CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78-098

Name: Kit for the Preparation of Technetium Tc 99m Sestamibi Injection

Sponsor: Mallinckrodt, Inc.

Approval Date: September 22, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-098

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-098

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-098

Mallinckrodt, Inc.
Attention: James W. Brodack, Ph.D.
Director, Regulatory Affairs
675 McDonnell Blvd.
Hazelwood, MO 63042

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 31, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.

Reference is also made to the tentative approval letter issued by this office on February 26, 2008, and to your amendments dated May 12, June 23, July 3, and September 9, 2008.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is approved effective on the date of this letter. The Division of Bioequivalence has determined your Kit for the Preparation of Technetium Tc 99m Sestamibi Injection to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Cardiolite Injection (Kit for the Preparation of Technetium Tc 99m Sestamibi Injection), of Bristol Myers Squibb Pharma Company.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "***Miscellaneous Correspondence - SPL for Approved ANDA 78-098***".

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Gary Buehler

9/22/2008 12:20:37 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-098

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-098

Mallinckrodt, Inc.
Attention: James W. Brodack, Ph.D.
Regulatory Affairs Manager
675 McDonnell Blvd.
Hazelwood, MO 63134

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 31, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.

Reference is also made to your amendments dated October 6, and December 14, 2007; and January 17, 2008.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the unexpired patent noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time, (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug (RLD) upon which you have based your ANDA, Cardiolite (Kit for the Preparation of Technetium Tc 99m Sestamibi Injection) of Bristol Myers Squibb Pharma Company, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the “Orange Book”), U.S. Patent No. 4,988,827 (the '827 patent), is scheduled to expire on July 29, 2008 (with pediatric exclusivity extension). Your ANDA contains a paragraph III certification to the '827 patent

under section 505(j)(2)(A)(vii)(III) of the Act stating that Mallinckrodt, Inc. will not market its Kit for the Preparation of Technetium Tc 99m Sestamibi Injection prior to the expiration of this patent. Therefore, final approval of your ANDA may not be made effective pursuant to section 505(j)(5)(B)(ii) of the Act until the '827 patent has expired, currently, July 29, 2008.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed approved

for marketing under section 505 of the Act, and will not be listed in the "Orange Book." Should you believe that there are grounds for issuing the final approval letter prior to July 29, 2008, you should amend your ANDA accordingly.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Dat Doan, Project Manager, at 240-276-8573.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
2/26/2008 02:07:27 PM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-098

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Kit for the Preparation of Technetium Tc 99m Sestamibi Injection safely and effectively. See full prescribing information for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.

Kit for the Preparation of Technetium Tc 99m Sestamibi Injection Kit for Intravenous use

Initial U.S. Approval: 2008

----------RECENT MAJOR CHANGES ----------

Use in specific populations (8.4)

Labeling describing pediatric studies of technetium Tc-99m sestamibi kit is approved for Lantheus Medical Imaging's technetium Tc-99m sestamibi kit. However due to Lantheus Medical Imaging's marketing exclusivity rights, a description of those studies does not appear in this technetium Tc-99m sestamibi kit labeling.

---------- INDICATIONS AND USAGE----------

Technetium Tc 99m Sestamibi, is a myocardial perfusion agent indicated for:

- detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects) (1)
- evaluating myocardial function and developing information for use in patient management decisions (1)

----------DOSAGE AND ADMINISTRATION----------

- For Myocardial Imaging: The suggested dose range for I.V. administration of Technetium Tc 99m Sestamibi in a single dose to be employed in the average patient (70 Kg) is 370-1110 MBq (10-30 mCi) (2).
- For Breast Imaging: The recommended dose range for I.V. administration of Technetium Tc 99m Sestamibi is a single dose of 740-1110 MBq (20-30 mCi) (2).

---------- DOSAGE FORMS AND STRENGTHS----------

- Kit for the Preparation of Technetium Tc 99m Sestamibi Injection is supplied as a 10 mL vial in a kit of five (5) (NDC # 0019-9092-B0) or a carton of thirty (30) (NDC # 0019-9092-D0), sterile and non-pyrogenic (3).
- Prior to lyophilization the pH is between 5.6–5.7. The contents of the vial are lyophilized and stored under nitrogen. Protect from light prior to reconstitution. Store at 15 –25 C (59 –77 F) before and after reconstitution (3).

---------- CONTRAINDICATIONS ----------

- None known.

---------- WARNINGS AND PRECAUTIONS ----------

- Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction and cerebrovascular events (5.1).
- Technetium Tc 99m Sestamibi has been rarely associated with acute severe allergic and anaphylactic events of angioedema and generalized urticaria. In some patients the allergic symptoms developed on the second injection during Technetium Tc 99m Sestamibi imaging (5.1).
- Caution should be exercised and emergency equipment should be available when administering Technetium Tc 99m Sestamibi (5.1).
- Before administering Technetium Tc 99m Sestamibi patients should be asked about the possibility of allergic reactions to either drug (5.1).
- The contents of the vial are intended only for use in the preparation of Technetium Tc 99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure (5.2).

---------- ADVERSE REACTIONS ----------

The following adverse reactions have been reported in > 0.5% of patients: signs and symptoms consistent with seizure occurring shortly after administration of the agent; transient arthritis; angioedema, arrhythmia, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity characterized by dyspnea, hypotension, bradycardia, asthenia, and vomiting within two hours after a second injection of Technetium Tc 99m Sestamibi. A few cases of flushing, edema, injection site inflammation, dry mouth, fever, pruritis, rash, urticaria and fatigue have also been attributed to administration of the agent (6).

To report SUSPECTED ADVERSE REACTIONS, contact Mallinckrodt Inc. at 1-800-778-7898 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Specific drug-drug interactions have not been studied (7).

---------- USE IN SPECIFIC POPULATIONS ----------

Labeling describing pediatric studies of technetium Tc-99m sestamibi kit is approved for Lantheus Medical Imaging's technetium Tc-99m sestamibi kit. However due to Lantheus Medical Imaging's marketing exclusivity rights, a description of those studies does not appear in this technetium Tc-99m sestamibi kit labeling (8.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: September 2008

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Myocardial Imaging: Technetium Tc 99m Sestamibi Injection is a myocardial perfusion agent that is indicated for detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects), in evaluating myocardial function and developing information for use in patient management decisions. Technetium Tc 99m Sestamibi evaluation of myocardial ischemia can be accomplished with rest and cardiovascular stress techniques (e.g., exercise or pharmacologic stress in accordance with the pharmacologic stress agent's labeling).

It is usually not possible to determine the age of a myocardial infarction or to differentiate a recent myocardial infarction from ischemia.

Breast Imaging: Technetium Tc 99m Sestamibi is indicated for planar imaging as a second line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass.

Technetium Tc 99m Sestamibi is not indicated for breast cancer screening, to confirm the presence or absence of malignancy, and it is not an alternative to biopsy.

2 DOSAGE AND ADMINISTRATION

For Myocardial Imaging: The suggested dose range for I.V. administration of Technetium Tc 99m Sestamibi in a single dose to be employed in the average patient (70 Kg) is 370–1110 MBq (10–30 mCi).

For Breast Imaging: The recommended dose range for I.V. administration of Technetium Tc 99m Sestamibi is a single dose of 740–1110 MBq (20–30 mCi).

2.1 Image Acquisition

Breast Imaging: It is recommended that images are obtained with a table overlay to separate breast tissue from the myocardium and liver, and to exclude potential activity that may be present in the opposite breast. For lateral images, position the patient prone with the isolateral arm comfortably above the head, shoulders flat against the table, head turned to the side and relaxed, with the breast imaged pendent through an overlay cutout. The breast should not be compressed on the overlay. For anterior images, position the patient supine with both arms behind the head. For either lateral or anterior images, shield the chest and abdominal organs, or remove them from the field of view.

For complete study, sets of images should be obtained five minutes after the injection, and in the following sequence:

Beginning five minutes after the injection of Technetium Tc 99m Sestamibi:

- ten-minute lateral image of breast with abnormality
- ten-minute lateral image of contralateral breast
- ten-minute anterior image of both breasts

2.2 Radiation Dosimetry

The radiation doses to organs and tissues of an average patient (70 Kg) per 1110 MBq (30 mCi) of Technetium Tc 99m Sestamibi injected intravenously are shown in **Table 1**.

Table 1. Radiation Absorbed Doses from Tc 99m Sestamibi

	Estimated Radiation Absorbed Dose			
	REST			
	2.0 hour void		4.8 hour void	
Organ	rads/30 mCi	mGy/1110 MBq	rads/30 mCi	mGy/1110 MBq
Breasts	0.2	2.0	0.2	1.9
Gallbladder Wall	2.0	20.0	2.0	20.0
Small Intestine	3.0	30.0	3.0	30.0
Upper Large Intestine Wall	5.4	55.5	5.4	55.5
Lower Large Intestine Wall	3.9	40.0	4.2	41.1
Stomach Wall	0.6	6.1	0.6	5.8
Heart Wall	0.5	5.1	0.5	4.9
Kidneys	2.0	20.0	2.0	20.0
Liver	0.6	5.8	0.6	5.7
Lungs	0.3	2.8	0.3	2.7
Bone Surfaces	0.7	6.8	0.7	6.4
Thyroid	0.7	7.0	0.7	2.4
Ovaries	1.5	15.5	1.6	15.5
Testes	0.3	3.4	0.4	3.9
Red Marrow	0.5	5.1	0.5	5.0
Urinary Bladder Wall	2.0	20.0	4.2	41.1
Total Body	0.5	4.8	0.5	4.8
	Estimated Radiation Absorbed Dose			
	STRESS			
	2.0 hour void		4.8 hour void	
Organ	rads/30 mCi	mGy/1110 MBq	rads/30 mCi	mGy/1110 MBq
Breasts	0.2	2.0	0.2	1.8
Gallbladder Wall	2.8	28.9	2.8	27.8
Small Intestine	2.4	24.4	2.4	24.4
Upper Large Intestine Wall	4.5	44.4	4.5	44.4
Lower Large Intestine Wall	3.3	32.2	3.3	32.2
Stomach Wall	0.6	5.3	0.5	5.2
Heart Wall	0.5	5.6	0.5	5.3
Kidneys	1.7	16.7	1.7	16.7
Liver	0.4	4.2	0.4	4.1
Lungs	0.3	2.6	0.2	2.4
Bone Surfaces	0.6	6.2	0.6	6.0
Thyroid	0.3	2.7	0.2	2.4
Ovaries	1.2	12.2	1.3	13.3
Testes	0.3	3.1	0.3	3.4
Red Marrow	0.5	4.6	0.5	4.4
Urinary Bladder Wall	1.5	15.5	3.0	30.0
Total Body	0.4	4.2	0.4	4.2

Radiation dosimetry calculations performed by Radiation Internal Dose Information Center, Oak Ridge Institute for Science and Education, PO Box 117, Oak Ridge, TN 37831-0117, (865) 576-3448.

