL of isosulfan BD injected around the tumor or biopsy site	Retrospective review of LNM procedures at a single center performed to evaluate patient level success rates	Patient level lymph node localization rates

Abbreviations: SCI - Technetium Tc 99m sulfur colloid injection; BD – Blue Dye (mainly 1% isosulfan blue, methylene blue also used in a small number of cases); mCi – millicuries; mL – milliliters.

5.2 Review Strategy

The sponsor submitted four literature publications containing paired data for Tc 99m-SCI and isosulfan blue dye in support of the proposed new indication in melanoma. These studies included 1 prospective and 3 retrospective studies, with varying objectives, but all containing comparisons of SCI and BD performance when used simultaneously for localizing lymph nodes. The statistical team conducted a meta-analysis of these studies, and the clinical reviewer describes these studies below.

5.3 Discussion of Individual Studies/Clinical Trials

Overview
The applicant did not sponsor any clinical investigations for this 505(b)(2) sNDA and relies solely on the four submitted literature publications for the proposed new indication.

Studies used for the primary statistical analysis:

Table 2: Study 1 by Alex et al

Published in 1998	
Objectives	To evaluate gamma-probe radio-localization of lymph nodes in stage N0 melanoma of the head and neck.
Study Design	Prospective, non-randomized study comparing performance characteristics of SCI and blue dye.
Population	patients with stage N0 intermediate thickness melanoma of the head and neck N=23
Age range (mean)	22-89 (56)
Male/Female (n)	70/30
Main enrollment criteria	Preoperative biopsy supported diagnosis of intermediate-thickness melanoma of the head and neck region.

Primary endpoint	surgeon lymph node resection success rates (patient level data)
Dose range (mean) of Tc-99m-SCI, range of saline volume used.	0.25 to 0.90 mCi (0.43 mCi) in volumes of 0.1 to 1.0 mL of normal saline
Dose of blue dye (1% isosulfan blue)	Not stated
Injection techniques:	SCI was injected intradermally around the circumference of the primary melanoma in all patients. In 12 patients, intradermal peritumoral injections were performed just prior to the lymph node resection procedure.
Time from SCI injection to beginning of lymph node localization procedure in OR.	24 hours
Nuclear imaging techniques	1. Planar gamma camera images acquired in the nuclear medicine department 20 minutes to 120 minutes after injection of SCI, marks placed on skin over areas of focal activity. 2. In the operating room, a hand-held gamma probe was used to measure areas of radiotracer accumulation. Counts were obtained over a 10 second interval.
Definition of "hot spot"	An area of accumulation with at least 15 counts in 10 seconds and a ratio of 3 times that of background.
Lymph node localization technique	After identifying a hot spot on the skin, a small incision was made and the surgical dissection proceeded, aided by the gamma probe in order to localize lymph nodes.
Reference standard	None. Blue dye served as a comparator for SCI performance.
Statistical analyses	Descriptive statistics were performed.

Statistical hypotheses	None
Safety assessments	No safety data was provided in the manuscript.

Study1 was a prospective, non-randomized investigation designed to evaluate the performance of sulfur colloid aided radio-localization of lymph nodes in patients with clinically lymph node negative, intermediate thickness melanoma of the head and neck region. All 23 enrolled subjects received sulfur colloid for performance of the lymph node localization procedure, but only 12 subjects received blue dye to assist in the identification of lymph nodes. No statistical hypotheses were tested in this study, only descriptive statistics were provided comparing the performance of SCI to blue dye for successful localization of lymph nodes.

The reviewer notes that because both imaging drugs were used together in 12 subjects at the same time during the lymph node localization procedure, it is difficult to completely separate out their individual performances. Thus, there is inherent bias in a study like this that affects the performance estimates of both blue dye and SCI. This study independently would not meet regulatory standards of a well controlled study. However, when taken in the context of what is known about the performance of SCI in the breast cancer population, combined with other studies submitted in this sNDA, it does add confidence to the performance of SCI in the melanoma population.