2.3 Instructions for Preparation

Preparation of the Technetium Tc 99m Sestamibi from the Kit for the Preparation of Technetium Tc 99m Sestamibi is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate Tc 99m Injection to the vial, inspect the vial carefully for the presence of damage, particularly cracks, and do not use the vial if found.

b. Waterproof gloves should be worn during the preparation procedure. Remove the plastic disc from the vial and swab the top of the vial closure with alcohol to sanitize the surface.

c. Place the vial in a suitable radiation shield with a fitted radiation cap.

d. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc 99m Injection [925–5550 MBq, (25–150 mCi)] in approximately 1 to 3 mL.

e. Aseptically add the Sodium Pertechnetate Tc 99m Injection to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.

f. Shake vigorously, about 5 to 10 quick upward-downward motions.

g. Remove the vial from the lead shield and place upright in an appropriately shielded and contained boiling water bath, such that the vial is suspended above the bottom of the bath, and boil for 10 minutes. Timing for 10 minutes is begun as soon as the water begins to boil again. Do not allow the boiling water to come in contact with the aluminum crimp.

h. Remove the vial from the water bath, place in the lead shield and allow to cool for fifteen minutes.

i. Using proper shielding, the vial contents should be visually inspected. Use only if the solution is clear and free of particulate matter and discoloration.

j. Assay the reaction vial using a suitable radioactivity calibration system. Record the Technetium Tc 99m concentration, total volume, assay time and date, expiration time and lot number on the radioassay information label and affix the label to the shield.

k. Store the reaction vial containing the Technetium Tc 99m Sestamibi at 15 to 25 C (59 to 77 F) until use; at such time the product should be aseptically withdrawn. Technetium Tc 99m Sestamibi should be used within six hours of preparation. The vial contains no preservative.

Note: Adherence to the above product reconstitution instructions is recommended.

Mallinckrodt Inc.'s Kit for the Preparation of Technetium Tc 99m Sestamibi Injection is not to be used with the Recon-

o-Stat™ thermal cycler due to the smaller vial size requirements of this heating device.

The potential for cracking and significant contamination exists whenever vials containing radioactive material are heated.

Product should be used within 6 hours after preparation.

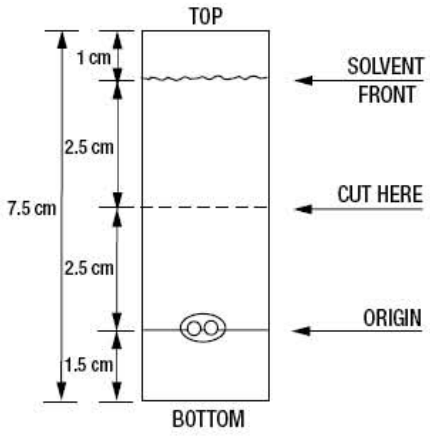
Final product with radiochemical purity of at least 90% was used in the clinical trials that established safety and effectiveness. The radiochemical purity was determined by the following method.

2.4 Determination of Radiochemical Purity in Technetium Tc 99m Sestamibi

1. Obtain a Baker-Flex Aluminum Oxide coated, plastic TLC plate, #1 B-F, pre-cut to 2.5 cm x 7.5 cm.
2. Dry the plate or plates at 100 C for 1 hour and store in a desiccator. Remove pre-dried plate from the desiccator just prior to use.
3. Apply 1 drop of ethanol* using a 1 mL syringe with a 22–26 gauge needle, 1.5 cm from the bottom of the plate. THE SPOT SHOULD NOT BE ALLOWED TO DRY.
4. Add 2 drops of Technetium Tc 99m Sestamibi solution, side by side on top of the ethanol* spot. Return the plate to a desiccator and allow the sample spot to dry (typically 15 minutes).
5. The TLC tank is prepared by pouring ethanol* to a depth of 3–4 mm. Cover the tank and let it equilibrate for ~10 minutes.
6. Develop the plate in the covered TLC tank in ethanol* for a distance of 5 cm from the point of application.
7. Cut the TLC plate 4 cm from the bottom and measure the Tc 99m activity in each piece by appropriate radiation detector.
8. Calculate the % Tc 99m Sestamibi as:

$$\%\ \text{Tc 99m Sestamibi} = \frac{\mu\text{Ci Top Piece}}{\mu\text{Ci Both Pieces}} \times 100$$

TLC Plate Diagram



*The ethanol used in this procedure should be 95% or greater. Absolute ethanol (99%) should remain at ≥ 95% ethanol content for one week after opening if stored tightly capped, in a cool dry place.

3 DOSAGE FORMS AND STRENGTHS

Kit for the Preparation of Technetium Tc 99m Sestamibi Injection is supplied as a 10 mL vial in a kit of five (5) (NDC # 0019-9092-B0) or a carton of thirty (30) (NDC # 0019-9092-D0), sterile and non-pyrogenic.

Prior to lyophilization the pH is between 5.6–5.7. The contents of the vial are lyophilized and stored under nitrogen. Protect from light prior to reconstitution. Technetium Tc 99m Sestamibi contains no preservatives.

Store at 15 –25 C (59 –77 F) before and after reconstitution.

Included in each five (5) vial kit is one (1) package insert and five (5) radioassay information labels. Included in each thirty (30) vial carton is one (1) package insert and thirty (30) radioassay information labels.

This reagent kit is approved by the U.S. Nuclear Regulatory Commission for distribution to persons licensed to use by-product material identified in §35.200 to 10 CFR Part 35, to persons who have a similar authorization issued by an Agreement State, and, outside the United States, to persons authorized by the appropriate authority.

4 CONTRAINDICATIONS

None known.

5 WARNINGS AND PRECAUTIONS

5.1 Warnings

In studying patients in whom cardiac disease is known or suspected, care should be taken to assure continuous monitoring and treatment in accordance with safe, accepted clinical procedure. Infrequently, death has occurred 4 to 24 hours after Tc 99m Sestamibi use and is usually associated with exercise stress testing [*see Warnings and Precautions (5.2)*].

Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction and cerebrovascular events. Caution should be used when pharmacologic stress is selected as an alternative to exercise; it should be used when indicated and in accordance with the pharmacologic stress agent's labeling.

Technetium Tc 99m Sestamibi has been rarely associated with acute severe allergic and anaphylactic events of angioedema and generalized urticaria. In some patients the allergic symptoms developed on the second injection during Tc 99m Sestamibi imaging. Patients who receive Technetium Tc 99m Sestamibi for either myocardial or breast imaging are receiving the same drug. Caution should be exercised and emergency equipment should be available when administering Technetium Tc 99m Sestamibi. Also, before administering Technetium Tc 99m Sestamibi Injection, patients should be asked about the possibility of allergic reactions to the drug.

5.2 General Precautions

The contents of the vial are intended only for use in the preparation of Technetium Tc 99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken to minimize radiation exposure to the patients consistent with proper patient management.

Contents of the kit before preparation are not radioactive. However, after the Sodium Pertechnetate Tc 99m Injection is added, adequate shielding of the final preparation must be maintained. The components of the kit are sterile and non-pyrogenic. It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation.

Technetium Tc 99m labeling reactions depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc 99m Injection containing oxidants should not be used.

Technetium Tc 99m Sestamibi should not be used more than six hours after preparation.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

The most frequent exercise stress test endpoints sufficient to stop the test reported during controlled studies (two-thirds were cardiac patients) were:

Fatigue	35%
Dyspnea	17%
Chest Pain	16%
ST-depression	7%
Arrhythmia	1%

6 ADVERSE REACTIONS

Adverse events were evaluated in 3741 adults who were evaluated in clinical studies. Of these patients, 3068 (77% men, 22% women, and 0.7% of the patients' genders were not recorded) were in cardiac clinical trials and 673 (100% women) in breast imaging trials. Cases of angina, chest pain, and death have occurred [*see Warnings and Precautions (5)*]. Adverse events reported at a rate of 0.5% or greater after receiving Technetium Tc 99m Sestamibi administration are shown in the following table:

Table 2

Selected Adverse Events Reported in > 0.5% of Patients Who Received Technetium Tc 99m Sestamibi in Either Breast or Cardiac Clinical Studies*				
Body System	**Breast Studies**	**Cardiac Studies**		
	Women n = 673	Women n = 685	Men n = 2361	Total n = 3046
Body as a Whole	21 (3 1%)	6 (0.9%)	17 (0.7%)	23 (0.8%)
Headache	11 (1.6%)	2 (0.3%)	4 (0.2%)	6 (0.2%)
Cardiovascular	9 (1.3%)	24 (3.5%)	75 (3.2%)	99 (3.3%)
Chest Pain/Angina	0 (0%)	18 (2.6%)	46 (1.9%)	64 (2.1%)
ST Segment Changes	0 (0%)	11 (1.6%)	29 (1.2%)	40 (1.3%)
Digestive System	8 (1.2%)	4 (0.6%)	9 (0.4%)	13 (0.4%)
Nausea	4 (0.6%)	1 (0.1%)	2 (0.1%)	3 (0.1%)
Special Senses	132 (19.6%)	62 (9.1%)	160 (6.8%)	222 (7.3%)
Taste Perversion	129 (19 2%)	60 (8.8%)	157 (6.6%)	217 (7.1%)
Parosmia	8 (1.2%)	6 (0.9%)	10 (0.4%)	16 (0.5%)
* Excludes the 22 patients whose genders were not recorded.				

In the clinical studies for breast imaging, breast pain was reported in 12 (1.7%) of the patients. In 11 of these patients the pain appears to be associated with biopsy/surgical procedures.

The following adverse reactions have been reported in ≤ 0.5% of patients: signs and symptoms consistent with seizure occurring shortly after administration of the agent; transient arthritis; angioedema, arrhythmia, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity characterized by dyspnea, hypotension, bradycardia, asthenia, and vomiting within two hours after a second injection of Technetium Tc 99m Sestamibi. A few cases of flushing, edema, injection site inflammation, dry mouth, fever, pruritus, rash, urticaria and fatigue have also been attributed to administration of the agent.

7 DRUG INTERACTIONS

Specific drug-drug interactions have not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc 99m Sestamibi. It is also not known whether Technetium Tc 99m Sestamibi can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc 99m Sestamibi should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

Technetium Tc 99m Pertechnetate is excreted in human milk during lactation. It is not known whether Technetium Tc 99m Sestamibi is excreted in human milk. Therefore, formula feedings should be substituted for breast feedings.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Labeling describing pediatric studies of technetium Tc-99m sestamibi kit is approved for Lantheus Medical Imaging's technetium Tc-99m sestamibi kit. However due to Lantheus Medical Imaging's marketing exclusivity rights, a description of those studies does not appear in this technetium Tc-99m sestamibi kit labeling.