Table 3: Study 2 by Constantine et al

Published in 1999	
Objectives	Evaluate the performance of SCI + blue dye for identifying lymph nodes in patients with melanoma who had previously undergone a wide excision.
Study Design	Single center retrospective review
Population	Patients with malignant melanoma of upper and lower extremities, trunk and head and neck region. N=142
Age range/mean	Not stated
Male/Female (%)	56/44
Main enrollment criteria	Biopsy supported diagnosis of melanoma

	≥ 1.0mm (average thickness = 2.5mm) or Clark's level ≥ IV with previous lymph node biopsy procedure or previous wide local excision.
Endpoint	Lymph node identification success rates
Dose of Tc 99m-SCI	total dose = 2.0 mCi (0.5 mCi X 4 doses)
Dose of blue dye (1% isosulfan blue)	3 ml Note – in the first 84 patients, blue dye only was used due to unavailability of a hand-held gamma probe. The remaining 58 patients received both BD and SCI.
Injection techniques:	SCI was injected intradermally at 4 sites around the melanoma site. For extremity sites, the extremity was elevated to approximately 45 degrees for 5–6 minutes to facilitate the flow of the dye to the regional nodal basin. For patients with trunk lesions off the midline, the injection was made with the patient in a lateral position and/or the operating table was tilted in such fashion as to facilitate by gravity the flow of the dye to the regional nodal basin. BD was injected just prior to the lymph node resection procedure.
Time from SCI injection to beginning of lymph node localization procedure in OR.	3 - 4 hours
Nuclear imaging technique	1. Planar gamma camera images were acquired in the nuclear medicine department to determine the nodal basin of drainage. 2. In the operating room, a hand-held gamma probe was used to measure areas of radiotracer activity.
Definition of "hot spot"	No provided. The manuscript simply refers

	to the “hottest spot” in a nodal basin.
Lymph node localization technique	The hand-held gamma probe was used to identify the “hottest spot” over a nodal basin. An incision was then carried out over this area toward where the lymph node was believed to be. As soon as the subcutaneous fat layer was incised, the probe was again used to help direct the dissection. Once the sentinel node was identified by staining with the blue dye, the radioactivity of this sentinel node was recorded in vivo and, after its removal, it was recorded ex vivo. The probe was also used to record radioactivity counts in the remaining nodal basin. If the remaining radioactivity counts were higher than 1/4 of the ex vivo radioactivity count of the sentinel node, additional searches were performed for sentinel nodes.
Reference standard	None. Blue dye served as a comparator for SCI performance.
Statistical analyses	Descriptive statistics were used to evaluate the performance of BD and SCI for localizing lymph nodes.
Statistical hypotheses	None.
Safety assessments	None discussed.

Study 2 was a retrospective review of 142 patients diagnosed with melanoma ≥ 1mm in thickness who had a previous biopsy (incisional or excisional) or wide excision. The study was conducted with the objective of evaluating the performance of SCI combined with blue dye for identifying sentinel lymph nodes after wide excision of melanoma lesions. Notably, only 26 of the total 142 subjects had a prior wide excision of their melanoma lesion, with the remaining 116 subjects had a previous biopsy only. Of the total 142 subjects, 84 underwent the LNB procedure aided by BD only. The remaining 58 subjects received both BD and SCI for performance of the LNB procedure. The performance of the LNB procedure was in accordance with standard clinical practice, with the hand-held gamma probe guiding the procedure and the blue dye used to visually confirm lymph nodes and lymphatic channels. For the group of subjects

receiving both BD and SCI for the LNB procedure, comparisons were made between the success rates for both imaging agent in localizing lymph nodes.

As mentioned above, it is difficult to completely separate out the individual performance characteristics of BD and SCI because both imaging drugs were used simultaneously together for the LNB procedures. Being a retrospective review, this study obviously does not independently meet regulatory standards, but does provide supportive data for the performance of SCI for localizing lymph nodes in this population.

Table 4: Study 3 by Pu et al

Published in 1999	
Objectives	Evaluate results from lymphatic mapping and sentinel lymph node biopsy in patients with lower extremity melanoma.
Study Design	Single center retrospective review
Population	Subjects with clinical stage I and II melanoma of the lower extremity N = 85
Mean age (years)	53.4
Male/Female (%)	73/27
Main enrollment criteria	Subjects with clinical stage I and II melanoma of the lower extremity who had prior SLB procedure before or after wide local excision
Endpoints	Lymph node identification success rates
Dose of Tc 99m-SCI	0.4 mCi
Dose of blue dye (1% isosulfan blue)	1 to 3 mL
Injection techniques:	SCI was injected intradermally in four areas around the primary melanoma or biopsy site. BD was injected using the same method as for SCI.

Time from injection to beginning of lymph node localization procedure in OR.	Not clearly stated. It appears two separate injections are made: one
Nuclear imaging technique	1. Planar gamma camera images were acquired in the nuclear medicine department to localize lymph nodes to the groin or popliteal areas. Ink marks were placed on the skin above focal areas of radiotracer activity to mark the suspected location of lymph nodes. 2. In the operating room, a hand-held gamma probe was used to measure areas of radiotracer activity.
Definition of "hot spot"	An in-vivo node with radioactivity greater than 3:1 over background or an ex-vivo node with a sentinel lymph node to non-sentinel lymph node ratio of greater than 10:1.
Lymph node localization technique	Attention is initially directed to the ink marks on the patient's skin placed in the nuclear medicine department with lymphoscintigraphy guidance. An incision is then made over the ink mark. The hand-held gamma probe is used to identify the area of greatest activity (counts per second), and the sentinel lymph node is traced and dissected out using the hand held probe as a guide. The afferent lymphatics are identified with blue dye and followed to the sentinel lymph nodes. All blue stained lymph nodes or "hot" lymph nodes are harvested and noted as sentinel lymph nodes. If necessary, additional sentinel lymph nodes are localized and removed until the activity in the basin(s) returns to the background level
Reference standard	None. Blue dye served as a comparator for SCI performance.

Statistical analyses	Descriptive statistics were used.
Statistical hypotheses	None
Safety assessments	No data provided.

Study 3 was a retrospective review of 85 patients previously undergoing lymph node biopsy procedures for melanoma lesions of the lower extremity at one clinical site. The study was conducted to evaluate the results of lymphatic mapping and SLN biopsy in these patients and to follow subjects for subsequent regional nodal metastases. All patients received both BD and SCI during the LNB procedure and the technique for localizing lymph nodes was consistent with clinical practice using the hand-held gamma probe to guide the surgical dissection. Results were given on a patient level as percentages of patients having "blue-stained" and "hot" nodes. Results were not given for percentages of patients with only blue-stained nodes, only hot nodes, or for complete failures.

Since this was a retrospective review, it does not independently meet regulatory standards, but is supportive data for the performance of SCI for localizing lymph nodes in this population.

Table 5: Study 4 by Sabel et al

Published in 2000	
Objectives	To perform a review of the institution's lymph node biopsy procedures in order to make improvements to the technique.
Study Design	Single center retrospective review
Population	Patients with clinically node negative melanoma Note – the average Breslow thickness was 2.44 mm. N = 182
Mean age (years)	53 ± 16
Male/Female (%)	53/47