Adverse events were evaluated in 609 pediatric patients from the three clinical studies described above. The frequency and the type of the adverse events were similar to the ones observed in the studies of Technetium Tc 99m Sestamibi in adults. Two of the 609 had a serious adverse event: one patient received a Technetium Tc 99m Sestamibi overdose but remained asymptomatic, and one patient had an asthma exacerbation following administration.

8.5 Geriatric Use

Of 3068 patients in clinical studies of Technetium Tc 99m Sestamibi for myocardial imaging, 693 patients were 65 or older and 121 were 75 or older.

Of 673 patients in clinical studies of Technetium Tc 99m Sestamibi for breast imaging, 138 patients were 65 or older and 30 were 75 or older.

Based on the evaluation of the frequency of adverse events and review of vital signs data, no overall differences in safety were observed between these subjects and younger subjects. Although reported clinical experience has not identified differences in response between elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Not applicable.

9.2 Abuse

Not applicable.

9.3 Dependence

Not applicable.

10 OVERDOSAGE

The clinical consequences of overdosing with Technetium Tc 99m Sestamibi are not known.

11 DESCRIPTION

Each 10 mL vial contains a sterile, non-pyrogenic, lyophilized mixture of:

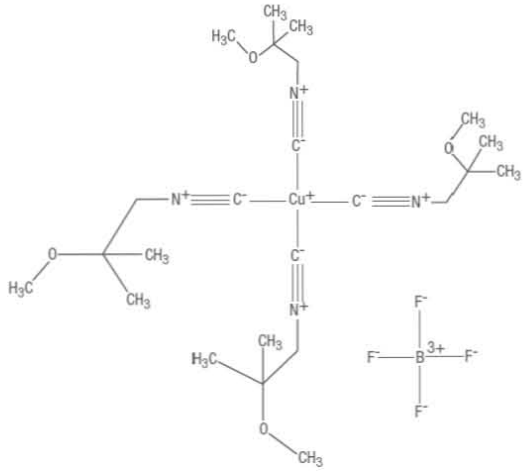
Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1 mg
Sodium Citrate Dihydrate - 2.6 mg
L-Cysteine Hydrochloride Monohydrate - 1 mg
Mannitol - 20 mg
Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) - 0.025 mg
Stannous Chloride, Dihydrate ($SnCl_2 \cdot 2H_2O$) - 0.075 mg
Tin Chloride (stannous and stannic) Dihydrate, maximum (as $SnCl_2 \cdot 2H_2O$) - 0.086 mg

Prior to lyophilization the pH is 5.6 to 5.7, and sodium hydroxide and/or hydrochloric acid may have been added for pH adjustment. The contents of the vial are lyophilized and stored under nitrogen.

This drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc 99m Injection. The pH of the reconstituted product is 5.5 (5.0–6.0). No bacteriostatic preservative is present.

The precise structure of the technetium complex is $Tc99m[MIBI]_6^+$ where MIBI is 2-methoxy isobutyl isonitrile.

Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate has the following structural formula:



The molecular formula is $C_{24}H_{44}N_4O_4BF_4Cu$, and the molecular weight is 602.98.

11.1 Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours.[1] Photons that are useful for detection and imaging studies are listed below in **Table 3**.

Table 3. Principal Radiation Emission Data

Radiation	Mean %/ Disintegration	Mean Energy (KeV)
Gamma-2	89.07	140.5

[1]Kocher, David, C., Radioactive Decay Data Tables, DOE/TIC-11026, 108(1981).

11.2 External Radiation

The specific gamma ray constant for Tc 99m is 5.4 microcoulombs/Kg-MBq-hr (0.78 R/mCi-hr) at 1 cm. The first half value layer is 0.017 cm of Pb. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in **Table 4**. To facilitate control of the radiation exposure from Megabequerel (millicurie) amounts of this radionuclide, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of 1,000.

Table 4. Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in **Table 5**.

Table 5. Physical Decay Chart; Tc 99m Half-Life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501		

* Calibration Time

12 CLINICAL PHARMACOLOGY

12.1 General

Technetium Tc 99m Sestamibi is a cationic Tc 99m complex which has been found to accumulate in viable myocardial tissue in a manner analogous to that of thallous chloride Tl-201. Scintigraphic images obtained in humans after the intravenous administration of the drug have been comparable to those obtained with thallous chloride Tl-201 in normal and abnormal myocardial tissue.

Animal studies have shown that myocardial uptake is not blocked when the sodium pump mechanism is inhibited. Although studies of subcellular fractionation and electron micrographic analysis of heart cell aggregates suggest that Tc 99m Sestamibi cellular retention occurs specifically within the mitochondria as a result of electrostatic interactions, the clinical relevance of these findings has not been determined.

The mechanism of Tc 99m Sestamibi localization in various types of breast tissue (e.g., benign, inflammatory, malignant, fibrous) has not been established.

12.2 Pharmacokinetics

Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that the fast clearing component clears with a $t_{½}$ of 4.3 minutes at rest, and clears with a $t_{½}$ of 1.6 minutes under exercise conditions. At five minutes post injection about 8% of the injected dose remains in circulation. There is less than 1% protein binding of Technetium Tc 99m Sestamibi in plasma. The myocardial biological half-life is approximately six hours after a rest or exercise injection. The biological half-life for the liver is approximately 30 minutes after a rest or exercise injection. The effective half-life of clearance (which includes both the biological half-life and radionuclide decay) for the heart is approximately 3 hours, and for the liver is approximately 30 minutes, after a rest or exercise injection. The ideal imaging time reflects the best compromise between heart count rate and surrounding organ uptake.

Myocardial uptake which is coronary flow dependent is 1.2% of the injected dose at rest and 1.5% of the injected dose at exercise. **Table 6** illustrates the biological clearance as well as effective clearance (which includes biological clearance and radionuclide decay) of Tc 99m Sestamibi from the heart and liver.

[Organ concentrations expressed as percentage of injected dose; data based on an average of 5 subjects at rest and 5 subjects during exercise.]

Table 6

REST

	Heart		Liver	
Time	**Biological**	**Effective**	**Biological**	**Effective**
5 min.	1.2	1.2	19.6	19.4
30 min.	1.1	1.0	12.2	11.5
1 hour	1.0	0.9	5.6	5.0
2 hours	1.0	0.8	2.2	1.7
4 hours	0.8	0.5	0.7	0.4

STRESS

	Heart		Liver	
Time	**Biological**	**Effective**	**Biological**	**Effective**
5 min.	1.5	1.5	5.9	5.8
30 min.	1.4	1.3	4.5	4.2
1 hour	1.4	1.2	2.4	2.1
2 hours	1.2	1.0	0.9	0.7
4 hours	1.0	0.6	0.3	0.2

A study in a dog myocardial ischemia model reported that Technetium Tc 99m Sestamibi undergoes myocardial distribution (redistribution), although more slowly and less completely than thallous chloride Tl-201. A

study in a dog myocardial infarction model reported that the drug showed no redistribution of any consequence. Definitive human studies to demonstrate possible redistribution have not been reported. In patients with documented myocardial infarction, imaging revealed the infarct up to four hours post dose.

12.3 Metabolism

The agent is excreted without any evidence of metabolism.

12.4 Elimination

The major pathway for clearance of Tc 99m Sestamibi is the hepatobiliary system. Activity from the gall bladder appears in the intestines within one hour of injection. Twenty-seven percent of the injected dose is excreted in the urine, and approximately thirty-three percent of the injected dose is cleared through the feces in 48 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In comparison with most other diagnostic technetium labeled radiopharmaceuticals, the radiation dose to the ovaries (1.5 rads/30 mCi at rest, 1.2 rads/30 mCi at exercise) is high. Minimal exposure (ALARA) is necessary in women of childbearing capability [*see Dosage and Administration (2.2)]*.

The active intermediate, $Cu(MIBI)_4BF_4$, was evaluated for genotoxic potential in a battery of five tests. No genotoxic activity was observed in the Ames, CHO/HPRT and sister chromatid exchange tests (all *in vitro*). At cytotoxic concentrations (>20 µg/mL), an increase in cells with chromosome aberrations was observed in the *in vitro* human lymphocyte assay. $Cu(MIBI)_4BF_4$ did not show genotoxic effects in the *in vivo* mouse micronucleus test at a dose which caused systemic and bone marrow toxicity (9 mg/kg, > 600 X maximal human dose).

14 CLINICAL STUDIES

Clinical Trials:

Myocardial Imaging: In a trial of rest and stress Tc 99m Sestamibi imaging, the relationship of normal or abnormal perfusion scans and long term cardiac events was evaluated in 521 patients (511 men, 10 women) with stable chest pain. There were 73.9% Caucasians, 25.9% Blacks and 0.2% Asians. The mean age was 59.6 years (range: 29 to 84 years). All patients had a baseline rest and exercise Tc 99m Sestamibi scan and were followed for 13.2 ± 4.9 months (range: 1 to 24 months). Images were correlated with the occurrence of a cardiac event (cardiac death or non-fatal myocardial infarction). In this trial as summarized in **Table 7**, 24/521 (4.6%) had a cardiac event.

Table 7. Cardiac Events

Baseline Scan[(a)]	**Proportion of patients with events by scan results[(a)]**	**Proportion of scan result in patients with events; N=24[(a)]**	**Proportion of event-free patients by scan result[(a)]**
Normal	1/206 (0.5%)	1/24 (4.2%)	205/206 (99.5%)
Abnormal	23/315 (7.3%)[(b)]	23/24 (95.8%)[(b)]	292/315 (92.7%)[(b)]

(a) Note: Similar findings were found in two studies with patients who had pharmacologic stress Tc 99m Sestamibi imaging.

(b) $p<0.01$

Although patients with normal images had a lower cardiac event rate than those with abnormal images, in all patients with abnormal images it was not possible to predict which patient would be likely to have further cardiac events; i.e., such individuals were not distinguishable from other patients with abnormal images.

The findings were not evaluated for defect location, disease duration, specific vessel involvement or intervening management.

In earlier trials, using a template consisting of the anterior wall, inferior-posterior wall and isolated apex, localization in the anterior or inferior-posterior wall in patients with suspected angina or coronary artery disease was shown. Disease localization isolated to the apex has not been established. In adults, Tc 99m Sestamibi has not been studied or evaluated in cardiac disorders other than coronary artery disease.

Breast Imaging: Technetium Tc 99m Sestamibi was evaluated in two multicenter, clinical trials of a total of 673 woman patients. Overall the mean age was 52 (range 23 to 87 years). The racial and ethnic representation was 70% Caucasian, 15% African-American, 14% Hispanic and 1% Asian.

Both clinical studies evaluated women who were referred for further evaluation for either: 1) a mammographically detected (with varying degrees of malignant likelihood) but not palpable breast lesion (study A, n=387, mean age = 54 years), or 2) a palpable breast lesion (study B, n=286, mean age = 50 years). In both studies all patients were scheduled for biopsy.