Main enrollment criteria	Patients with clinically node negative melanoma who had prior SLB procedure
Endpoint	Lymph node identification success rates
Dose of Tc-99m-SCI	1 mCi total dose (0.25 mCi X 4 doses)
Dose of blue dye (1% isosulfan blue)	1 to 3 mL
Injection technique	SCI
Time from injection to beginning of lymph node localization procedure in OR.	SCI – 2 to 4 hours BD – 10 to 20 minutes
Nuclear imaging technique	1. Dynamic and static planar gamma camera images were acquired in the nuclear medicine department to localize lymph nodes. Ink marks were placed on the skin above the most intense areas of radiotracer activity to mark suspected location of lymph nodes. 2. In the operating room, a hand-held gamma probe was used to measure areas of highest radiotracer activity.
Criteria for defining lymph nodes with SCI	Not described in detail. Areas of “highest” counts were used to identify lymph nodes.
Lymph node localization technique	The surgical incision was made over the area of highest counts seen with the hand-held gamma probe. Then, blue-stained lymph nodes were removed and the ex-vivo counts were recorded. The level of radioactivity in the excised lymph node and the level of radioactivity in the background were measured. If radioactivity did not decrease to background levels in the basin, the gamma probe was used to direct further dissection and excise additional SLNs.

Reference standard	None. Blue dye served as a comparator for SCI performance.
Statistical analyses	Descriptive statistics were performed.
Statistical hypotheses	None
Safety assessments	No data provided in the manuscript.

Study 4 was another single center retrospective review of 182 lymph node biopsy procedures performed in order to evaluate success rates and potentially improve the center's protocol. The initial 88 patients received BD only for the procedure. Beginning approximately half way through the time period covered by this review, the center began using Tc-99m SCI combined with BD to perform the LNB procedure. The manuscript states preoperative lymphoscintigraphy was performed "routinely" to identify the lymph node basins and ink marks were placed on the skin to identify potential nodes. The intraoperative technique for localizing lymph nodes was consistent with clinical practice and similar to the other 3 studies; ink marks were used to identify potential areas of lymph nodes, then incision was carried out in this location guided by the use of the hand-held gamma probe. Blue dye was used to help visualize and confirm the lymph nodes and lymphatic channels.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The sponsor's proposed new addition to the indication statement is:

"Localization of lymph nodes draining a primary tumor in patients with breast cancer (b) (4) malignant melanoma when used with a hand-held gamma counter."

6.1.1 Methods

There were 8 studies of melanoma patients that met inclusion/exclusion criteria for efficacy analysis. The main pre-specified inclusion criteria are outlined below:

- U.S. human studies conducted after 1990 using a combination technique of SCI and BD for lymph node localization in melanoma patients and reporting efficacy outcomes of interest.
- Studies needed to be full-length published articles.
- Studies of prospective or retrospective design were allowed.
- A study must have reported rates of lymph node detection using both SCI and BD (with BD as the reference standard). Studies comparing the combination technique of SCI and BD to any of the agents alone were also eligible.
- Patient-level and/or node-level rates must have been reported separately for at least one agent (SCI and/or BD) in addition to the overall lymph node localization rate using SCI +BD.
- As the goal of the sponsor's review was to estimate the performance of SCI and BD in lymph node localization, rather than establishing accurate nodal staging, the sponsor did not require studies to report results of histopathologic examination of excised nodes.

The studies varied in objectives, design, and data reporting; they also contained small variations in the lymph node mapping procedures. They are a mix of prospective and retrospective studies that were not necessarily designed to compare the SCI plus BD combined technique to BD only or SCI only techniques. However, using the protocol defined inclusion/exclusion criteria, 4 studies were identified for which paired outcome data from patients evaluated for both SCI success and Blue Dye success were available. This efficacy review focuses on the statistical team's meta-analysis of those four publications.

The endpoints compared for the meta-analysis are localization success rates for Tc 99m sulfur colloid and blue dye. These combined data may be used as support for the clinical usefulness of Tc 99m sulfur colloid injection for the above new indication.

6.1.2 Demographics

Table 6: Demographics of enrolled patients by study.

Study	Study 1	Study 2	Study 3	Study 4
Age (years)	22 to 89 (mean = 56)	Not provided	15 to 82 (mean = 53)	24 to 93 (mean not given)
Female (%)	30	44	27	47
Ethnicity	Not provided	Not provided	Not provided	Not provided

Reviewer's comments:

The reviewer believes patients enrolled in the submitted literature publications are reflective of the proposed target population. It is not expected that differences in age, gender or ethnicity would result in clinically meaningful differences in the performance of Tc 99m sulfur colloid injection for the localization of lymph nodes.

6.1.3 Subject Disposition

Details regarding study subject dispositions are not contained in the submitted literature publications.

6.1.4 Analysis of Endpoint(s)

The efficacy endpoints for the meta-analysis are patient-level lymph node localization (identification) rates when using Tc-99m sulfur colloid and blue dye. Localization rates were given as percentage of patients in each study for which either SCI or BD allowed successful identification of a lymph node during the LN biopsy procedure. Meta analytic methods were used to test the protocol-defined primary hypothesis that the Odds ratio (OR) for LN "localization" using SCI is non-inferior to OR of having LN localization using BD (i.e. OR < 0.85 vs. OR >= 0.85). This NI margin of 0.85 translates to testing that SCI rate is no lower than 77.3% assuming that the localization rate using BD is approximately 80%. The odds ratio for a given patient was defined as: the odds of a patient having at least one "hot" node localization versus the odds of a patient having at least one "blue" node localization. The secondary hypothesis that odds ratio for LN "localization" using SCI + BD is superior to OR for LN localization using the BD alone technique (i.e., OR <= 1 vs OR > 1) was also tested using meta-analytical techniques.

Table 7. Summary of Odds Ratios for Comparing BD to SCI

	Number of Studies	Number of Patients	Odds Ratio	95% Confidence Interval
BD to SCI	4	249	5.25	(2.08, 13.24)
BD+SCI to BD	4	249	15.14	(3.89, 58.92)

The FDA statistical reviewer determined that the odds ratio favored SCI over BD and SCI plus BD over BD. Therefore the protocol-defined non-inferiority and superiority null hypotheses were rejected for all the efficacy populations of interest. For the SCI vs. BD analysis, the point estimate for the odds ratio and 95% CI is 5.25 (2.08, 13.24). For the SCI plus BD vs. BD analysis, the point estimate for the odds ratio and 95% CI is 15.14 (3.89, 58.92).

In order to evaluate a potentially more meaningful comparison between the BD and SCI performances than would be provided by odds ratios, the odds ratio analysis was supplemented with a direct, patient level, comparison of SCI versus BD lymph node localization statistics. In the below table 8, "BD present" refers to the percentage of patients in which there was successful lymph node localization with blue dye, whereas "SCI present" refers to the percentage of patients that had lymph nodes successfully localized using Tc-99m sulfur colloid. "Only BD present" refers to the percentage of patients in which the lymph node(s) were successfully localized with BD only, and "Only SCI present" refers to the percentage of patients in which the lymph node(s) were successfully localized with SCI only.

Table 8: Lymph Node Localization Success Rates in Melanoma Patients.

Number of Clinical Studies	Total Number of Patients	BD present	SCI present	Only BD present	Only SCI present	Neither SCI nor BD present
4	249	83.6 %	96.4 %	3.2 %	15.5 %	1.6 %

Reviewer's Comments:

The above analyses are of patient level data for 249 subjects. The results clearly show higher lymph node "localization rates" when SCI is used in combination with blue dye. An additional important finding is the percentage of patients in which "only SCI' was successful is approximately five times the number of patients in which "only blue dye" successfully identified lymph nodes. This finding supports the belief that using SCI during LN biopsy procedures allows surgeons to identify lymph nodes potentially missed if using the blue dye only technique. These data, which are consistent with the findings in the breast cancer population, provide strong support for the clinical usefulness of Tc 99m sulfur colloid injection in the melanoma population.

6.1.5 Analysis of Secondary Endpoints(s)

There are no secondary endpoints to report for the meta-analysis data.