Technetium Tc 99m Sestamibi (20–30 mCi) was injected intravenously in a vein that was contralateral to the breast lesion in question. Planar imaging was completed with a high resolution collimator with a 10% window centered at 140 KeV, and 128 x 128 matrix. An initial marker image, that was not used in the data analysis, was obtained using a cobalt Co57 point source as a marker of a palpable mass. Images were obtained 5 minutes after injection as follows: lateral image of the affected breast for 10 minutes, lateral image of the contralateral breast for 10 minutes, and an anterior image of both breasts for 10 minutes. For the lateral image the patients were positioned in a prone position. For the anterior image, the patients were supine. The Technetium Tc 99m Sestamibi scintigraphic images were read in a randomized method by two groups of three blinded readers. Technetium Tc 99m Sestamibi uptake was scored as: normal (no uptake), equivocal, low, moderate, or high uptake. The results of Technetium Tc 99m Sestamibi images and mammography were analyzed in comparison to histopathologic findings of malignant or non-malignant disease.

As shown in **Table 8** for the 483 evaluable patients, the sensitivity and specificity of any degree of Technetium Tc 99m Sestamibi uptake appear to vary with the presence or absence of palpable mass.

Table 8

Overall Technetium Tc 99m Sestamibi Blinded Results of Target Lesions[(a)] Identified at Study Entry[(b)]		
STATISTIC	Study A Non-Palpable Mass and an Abnormal Mammogram	Study B Palpable Mass
Number of Patients and Lesions	N=277 Patients with 300 Lesions	N=206 Patients with 240 Lesions
Sensitivity	52(42,62)[(c)]	76(67,83)
Specificity	94(89,96)	85(77,91)
PPV[(d)]	79(67,88)	83(74,89)
NPV[(d)]	80(74,85)	78(69,84)
Agreement	80(75,85)	80(75,85)
Prevalence	32(27,37)	49(43,56)

(a) Excludes all discordant lesions not identified at entry and excludes 25 equivocal interpretations from Study A and 32 equivocal interpretations from Study B (*see* **Tables 9** *and* **10**)

(b) some patients had more than one target lesion

(c) Median and approximated 95% Confidence Interval

(d) PPV = Positive Predict Value; NPV = Negative Predict Value

In separate retrospective subset analyses of 259 patients with dense (heterogeneously/extremely dense) and 275 patients with fatty (almost entirely fat/numerous vague densities) breast tissue, the Technetium Tc 99m Sestamibi results were similar. Overall, the studies were not designed to compare the performance of Technetium Tc 99m Sestamibi with the performance of mammography in patients with breast densities or other coexistent breast tissue disorders.

In general the histology seems to correlate with the degree of Technetium Tc 99m Sestamibi uptake. As shown in **Tables 9** and **10**, the majority of the normal Technetium Tc 99m Sestamibi images are associated with non-malignant tissue (78–81%) and the majority of low, moderate or high uptake Technetium Tc 99m Sestamibi images are associated with malignant disease (79–83%). In an individual patient, however, the intensity of Technetium Tc 99m Sestamibi uptake can not be used to confirm the presence or absence of malignancy. Equivocal results do not have a correlation with histology.

Table 9

Degree of Technetium Tc 99m Sestamibi Breast Imaging Uptake in Comparison to Histopathology Results in Patients with Mammographically Detected Non-Palpable Lesions* (Study A)			
	Normal Uptake N = 249 lesions	Equivocal Uptake N = 25 lesions	Low, Moderate or High Uptake

			N = 66 lesions
Non-malignant**	201 (81%)	14 (56%)	14 (21%)
Malignant	48 (19%)	11 (44%)	52 (79%)

* Median finding for 3 blinded readers

** Includes benign tissue, fibroadenoma, benign intramammary nodes, radial scar

Table 10

Degree of Technetium Tc 99m Sestamibi Breast Imaging Uptake in Comparison to Histopathology Results in Patients with Palpable Lesions* (Study B)

	Normal Uptake N = 129 lesions	Equivocal Uptake N = 32 lesions	Low, Moderate or High Uptake N = 115 lesions
Non-malignant**	100 (78%)	19 (59%)	20 (17%)
Malignant	29 (22%)	13 (41%)	95 (83%)

* Median finding for 3 blinded readers

** Includes benign tissue, fibroadenoma, benign intramammary nodes, radial scar

An estimate of the likelihood of malignancy based on the Technetium Tc 99m Sestamibi uptake score in combination with the mammographic score has not been studied.

In these two studies approximately 150 additional, non-biopsied lesions were found to be positive after Technetium Tc 99m Sestamibi imaging. These lesions were identified in sites that did not physically correlate with identified entry criteria mammographic lesions and these lesions were not palpable. These lesions were not biopsied. Whether these lesions were benign or malignant is not known. Technetium Tc 99m Sestamibi uptake can occur in both benign and malignant disease. THE CLINICAL USEFULNESS OF A POSITIVE Technetium Tc 99m Sestamibi IMAGE IN THE ABSENCE OF AN ABNORMAL MAMMOGRAM OR A PALPABLE LESION IS NOT KNOWN.

15 REFERENCES

Not applicable.

16 HOW SUPPLIED/STORAGE AND HANDLING

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to patient administration. Radiochemical purity should be checked prior to patient administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Store at 15 –25 C (59 –77 F) before and after reconstitution. Protect from light prior to reconstitution.

17 PATIENT COUNSELING INFORMATION

CARDIOLITE® and MIRALUMA® are different names for the same drug (Kit for the Preparation of Technetium Tc 99m Sestamibi Injection). Patients should be advised to inform their health care provider if they had an allergic reaction to either drug or if they had an imaging study with either drug.

A092I3

Manufactured and Distributed By
Mallinckrodt Inc.
Hazelwood, MO 63042 USA

Rev 090808

tyco Healthcare

Mallinckrodt

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-098

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
APPROVAL SUMMARY (Supersedes summary dated February 6, 2008)
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-098 Date of Submission: September 9, 2008

Applicant's Name: Mallinckrodt Inc.

Established Name: Kit for Preparation of Technetium Tc 99m Sestamibi Injection

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BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling?

Yes.

Container Label:
Satisfactory in FPL – 1/17/2008 submission.

Carton Labeling: (5 Vials and 30 Vials)
Satisfactory in FPL – 1/17/2008 submission.

Professional Package Insert Labeling:
Satisfactory in FPL – 9/9/2008 submission.

Radioassay Label:
Satisfactory in FPL – 1/17/2008 submission.

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cardiolite

NDA Number: NDA 19-785

NDA Drug Name: Cardiolite (Technetium Tc 99m Sestamibi Kit)

NDA Firm**:** Bristol Myers Squibb

Date of Approval of NDA Insert and supplement #: NDA 19-785/ S-018, (approved 4/30/2008).

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD

1. MODELING LABELING

Labeling review based on the reference listed drug, by Bristol Myers Squibb, "Cardiolite (Technitium Tc 99m Sestamibi Kit)", approved January 22, 2002, (NDA 19-785/S-012). BMS also markets the product "Miraluma" under NDA 19-785. Although the labeling from S-012 is not available electronically, there are no PN labeling supplements for the RLD. Therefore, last labeling available electronically in Y-015 (dated 2/8/2006), may be used as a model. This labeling agrees with RLD labeling (rev. May 2003), submitted by the applicant. See notes below regarding labeling:

Please adequately explain why you have not provided vial shield labels with your application as referenced in this section. This is part of the approved labeling of the RLD and therefore we believe that it should be provided for in your application. We refer you to 21 CFR 314.94(a)(t3)(iv), for guidance.

The vial shield labels are referred to as Radioassay Information Labels in Mallinckrodt's application, and have been provided in the labeling section. The proposed 5-vial kit label, 30-vial kit carton, and package insert consistently refer to the label as the Radioassay Information Label. The RLD labeling uses the term vial shield label, a term not used in current Mallinckrodt labels or labeling.

Mallinckrodt does not intend to provide a separate radioactive material label, which has the radioactive material symbol and the words CAUTION: RADIOACTIVE MATERIAL. . The symbol and caution statement are on the Radioassay Information Label, which is provided with both radiopharmaceutical kit packaging configurations.

Is your kit being reviewed by the U.S. Nuclear Regulatory Commission?

The text has been removed from the labeling. The kit will not be reviewed by the U.S. Nuclear Regulatory Commission (NRC). Non-radioactive reagent kits are not required to be included on distribution licenses by the NRC.

if so, please describe exactly who is reviewing the kit (include contact information) and what has been forwarded for review.

No review will be performed by NRC.

Note *** The Orange Book does not capture a potency for this product due to degradation.

Update September 16, 2008, submission:

Labeling review based on the reference listed drug, by Bristol Myers Squibb, "Cardiolite (Technitium Tc 99m Sestamibi Kit)", approved April 30, 2008, (NDA 19-785/S-018). Supplement 18 received 3 year pediatric exclusivity for altered patient population (see FTR #2 below) and labeling was approved in the PLR format. The sponsor was forwarded a labeling model developed in OGD after consulting OND, the "PEDs" group, and OCC. Disclaimers were inserted into the labeling regarding pediatric information.

2. PATENTS/ EXCLUSIVITIES:

Patent Data
Exclusivity Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
019785	001	4885100	SEP 11, 2007			
019785	001	4894445	JAN 16, 2007			U-337
019785	001	4988827	JAN 29, 2008			
019785	001	5324824	JAN 16, 2007			

Code	Definition
U-337	USE OF CARDIOLITE/MIRALUMA KIT FOR THE PREPARATION OF TC99M SESTAMIBI

There is no unexpired exclusivity for this product.

The applicant has made a Paragraph III certification to the unexpired patents. The O-Book lists Cardiolite and Miraluma as two separate products under the same NDA. Patents and Use codes are the same for both products. Although the applicant references Cardiolite, all information regarding the indication for Miraluma is retained in the applicant's labeling (as it appears in Cardiolite labeling). However, whereas Cardiolite labeling refers to "Miraluma" for breast imaging, the applicant has used the established name of the product, implying that the proposed product may be used for either indication. However, although the two products are listed separately on the BMS web site, the link to Miraluma takes the reader to the Cardiolite web site:

Cardiolite® (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

Catalog Numbers	
CA2D	2-vial kit
CAKD	5-vial kit

Call **1-800-299-3431** to place an order.

miraluma® (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

Catalog Numbers	
CA2D	2-vial kit
CAKD	5-vial kit

Call **1-800-299-3431** to place an order.

I called the BMS phone number and asked the representative what product I would get if I ordered Miraluma and she said that I would get Cardiolite. Therefore, in reality, there is only one product, Cardiolite (not 2 as listed in the O-Book).