6.1.6 Additional Efficacy Evaluations

There are no additional efficacy evaluations to report.

6.1.6 Subpopulations

No specific subpopulations were identified that exhibited differences in efficacy measurements.

Overall Reviewer Comments Regarding Efficacy:

Following evaluation of the above data, this clinical reviewer believes the totality of submitted data provides clear and consistent support for the clinical usefulness of Tc 99m sulfur colloid injection as an aid for localizing lymph nodes during LN biopsy procedures in melanoma patients. The submitted publications show consistent, favorable results for Tc 99m sulfur colloid. When taken in context with the recent data reviewed for breast cancer patients, there is overwhelming support in favor of the drug's utility for localizing lymph nodes.

7 Review of Safety

Safety Summary

No new safety data were submitted with this supplemental NDA.

Safety data for Tc 99m sulfur colloid injection is available from post-marketing data and the 19 literature publications submitted and reviewed for supplement #34 (breast cancer indication).

The sponsor estimates there have been approximately (b) (4) doses (for all clinical uses and routes of administration) of the product administered over the past 25 years. There have been no known deaths related to Tc 99m sulfur colloid administration during this time period. In the 19 literature publications, there were no reported adverse events attributed to Tc 99m sulfur colloid injection.

In the post-marketing data, the most frequently reported systemic AEs, across all categories of use and routes of administration, include:
rash, allergic reaction, urticaria, anaphylaxis/anaphylactic shock, and hypotension.

Less frequently reported systemic AEs in the post-marketing data are:
cardiopulmonary arrest, seizures, dyspnea, bronchospasm, abdominal pain, flushing, nausea, vomiting, dizziness, itching, fever, chills, perspiration, numbness, and dizziness. Local injection site reactions, including burning, blanching, erythema, sclerosis, swelling, eschar, and scarring, have also been reported.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

There were no clinical trials designed to evaluate the safety of Tc 99m sulfur colloid injection for then new indication.

7.1.2 Categorization of Adverse Events

There were no reported adverse events associated with Tc 99m sulfur colloid in the 19 previously submitted and reviewed literature publications. Adverse events investigators attributed to BD were reported; these included allergic reactions, rash and urticaria, anaphylaxis, hypotension, and lymphedema.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The only data to report is from the submitted literature publications. The patient populations in those studies largely reflect the target patient population for the new indication.

7.2.2 Explorations for Dose Response

Not performed for this 505(b)(2) sNDA.

7.2.3 Special Animal and/or In Vitro Testing

Not performed.

7.2.4 Routine Clinical Testing

Not performed.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see clinical pharmacology section.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in the 19 literature publications. Additionally, from review of the post-marketing data covering over 25 years, there are no deaths attributable to Tc 99m sulfur colloid administration to report.

7.3.2 Nonfatal Serious Adverse Events

In the post-marketing data, the occurrences of anaphylaxis/anaphylactic shock, allergic reactions with hypotension combined with unresponsiveness and/or fainting have been reported.

7.3.3 Dropouts and/or Discontinuations

No information to report.

7.3.4 Significant Adverse Events

In the post-marketing data, the occurrence of rashes, allergic reactions, urticaria, burning/erythema at the injection site, dizziness, vomiting, agitation, fevers, flushing, palpitations, headache and swelling in the extremities have all been reported.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the post-marketing data, the most frequently reported systemic AEs, across all categories of use and routes of administration, include:
rash, allergic reaction, urticaria, anaphylaxis/anaphylactic shock, and hypotension.

7.4.2 Laboratory Findings

No data to report.

7.4.3 Vital Signs

No data to report.

7.4.4 Electrocardiograms (ECGs)

No data to report.

7.4.5 Special Safety Studies/Clinical Trials

None conducted.

7.4.6 Immunogenicity

No data to report.

7.5 Other Safety Explorations

No data to report.

7.6 Additional Safety Evaluations

No data to report.

7.7 Additional Submissions / Safety Issues

Annual/Safety Report Submission:
The sponsor submitted their annual report on 6/15/2012, which covers the period 4/17/2011 to 4/16/2012 and contains safety reports for that period, including:

- One 15 day adverse event summary: A patient contacted Pharmalucence to report gradual onset of vomiting, chest pains, and shortness of breath two days post injection with Sulfur Colloid. The patient also stated she has hypothyroid since her release and was on an unknown medication. The patient fully recovered and was released from the hospital. This was reported to FDA on 8/22/2011. The sponsor concluded this 15 day alert report does not change the risk/benefit ratio for the drug and this reviewer agrees with that assessment. The event was either likely unrelated to study drug administration or represented a delayed hypersensitivity type reaction

(labeled). Of note, the sponsor states: "Since 1986, less than six (6) SAEs have been reported in the use of Sulfur Colloid."

- Three reports of adverse drug experiences: Two of these three adverse drug experiences (itching, rash) were non-serious and are mentioned in the PI. The other event occurred in a 48 year old female with a history of seizure disorder who received 4 periareolar injections of SCI for sentinel node localization prior to surgery. Later that afternoon the physician stating the patient had a seizure, although not witnessed. The patient had not taken her usual seizure medications that morning and this event was concluded likely related to her underlying medical history. However, please note that seizures are a very infrequent, but known expected AE stated in the PI.

- Two reports of altered biodistribution experiences were also submitted during the reporting period. These reports involved two patients from one center, along with one different patient from a different center. No root cause was identified, but the altered biodistribution was attributed to a high amount of unbound 99mTc-pertechnetate, which is a known occurrence for the use of Tc 99-SCI.

- Two other events reported were: 1) a high amount of residual activity in a syringe for a liver/spleen study in a child, and 2) no migration of SCI during a lymphoscintigraphy study. Pharmalucence is working with the reporting facilities on these events, and the reviewer believes these events do not change the safety/benefit profile of the drug.

The sponsor states: Pharmalucence continues to review Adverse Drug Experiences as they are received, and a comparison is made to the "Adverse Reactions" section of the package insert to ensure it contains current information. There is no evidence that any of the adverse events received represent any new or increased risk for patient safety."

The sponsor concluded that "there is no new information received as a result of all adverse events/patient incidents during this reporting period, and the risk profile of the Sulfur Colloid drug product remains unchanged." The reviewer agrees with this conclusion.

The annual report submission contains no other new information to discuss.

8 Post-market Experience

Over the past 25 years, the sponsor estimates that approximately (b) (4) doses of Tc 99m-SCI have been administered. The sponsor reports a current distribution of approximately (b) (4) multi-dose kits annually.

Adverse events (AEs) reported spontaneously to the sponsor for this 25 year period covers all routes and uses of SCI (not just subcutaneous administration for use in lymphatic mapping).

The most frequently reported systemic AEs, including all uses and routes of administration, include:
rash, allergic reaction, urticaria, anaphylaxis/anaphylactic shock, and hypotension.

Less frequently reported systemic AEs are:
cardiopulmonary arrest, seizures, dyspnea, bronchospasm, abdominal pain, flushing, nausea, vomiting, dizziness, itching, fever, chills, perspiration, numbness, and dizziness. Local injection site reactions, including burning, blanching, erythema, sclerosis, swelling, eschar, and scarring, have also been reported.

Events reported to be specifically associated with the use of subcutaneous SCI for lymph node localization are anaphylaxis, rash, flushing, and injection site reactions including burning, sclerosis, swelling, eschar, blanching, erythema, scarring, and blistering.

9 Appendices

9.1 References:

1. An UpToDate literature search and review was performed 2/24/2012 and used as a resource for this document.

9.2 Advisory Committee Meeting

This application was not the subject of an advisory committee meeting.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHILLIP B DAVIS
07/16/2012

LUCIE L YANG
07/16/2012