O-Book:

Active Ingredient:	TECHNETIUM TC-99M SESTAMIBI KIT
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	CARDIOLITE
Applicant:	BRISTOL MYERS SQUIBB
Strength:	N/A
Application Number:	019785
Product Number:	001
Approval Date:	Dec 21, 1990
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	TECHNETIUM TC-99M SESTAMIBI KIT
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MIRALUMA
Applicant:	BRISTOL MYERS SQUIBB

Strength:	N/A
Application Number:	019785
Product Number:	003
Approval Date:	May 23, 1997
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

It is my understanding that an ANDA can not reference two products. However, since in reality there is only one RLD product, I have asked O-Book person, Harvey Greenberg, whether the O-Book can be revised to reflect one product number for Cardiolite/Miraluma.

At present, the applicant's product is labeled for indications from two different products.

PACKAGE INSERT LABELING MAY DEPEND ON THE ANSWER TO THIS QUESTION.

Update September 16, 2008, review:

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
019785	001	4885100	Sep 11, 2007				
019785	001	4988827	Jan 29, 2008				
019785	001	4988827*PED	Jul 29, 2008				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
019785	001	PED	Oct 30, 2011
019785	001	M-54	Apr 30, 2011

Code	Definition
M-54	INFORMATION FROM PEDIATRIC STUDIES ADDED TO LABEL

The sponsor has updated the patent and exclusivity certification to reflect these updates.

Miraluma now appears in the discontinued section of the Orange Book. The web site: http://www.miraluma.com/

...now has the following message: This site is no longer available.

While the HIGHLIGHTS section of the newly approved PLR sites only the cardiac indication, the complete labeling has the breast imaging indication too. Labeling reviewer, Jim Barlow asked:

Good morning Dr. Gorovets,
I have a question for you concerning the highlights section of this NDA 19-785. I see that the Miraluma indications were never included on your Highlights page and yet there are found throughout the insert. Has this drug product been discontinued? Should it still be mentioned in your labeling? If so shouldn't it be in the Highlights section? Hate to bother you so much about this, we are just getting ready to approve the first generic and I want to make sure I do this right!!

Regards,
Jim

PS The cc person is my collegue helping me with my reviews

September 17, 2008:

Jim heard back from the OND review division that the RLD labeling was intentionally approved without reference to the breast imaging indication because it is not the major indication. We will follow suit for generic applicants.

3. **INACTIVE INGREDIENTS;** The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section appearing in the chemistry review. Each 10 mL vial contains a lyophilized powder of:

1.0 mg $[Cu(MIBI)_4]BF_4$ (active where MIBI=2-methoxy isobutyl isonitrile)
0.025-0.75 mg Stannous Chloride Dihydrate
1.0 mg L-Cysteine Hyrochloride Monohydrate
2.6 mg Sodium Citrate Dihydrate
20 mg D-Mannitol
Prior to lyophilization, the pH of the aqueous bulk dispensing solution is adjusted with sodium hydroxide and/or hydrochloric acid to pH = 5.6.

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON:**

- **USP:**

Packaging and storage—Preserve in single-dose or multiple-dose containers.

Labeling—Label it to include the following, in addition to the information specified for *Labeling* under

Injections ⟨ 1 ⟩: the time and date of constitution; the volume of constitution; the amount of ^{99m}Tc as labeled sestamibi expressed as total megabecquerels (or millicuries) per mL at the time of constitution; the expiration date and time; the lot number; and the statement "Caution—Radioactive Material." The labeling indicates that in making dosage calculations, correction is to be made for radioactive decay, and also indicates that the radioactive half-life of ^{99m}Tc is 6.0 hours.

- **RLD:** Store at 15-25°C before and after reconstitution. …and, under Instructions, "Technetium Tc 99m Sestamibi should be used within 6 hours of preparation", and "Product should be used within 6 hours after preparation. "

- **ANDA:** Same as RLD, however, ANDA is additionally labeled, "Protect from light prior to reconstitution" (insert). From the "Summary of Chemistry Assessments" in the chemist's review: "Vials should be protected from light prior to reconstitution and contains no preservatives. "

5. **PACKAGING CONFIGURATIONS**

RLD: Made available in kits consisting of 2, 5, or 20 reaction vials.
ANDA: Made available in kits consisting of 5 or 30 reaction vials.

See FTR below regarding the use of this product in the themal cycler:

We note that you have deleted all information regarding the use of your product with a thermal cycler. Annotated labeling provided with your application fails to adequately address, justify, and explain why your product labeling limits the method for preparation to the water bath procedure while the RLD product may be prepared using either method. Please provide a full explanation.

The Recon-O-Stat (thermal cycler) was designed for use with the Cardiolite® vial, which is a 5 mL vial. A tungsten vial shield is an integral part of the device, as the tungsten shield is specially designed for the heat pump effect

and to provide shielding from radiation exposure. The Mallinckrodt vial, a 10 mL vial, will not completely fit in the tungsten lead shield. The lid cannot be put in place with the 10 mL vial, adversely affecting the heating profile and the radiation protection.

A second reason for not providing instructions for use of the Recon-O-Stat in the package insert is that the Recon-O-Stat thermal cycler is no longer available from Bristol-Myers Squibb. The units were custom-made for Bristol-Myers Squibb, and Bristol-Myers Squibb discontinued distributing the Recon-O-Stat units approximately one year ago. Even if a customer had a Recon-O-Stat thermal cycler and purchased a Mallinckrodt TechneScan Sestamibi kit, the Recon-O-Stat should not be used to heat the ^{99m}Tc Sestamibi because of the height difference in the 10 mL vial, as explained in the previous paragraph.

The sponsor was requested to add a statement in the Directions section that this product may not be used with the thermal cycler.

6. A proprietary name consult for "TechneScan Sestamibi" was sent to DMETS in the ODS on 4/18/2007 (see DFS). DMETS was also requested to address established name confusion between Tc99m products. DMETS was also notified that a consult for a similar name for ANDA 77-328 was also sent for review, TechneScan MDP. With the October 6, amendment, Mallinckrodt proposes deleting the "TechneScan" part of the name. We sent the new proposal over to DMETS who has assigned the consult the number, 07-892. On January 10, 2008, I contacted DMETS via the OSE consults mailbox to explain that the sponsor has WD any proposal for a proprietary name at this time, but that we would still like an answer regarding potential for established name confusion.

Other products listed in O-Book with the TechneScan name:

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
017842	BS	No	TECHNETIUM TC-99M ALBUMIN AGGREGATED KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN MAA	MALLINCKRODT
018272		No	TECHNETIUM TC-99M GLUCEPTATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN GLUCEPTATE	DRAXIMAGE
019882		No	TECHNETIUM TC-99M MERTIATIDE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN MAG3	MALLINCKRODT
018321		Yes	TECHNETIUM TC-99M OXIDRONATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN	MALLINCKRODT
017538	AP	No	TECHNETIUM TC-99M PYROPHOSPHATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN PYP KIT	MALLINCKRODT

OSE status of the consult was requested with the September, 2008 review:

Please provide status of the above referenced consult sent to DMETS in April of 2007.

In subsequent communication with DMETS regarding this consult, OGD relayed that although the sponsor had withdrawn the proposed proprietary name, the following issue required resolution:

```
...we have become aware of many medication errors which have resulted in
the
administration of the incorrect Tc 99m imaging/diagnostic agent. We
would like to take
advantage of any labeling safety measure to prevent this type of
confusion for this generic
product. In addition to the proprietary name review, please make
recommendations concerning
prevention of confusion of this Tc 99m product with other Tc 99m
products.
```

7. CONTAINER/CLOSURE

The lyophilized nonradioactive drug product Techne Scan Sestamibi, is contained in a 10 mL glass tubing vial sealed with a 20 mm gray butyl rubber lyophilization stopper and an aluminum crimp cap seal.

8. FINISHED DOSAGE MANUFACTURING FACILITY

This product is manufactured at the Mallinckrodt facility in Maryland Heights, Missouri (below address). The Manufactured by statement lists the corporate address, Mallinckrodt Inc., in St. Louis, MO.

Mallinckrodt Inc
2703 Wagner Place,
Maryland Heights, MO 63043

9. NOTE REGARDING LABELING FROM CHEMISTRY REVIEW

Reviewer's Assessment:
PI and container labels are conform to CMC as reviewed in this ANDA and are consistent with the innovator's PI and container labels; however, all sections of the PI and container labels should add the manufacturer's name to appropriate sections where the distributor's name are denoted. The PI and container labels are otherwise adequate from a CMC prospective.

10. FIRST GENERIC?

Marty,

The following appears on the filing checklist for this application:

First Generic Product Received? NO PER MARTY 3/9/06
SEE MARTY FOR MORE DETAILS

Could you explain why this is not a first generic? The filing sheet refers to related ANDA (b) (4) a (b) (4) product. But that is a *completely* different and chemically unrelated product, similar only by virtue of the fact that (b) (4)

Additionally, the CIS-USA imaging agent (which also employs Tc imaging) filed under ANDA 78-242 did get first generic status.

Charlie,

This ANDA was not designated as a first generic for the following reasons. First as an injectable drug product the DBE does not need to initially evaluate any studies as the product is an injectable solution that is eligible for a waiver of BE. Second the reviews for these drug products actually take place outside of OGD as OGD does not have anyone with the technical background to review these ANDAs. The first submission (b) (4) from (b) (4) was probably designated as a first generic which would have been the error. It's true that these ANDAs will represent First Generic approvals for purposes of bringing generics to the market but RSB uses the first generic designation to trigger additional reviews within OGD. In this case it wasn't necessary.

Thanks,

Marty

Date of Review: September 16, 2008 **Date of Submission: September 9, 2008**

Primary Reviewer: Charlie Hoppes **Date:**

Team Leader: John Grace **Date:**

12 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI) IMMEDIATELY FOLLOWING THIS PAGE

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

/s/

Charles Hoppes
9/17/2008 01:05:04 PM
LABELING REVIEWER

John Grace
9/18/2008 11:08:22 AM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
APPROVAL SUMMARY
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-098 Date of Submission: January 17, 2008

Applicant's Name: Mallinckrodt Inc.

Established Name: Kit for Preparation of Technetium Tc 99m Sestamibi Injection

---

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling?

Yes

Container Label:
Satisfactory in FPL – 1/17/2008 submission.

Carton Labeling: (5 Vials and 30 Vials)
Satisfactory in FPL – 1/17/2008 submission.

Professional Package Insert Labeling:
Satisfactory in FPL – 1/17/2008 submission.

Radioassay Label:
Satisfactory in FPL – 1/17/2008 submission.

Revisions needed post-approval:
The DMETS Consult is still pending, although the sponsor is not pursuing a proprietary name at this time, DMETS may have labeling comments since we requested input regarding potential for confusion due to similar established names for this class of products.

BASIS OF APPROVAL:
Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cardiolite

NDA Number: NDA 19-785

NDA Drug Name: Cardiolite (Technetium Tc 99m Sestamibi Kit)

NDA Firm**:** Bristol Myers Squibb

Date of Approval of NDA Insert and supplement #: NDA 19-785/ S-012, (approved 1/22/2002).

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD

1. MODELING LABELING

Labeling review based on the reference listed drug, by Bristol Myers Squibb, "Cardiolite (Technitium Tc 99m Sestamibi Kit)", approved January 22, 2002, (NDA 19-785/S-012). BMS also markets the product "Miraluma" under NDA 19-785. Although the labeling from S-012 is not available electronically, there are no PN labeling supplements for the RLD. Therefore, last labeling available electronically in Y-015 (dated 2/8/2006), may be used as a model. This labeling agrees with RLD labeling (rev. May 2003), submitted by the applicant. See notes below regarding labeling:

Please adequately explain why you have not provided vial shield labels with your application as referenced in this section. This is part of the approved labeling of the RLD and therefore we believe that it should be provided for in your application. We refer you to 21 CFR 314.94(a)(t3)(iv), for guidance.

The vial shield labels are referred to as Radioassay Information Labels in Mallinckrodt's application, and have been provided in the labeling section. The proposed 5-vial kit label, 30-vial kit carton, and package insert consistently refer to the label as the Radioassay Information Label. The RLD labeling uses the term vial shield label, a term not used in current Mallinckrodt labels or labeling.

Mallinckrodt does not intend to provide a separate radioactive material label, which has the radioactive material symbol and the words CAUTION: RADIOACTIVE MATERIAL. . The symbol and caution statement are on the Radioassay Information Label, which is provided with both radiopharmaceutical kit packaging configurations.

Is your kit being reviewed by the U.S. Nuclear Regulatory Commission?

The text has been removed from the labeling. The kit will not be reviewed by the U.S. Nuclear Regulatory Commission (NRC). Non-radioactive reagent kits are not required to be included on distribution licenses by the NRC.

if so, please describe exactly who is reviewing the kit (include contact information) and what has been forwarded for review.

No review will be performed by NRC.

Note *** The Orange Book does not capture a potency for this product due to degradation.

2. PATENTS/ EXCLUSIVITIES:

Patent Data
Exclusivity Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
019785	001	4885100	SEP 11, 2007			
019785	001	4894445	JAN 16, 2007			U-337
019785	001	4988827	JAN 29, 2008			
019785	001	5324824	JAN 16, 2007			

Code	Definition
U-337	USE OF CARDIOLITE/MIRALUMA KIT FOR THE PREPARATION OF TC99M SESTAMIBI

There is no unexpired exclusivity for this product.

The applicant has made a Paragraph III certification to the unexpired patents. The O-Book lists Cardiolite and Miraluma as two separate products under the same NDA. Patents and Use codes are the same for both products. Although the applicant references Cardiolite, all information regarding the indication for Miraluma is retained in the applicant's labeling (as it appears in Cardiolite labeling). However, whereas Cardiolite labeling refers to "Miraluma" for breast imaging, the applicant has used the established name of the product, implying that the proposed product may be used for either indication.

However, although the two products are listed separately on the BMS web site, the link to Miraluma takes the reader to the Cardiolite web site:

Cardiolite® (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

Catalog Numbers	
CA2D	2-vial kit
CAKD	5-vial kit

Call **1-800-299-3431** to place an order.

miraluma® (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

Catalog Numbers	
CA2D	2-vial kit
CAKD	5-vial kit

Call **1-800-299-3431** to place an order.

I called the BMS phone number and asked the representative what product I would get if I ordered Miraluma and she said that I would get Cardiolite. Therefore, in reality, there is only one product, Cardiolite (not 2 as listed in the O-Book).

O-Book:

Active Ingredient:	TECHNETIUM TC-99M SESTAMIBI KIT
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	CARDIOLITE
Applicant:	BRISTOL MYERS SQUIBB
Strength:	N/A
Application Number:	019785
Product Number:	001
Approval Date:	Dec 21, 1990
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	TECHNETIUM TC-99M SESTAMIBI KIT
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MIRALUMA
Applicant:	BRISTOL MYERS SQUIBB
Strength:	N/A
Application Number:	019785
Product Number:	003
Approval Date:	May 23, 1997

Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

It is my understanding that an ANDA can not reference two products. However, since in reality there is only one RLD product, I have asked O-Book person, Harvey Greenberg, whether the O-Book can be revised to reflect one product number for Cardiolite/Miraluma.

At present, the applicant's product is labeled for indications from two different products.

PACKAGE INSERT LABELING MAY DEPEND ON THE ANSWER TO THIS QUESTION.

3. **INACTIVE INGREDIENTS;** The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section appearing in the chemistry review. Each 10 mL vial contains a lyophilized powder of:

1.0 mg $[Cu(MIBI)_4]BF_4$ (active where MIBI=2-methoxy isobutyl isonitrile)
0.025-0.75 mg Stannous Chloride Dihydrate
1.0 mg L-Cysteine Hyrochloride Monohydrate
2.6 mg Sodium Citrate Dihydrate
20 mg D-Mannitol
Prior to lyophilization, the pH of the aqueous bulk dispensing solution is adjusted with sodium hydroxide and/or hydrochloric acid to pH = 5.6.

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON:**

- **USP:**

Packaging and storage—Preserve in single-dose or multiple-dose containers.

Labeling—Label it to include the following, in addition to the information specified for *Labeling* under

Injections ⟨ 1 ⟩: the time and date of constitution; the volume of constitution; the amount of ^{99m}Tc as labeled sestamibi expressed as total megabecquerels (or millicuries) per mL at the time of constitution; the expiration date and time; the lot number; and the statement "Caution—Radioactive Material." The labeling indicates that in making dosage calculations, correction is to be made for radioactive decay, and also indicates that the radioactive half-life of ^{99m}Tc is 6.0 hours.

- **RLD:** Store at 15-25°C before and after reconstitution. …and, under Instructions, "Technetium Tc 99m Sestamibi should be used within 6 hours of preparation", and "Product should be used within 6 hours after preparation. "

- **ANDA:** Same as RLD, however, ANDA is additionally labeled, "Protect from light prior to reconstitution" (insert). From the "Summary of Chemistry Assessments" in the chemist's review: "Vials should be protected from light prior to reconstitution and contains no preservatives. "

5. **PACKAGING CONFIGURATIONS**

RLD: Made available in kits consisting of 2, 5, or 20 reaction vials.
ANDA: Made available in kits consisting of 5 or 30 reaction vials.

See FTR below regarding the use of this product in the themal cycler:

We note that you have deleted all information regarding the use of your product with a thermal cycler. Annotated labeling provided with your application fails to adequately address, justify, and explain why your product labeling limits the method for preparation to the water bath procedure while the RLD product may be prepared using either method. Please provide a full explanation.

The Recon-O-Stat (thermal cycler) was designed for use with the Cardiolite® vial, which is a 5 mL vial. A tungsten vial shield is an integral part of the device, as the tungsten shield is specially designed for the heat pump effect

and to provide shielding from radiation exposure. The Mallinckrodt vial, a 10 mL vial, will not completely fit in the tungsten lead shield. The lid cannot be put in place with the 10 mL vial, adversely affecting the heating profile and the radiation protection.

A second reason for not providing instructions for use of the Recon-O-Stat in the package insert is that the Recon-O-Stat thermal cycler is no longer available from Bristol-Myers Squibb. The units were custom-made for Bristol-Myers Squibb, and Bristol-Myers Squibb discontinued distributing the Recon-O-Stat units approximately one year ago. Even if a customer had a Recon-O-Stat thermal cycler and purchased a Mallinckrodt TechneScan Sestamibi kit, the Recon-O-Stat should not be used to heat the ^{99m}Tc Sestamibi because of the height difference in the 10 mL vial, as explained in the previous paragraph.

The sponsor was requested to add a statement in the Directions section that this product may not be used with the thermal cycler.

6. A proprietary name consult for "TechneScan Sestamibi" was sent to DMETS in the ODS on 4/18/2007 (see DFS). DMETS was also requested to address established name confusion between Tc99m products. DMETS was also notified that a consult for a similar name for ANDA 77-328 was also sent for review, TechneScan MDP. With the October 6, amendment, Mallinckrodt proposes deleting the "TechneScan" part of the name. We sent the new proposal over to DMETS who has assigned the consult the number, 07-892. On January 10, 2008, I contacted DMETS via the OSE consults mailbox to explain that the sponsor has WD any proposal for a proprietary name at this time, but that we would still like an answer regarding potential for established name confusion.

Other products listed in O-Book with the TechneScan name:

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
017842	BS	No	TECHNETIUM TC-99M ALBUMIN AGGREGATED KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN MAA	MALLINCKRODT
018272		No	TECHNETIUM TC-99M GLUCEPTATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN GLUCEPTATE	DRAXIMAGE
019882		No	TECHNETIUM TC-99M MERTIATIDE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN MAG3	MALLINCKRODT
018321		Yes	TECHNETIUM TC-99M OXIDRONATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN	MALLINCKRODT
017538	AP	No	TECHNETIUM TC-99M PYROPHOSPHATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN PYP KIT	MALLINCKRODT

7. CONTAINER/CLOSURE

The lyophilized nonradioactive drug product Techne Scan Sestamibi, is contained in a 10 mL glass tubing vial sealed with a 20 mm gray butyl rubber lyophilization stopper and an aluminum crimp cap seal. See comments below regarding the statement to discard unused portion for the container label:

B. *CONTAINER LABEL*

If space permits, add the statement, "Use within 6 hours of reconstitution."

Response: On January 16, 2008, Mallinckrodt contacted Mr. Charlie Hoppes in the Division of Labeling and Program Support to discuss the addition of the requested text to the container (vial) label and to provide additional information regarding the ability to view the above text after reconstitution of the vial contents with radioactive technetium Tc 99m. According to the instructions in the labeling text for the preparation of the radioactive drug product, the vial containing the lyophilized contents is initially placed in a radiation shield with a fitted radiation cap. Once radioactivity is introduced into the vial, the vial is not removed from the radiation shield per radiation safety practice. After the addition of the specified amount of Sodium Pertechnetate Tc 99m Injection to the vial and subsequent heating and cooling steps, the Radioassay Information Label is filled out with the appropriate assay data and the label is affixed to the outside of the radiation shield. The

Radioassay Information Label contains the statement "Use within 6 hours of reconstitution" and can be readily viewed by the end user.

After the above discussion, Mr. Hoppes agreed that no additional changes were needed to the container label.

8. FINISHED DOSAGE MANUFACTURING FACILITY

This product is manufactured at the Mallinckrodt facility in Maryland Heights, Missouri (below address). The Manufactured by statement lists the corporate address, Mallinckrodt Inc., in St. Louis, MO.

Mallinckrodt Inc
2703 Wagner Place,
Maryland Heights, MO 63043

9. NOTE REGARDING LABELING FROM CHEMISTRY REVIEW

Reviewer's Assessment:
PI and container labels are conform to CMC as reviewed in this ANDA and are consistent with the innovator's PI and container labels; however, all sections of the PI and container labels should add the manufacturer's name to appropriate sections where the distributor's name are denoted. The PI and container labels are otherwise adequate from a CMC prospective.

10. FIRST GENERIC?

Marty,

The following appears on the filing checklist for this application:

First Generic Product Received? NO PER MARTY 3/9/06
SEE MARTY FOR MORE DETAILS

Could you explain why this is not a first generic? The filing sheet refers to related ANDA (b) (4) a (b) (4) product. But that is a *completely* different and chemically unrelated product, similar only by virtue of the fact that (b) (4).

Additionally, the CIS-USA imaging agent (which also employs Tc imaging) filed under ANDA 78-242 did get first generic status.

Charlie,

This ANDA was not designated as a first generic for the following reasons. First as an injectable drug product the DBE does not need to initially evaluate any studies as the product is an injectable solution that is eligible for a waiver of BE. Second the reviews for these drug products actually take place outside of OGD

as OGD does not have anyone with the technical background to review these ANDAs. The first submission (b) (4) from (b) (4) was probably designated as a first generic which would have been the error. It's true that these ANDAs will represent First Generic approvals for purposes of bringing generics to the market but RSB uses the first generic designation to trigger additional reviews within OGD. In this case it wasn't necessary.

Thanks,

Marty

11. SPL - Consistent with labeling submitted 1/17/08.

Kit for the Preparation of Technetium Tc 99m Sestamibi (Kit for the Preparation of Technetium Tc 99m Sestamibi)

PRODUCT INFO

Product Code	0019-9092	Dosage Form	INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION
Route Of Administration	INTRAVENOUS	DEA Schedule	

INGREDIENTS

Name (Active Moiety)	Type	Strength
tetrakis (2methoxy isobutyl isonitrile) copper (I) tetrafluoroborate (tetrakis (2-methoxy isobutyl isonitrile) copper (I) tetrafluoroborate)	Active	1 MILLIGRAM In 1 BOTTLE
sodium citrate dihydrate	Inactive	2.6 MILLIGRAM In 1 BOTTLE
L-cysteine hydrochloride monohydrate	Inactive	1 MILLIGRAM In 1 BOTTLE
mannitol	Inactive	20 MILLIGRAM In 1 BOTTLE
stannous chloride dihydrate	Inactive	0.075 MILLIGRAM In 1 BOTTLE

IMPRINT INFORMATION

Characteristic	Appearance	Characteristic	Appearance
Color		Score	
Shape		Symbol	
Imprint Code		Coating	
Size			

PACKAGING

#	NDC	Package Description	Multilevel Packaging
1	0019-9092-B0	5 BOTTLE In 1 CELLO PACK	None
2	0019-9092-D0	30 BOTTLE In 1 CARTON	None

Date of Review: February 6, 2008 **Date of Submission: January 17, 2008**

Primary Reviewer: Charlie Hoppes **Date:**

Team Leader: John Grace **Date:**

4 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI) IMMEDIATELY FOLLOWING THIS PAGE

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

/s/

Charles Hoppes
2/6/2008 09:26:02 AM
LABELING REVIEWER

John Grace
2/6/2008 11:28:57 AM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING #3
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-098 Date of Submission: December 14, 2007

Applicant's Name: Mallinckrodt Inc.

Established Name: Kit for Preparation of Technetium Tc 99m Sestamibi Injection

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Labeling Deficiencies:

A. GENERAL COMMENT

1. We acknowledge your comments that you withdrawal proposal of the proprietary name, "Sestamibi" and that you intend to market with the established name at this time. Although the Division of Medication Errors and Technical Support (DMETS) has been notified, we expect that they will finish their review and provide comments on labels and labeling as well as comments regarding mitigation of error potential with respect to the established name of this product. We will forward any DMETS comments when they become available to us.

2. We acknowledge your comment, following discussions with CDR Koung Lee, regarding a commitment to provide SPL labeling within 14 days post approval of this application.

B. CONTAINER LABEL

If space permits, add the statement, "Use within 6 hours of reconstitution."

Submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling?

No, sponsor submitted draft on 12/14/2007.

Container Label:
See Comments above

Carton Labeling: (5 Vials and 30 Vials)
Satisfactory in draft – 12/14/2007 submission.

Professional Package Insert Labeling:
Satisfactory in draft – 12/14/2007 submission.

Radioassay Label:
Satisfactory in draft – 12/14/2007 submission.

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cardiolite

NDA Number: NDA 19-785

NDA Drug Name: Cardiolite (Technetium Tc 99m Sestamibi Kit)

NDA Firm**:** Bristol Myers Squibb

Date of Approval of NDA Insert and supplement #: NDA 19-785/ S-012, (approved 1/22/2002).

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD

1. MODELING LABELING

Labeling review based on the reference listed drug, by Bristol Myers Squibb, "Cardiolite (Technitium Tc 99m Sestamibi Kit)", approved January 22, 2002, (NDA 19-785/S-012). BMS also markets the product "Miraluma" under NDA 19-785. Although the labeling from S-012 is not available electronically, there are no PN labeling supplements for the RLD. Therefore, last labeling available electronically in Y-015 (dated 2/8/2006), may be used as a model. This labeling agrees with RLD labeling (rev. May 2003), submitted by the applicant. See notes below regarding labeling:

Please adequately explain why you have not provided vial shield labels with your application as referenced in this section. This is part of the approved labeling of the RLD and therefore we believe that it should be provided for in your application. We refer you to 21 CFR 314.94(a)(t3)(iv), for guidance.

The vial shield labels are referred to as Radioassay Information Labels in Mallinckrodt's application, and have been provided in the labeling section. The proposed 5-vial kit label, 30-vial kit carton, and package insert consistently refer to the label as the Radioassay Information Label. The RLD labeling uses the term vial shield label, a term not used in current Mallinckrodt labels or labeling.

Mallinckrodt does not intend to provide a separate radioactive material label, which has the radioactive material symbol and the words CAUTION: RADIOACTIVE MATERIAL. . The symbol and caution statement are on the Radioassay Information Label, which is provided with both radiopharmaceutical kit packaging configurations.

Is your kit being reviewed by the U.S. Nuclear Regulatory Commission?

The text has been removed from the labeling. The kit will not be reviewed by the U.S. Nuclear Regulatory Commission (NRC). Non-radioactive reagent kits are not required to be included on distribution licenses by the NRC.

if so, please describe exactly who is reviewing the kit (include contact information) and what has been forwarded for review.

No review will be performed by NRC.

Note *** The Orange Book does not capture a potency for this product due to degradation.

2. PATENTS/ EXCLUSIVITIES:

Patent Data
Exclusivity Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
019785	001	4885100	SEP 11, 2007			
019785	001	4894445	JAN 16, 2007			U-337
019785	001	4988827	JAN 29, 2008			
019785	001	5324824	JAN 16, 2007			

Code	Definition
U-337	USE OF CARDIOLITE/MIRALUMA KIT FOR THE PREPARATION OF TC99M SESTAMIBI

There is no unexpired exclusivity for this product.

The applicant has made a Paragraph III certification to the unexpired patents. The O-Book lists Cardiolite and Miraluma as two separate products under the same NDA. Patents and Use codes are the same for both products. Although the applicant references Cardiolite, all information regarding the indication for Miraluma is retained in the applicant's labeling (as it appears in Cardiolite labeling). However, whereas Cardiolite labeling refers to "Miraluma" for breast imaging, the applicant has used the established name of the product, implying that the proposed product may be used for either indication.

However, although the two products are listed separately on the BMS web site, the link to Miraluma takes the reader to the Cardiolite web site:

Cardiolite® (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

Catalog Numbers	
CA2D	2-vial kit
CAKD	5-vial kit

Call **1-800-299-3431** to place an order.

miraluma® (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

Catalog Numbers	
CA2D	2-vial kit
CAKD	5-vial kit

Call **1-800-299-3431** to place an order.

I called the BMS phone number and asked the representative what product I would get if I ordered Miraluma and she said that I would get Cardiolite. Therefore, in reality, there is only one product, Cardiolite (not 2 as listed in the O-Book).

O-Book:

Active Ingredient:	TECHNETIUM TC-99M SESTAMIBI KIT
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	CARDIOLITE
Applicant:	BRISTOL MYERS SQUIBB
Strength:	N/A
Application Number:	019785
Product Number:	001
Approval Date:	Dec 21, 1990
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	TECHNETIUM TC-99M SESTAMIBI KIT
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MIRALUMA
Applicant:	BRISTOL MYERS SQUIBB
Strength:	N/A
Application Number:	019785
Product Number:	003
Approval Date:	May 23, 1997

Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

It is my understanding that an ANDA can not reference two products. However, since in reality there is only one RLD product, I have asked O-Book person, Harvey Greenberg, whether the O-Book can be revised to reflect one product number for Cardiolite/Miraluma.

At present, the applicant's product is labeled for indications from two different products.

PACKAGE INSERT LABELING MAY DEPEND ON THE ANSWER TO THIS QUESTION.

3. **INACTIVE INGREDIENTS;** The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section appearing in the chemistry review. Each 10 mL vial contains a lyophilized powder of:

1.0 mg $[Cu(MIBI)_4]BF_4$ (active where MIBI=2-methoxy isobutyl isonitrile)
0.025-0.75 mg Stannous Chloride Dihydrate
1.0 mg L-Cysteine Hyrochloride Monohydrate
2.6 mg Sodium Citrate Dihydrate
20 mg D-Mannitol
Prior to lyophilization, the pH of the aqueous bulk dispensing solution is adjusted with sodium hydroxide and/or hydrochloric acid to pH = 5.6.

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON:**

- **USP:**

Packaging and storage—Preserve in single-dose or multiple-dose containers.

Labeling—Label it to include the following, in addition to the information specified for *Labeling* under

Injections ⟨ 1 ⟩: the time and date of constitution; the volume of constitution; the amount of ^{99m}Tc as labeled sestamibi expressed as total megabecquerels (or millicuries) per mL at the time of constitution; the expiration date and time; the lot number; and the statement "Caution—Radioactive Material." The labeling indicates that in making dosage calculations, correction is to be made for radioactive decay, and also indicates that the radioactive half-life of ^{99m}Tc is 6.0 hours.

- **RLD:** Store at 15-25°C before and after reconstitution. …and, under Instructions, "Technetium Tc 99m Sestamibi should be used within 6 hours of preparation", and "Product should be used within 6 hours after preparation. "

- **ANDA:** Same as RLD, however, ANDA is additionally labeled, "Protect from light prior to reconstitution" (insert). From the "Summary of Chemistry Assessments" in the chemist's review: "Vials should be protected from light prior to reconstitution and contains no preservatives. "

5. **PACKAGING CONFIGURATIONS**

RLD: Made available in kits consisting of 2, 5, or 20 reaction vials.
ANDA: Made available in kits consisting of 5 or 30 reaction vials.

See FTR below regarding the use of this product in the themal cycler:

We note that you have deleted all information regarding the use of your product with a thermal cycler. Annotated labeling provided with your application fails to adequately address, justify, and explain why your product labeling limits the method for preparation to the water bath procedure while the RLD product may be prepared using either method. Please provide a full explanation.

The Recon-O-Stat (thermal cycler) was designed for use with the Cardiolite® vial, which is a 5 mL vial. A tungsten vial shield is an integral part of the device, as the tungsten shield is specially designed for the heat pump effect

and to provide shielding from radiation exposure. The Mallinckrodt vial, a 10 mL vial, will not completely fit in the tungsten lead shield. The lid cannot be put in place with the 10 mL vial, adversely affecting the heating profile and the radiation protection.

A second reason for not providing instructions for use of the Recon-O-Stat in the package insert is that the Recon-O-Stat thermal cycler is no longer available from Bristol-Myers Squibb. The units were custom-made for Bristol-Myers Squibb, and Bristol-Myers Squibb discontinued distributing the Recon-O-Stat units approximately one year ago. Even if a customer had a Recon-O-Stat thermal cycler and purchased a Mallinckrodt TechneScan Sestamibi kit, the Recon-O-Stat should not be used to heat the ^{99m}Tc Sestamibi because of the height difference in the 10 mL vial, as explained in the previous paragraph.

The sponsor was requested to add a statement in the Directions section that this product may not be used with the thermal cycler.

6. A proprietary name consult for "TechneScan Sestamibi" was sent to DMETS in the ODS on 4/18/2007 (see DFS). DMETS was also requested to address established name confusion between Tc99m products. DMETS was also notified that a consult for a similar name for ANDA 77-328 was also sent for review, TechneScan MDP. With the October 6, amendment, Mallinckrodt proposes deleting the "TechneScan" part of the name. We sent the new proposal over to DMETS who has assigned the consult the number, 07-892. On January 10, 2008, I contacted DMETS via the OSE consults mailbox to explain that the sponsor has WD any proposal for a proprietary name at this time, but that we would still like an answer regarding potential for established name confusion.

Other products listed in O-Book with the TechneScan name:

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
017842	BS	No	TECHNETIUM TC-99M ALBUMIN AGGREGATED KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN MAA	MALLINCKRODT
018272		No	TECHNETIUM TC-99M GLUCEPTATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN GLUCEPTATE	DRAXIMAGE
019882		No	TECHNETIUM TC-99M MERTIATIDE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN MAG3	MALLINCKRODT
018321		Yes	TECHNETIUM TC-99M OXIDRONATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN	MALLINCKRODT
017538	AP	No	TECHNETIUM TC-99M PYROPHOSPHATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN PYP KIT	MALLINCKRODT

7. CONTAINER/CLOSURE

The lyophilized nonradioactive drug product Techne Scan Sestamibi, is contained in a 10 mL glass tubing vial sealed with a 20 mm gray butyl rubber lyophilization stopper and an aluminum crimp cap seal.

8. FINISHED DOSAGE MANUFACTURING FACILITY

This product is manufactured at the Mallinckrodt facility in Maryland Heights, Missouri (below address). The Manufactured by statement lists the corporate address, Mallinckrodt Inc., in St. Louis, MO.

Mallinckrodt Inc
2703 Wagner Place,
Maryland Heights, MO 63043

9. NOTE REGARDING LABELING FROM CHEMISTRY REVIEW

Reviewer's Assessment:
PI and container labels are conform to CMC as reviewed in this ANDA and are consistent with the

innovator's PI and container labels; however, all sections of the PI and container labels should add the manufacturer's name to appropriate sections where the distributor's name are denoted. The PI and container labels are otherwise adequate from a CMC prospective.

10. FIRST GENERIC?

Marty,

The following appears on the filing checklist for this application:

First Generic Product Received? NO PER MARTY 3/9/06
SEE MARTY FOR MORE DETAILS

Could you explain why this is not a first generic? The filing sheet refers to related ANDA (b) (4) a (b) (4) product. But that is a *completely* different and chemically unrelated product, similar only by virtue of the fact that (b) (4)

Additionally, the CIS-USA imaging agent (which also employs Tc imaging) filed under ANDA 78-242 did get first generic status.

Charlie,

This ANDA was not designated as a first generic for the following reasons. First as an injectable drug product the DBE does not need to initially evaluate any studies as the product is an injectable solution that is eligible for a waiver of BE. Second the reviews for these drug products actually take place outside of OGD as OGD does not have anyone with the technical background to review these ANDAs. The first submission (b) (4) from (b) (4) was probably designated as a first generic which would have been the error. It's true that these ANDAs will represent First Generic approvals for purposes of bringing generics to the market but RSB uses the first generic designation to trigger additional reviews within OGD. In this case it wasn't necessary.

Thanks,

Marty

Date of Review: January 11, 2008 **Date of Submission: December 14, 2007**

Primary Reviewer: Charlie Hoppes **Date:**

Team Leader: John Grace **Date:**

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

/s/

Charles Hoppes
1/14/2008 07:17:24 AM
LABELING REVIEWER

John Grace
1/15/2008 12:25:08 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-098 Date of Submission: October 6, 2007

Applicant's Name: Mallinckrodt Inc.

Established Name: TechneScan® Sestamibi (Kit for Preparation of Technetium Tc 99m Sestamibi Injection)

Labeling Deficiencies:

A. GENERAL COMMENT

We acknowledge your comments that you propose to drop "TechneScan" for your line of Tc 99m radiopharmaceuticals. However, labeling submitted retains that nomenclature. Please delete. Additionally, we acknowledge your proposal to retain "Sestamibi" as a proprietary name to differentiate this product from other Tc-containing radiopharmaceuticals. We have contacted the Division of Medication Errors and Technical Support (DMETS), regarding this proposal and will forward their comments to you when they become available to us.

B. CONTAINER LABEL

See GENERAL COMMENT

C. CARTON LABELING (5 Vial Kits and 30 Vial Kits)

1. See GENERAL COMMENT

2. Add the statement, "Use within 6 hours of reconstitution."

3. Combine the statements, "Diagnostic Agent for Intravenous Use.", and "FOR INTRAVENOUS USE AFTER LABELING WITH ADDITIVE-FREE TECHNETIUM Tc 99m.", to read, "DIAGNOSTIC AGENT FOR INTRAVENOUS USE AFTER LABELING WITH ADDITIVE-FREE TECHNETIUM Tc 99m."

D. PHYSICIAN INSERT

1. GENERAL

Please note that you are required to submit SPL labeling from which we will review the data elements. For additional information, please refer to 21 CFR 314.94(d)(ii), the SPL Implementation Guide for FDA Content of Labeling Submissions at:
http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf
…and Docket 92S-0251, Memorandum 32.

2. PRECAUTIONS (Information for Patients)

Revise this section to read as follows:

CARDIOLITE® and MIRALUMA® are different names for the same drug, (Kit for Preparation of Technetium Tc 99m Sestamibi Injection). Patients should be advised to inform their health care provider if they had an allergic reaction to either drug or if they had an imaging study with either drug.

Include a disclaimer with the manufacturer's name for the products, CARDIOLITE® and MIRALUMA®.

3. DOSAGE AND ADMINISTRATION

Bold the subsection heading, "**For Myocardial Imaging**".

4. DIRECTIONS

We acknowledge your comments regarding omission of text referencing the thermal cycler. Please make a comment in this section that your product is not for use with that device.

5. HOW SUPPLIED

a. Revise such that your storage statement appears as a distinct labeling statement.

b. We acknowledge comments that your kit will not be reviewed by the Nuclear Regulatory Commission. Please revise to add the following statement appearing on marketed radio-diagnostic products:

> This reagent kit is approved by the U.S. Nuclear Regulatory Commission for distribution to persons licensed to use by-product material identified in §35.200 to 10 CFR Part 35, to persons who have a similar authorization issued by an Agreement State, and, outside the United States, to persons authorized by the appropriate authority.

Alternatively, comment as to why the above statement should not appear on labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission and except where requested otherwise, please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling?

Container Label:
See Comments above

Carton Labeling: (5 Vials and 30 Vials)
See Comments above

Professional Package Insert Labeling:
See Comments above

Radioassay Label:
Satisfactory in 10/6/2007 amendment.

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cardiolite

NDA Number: NDA 19-785

NDA Drug Name: Cardiolite (Technetium Tc 99m Sestamibi Kit)

NDA Firm**:** Bristol Myers Squibb

Date of Approval of NDA Insert and supplement #: NDA 19-785/ S-012, (approved 1/22/2002).

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD

1. MODELING LABELING

Labeling review based on the reference listed drug, by Bristol Myers Squibb, "Cardiolite (Technitium Tc 99m Sestamibi Kit)", approved January 22, 2002, (NDA 19-785/S-012). BMS also markets the product "Miraluma" under NDA 19-785. Although the labeling from S-012 is not available electronically, there are no PN labeling supplements for the RLD. Therefore, last labeling available electronically in Y-015 (dated 2/8/2006), may be used as a model. This labeling agrees with RLD labeling (rev. May 2003), submitted by the applicant. See notes below regarding labeling:

Please adequately explain why you have not provided vial shield labels with your application as referenced in this section. This is part of the approved labeling of the RLD and therefore we believe that it should be provided for in your application. We refer you to 21 CFR 314.94(a)(t3)(iv), for guidance.

The vial shield labels are referred to as Radioassay Information Labels in Mallinckrodt's application, and have been provided in the labeling section. The proposed 5-vial kit label, 30-vial kit carton, and package insert consistently refer to the label as the Radioassay Information Label. The RLD labeling uses the term vial shield label, a term not used in current Mallinckrodt labels or labeling.

Mallinckrodt does not intend to provide a separate radioactive material label, which has the radioactive material symbol and the words CAUTION: RADIOACTIVE MATERIAL. . The symbol and caution statement are on the Radioassay Information Label, which is provided with both radiopharmaceutical kit packaging configurations.

Is your kit being reviewed by the U.S. Nuclear Regulatory Commission?

The text has been removed from the labeling. The kit will not be reviewed by the U.S. Nuclear Regulatory Commission (NRC). Non-radioactive reagent kits are not required to be included on distribution licenses by the NRC.

if so, please describe exactly who is reviewing the kit (include contact information) and what has been forwarded for review.

No review will be performed by NRC.

Note *** The Orange Book does not capture a potency for this product due to degradation.

2. PATENTS/ EXCLUSIVITIES:

Patent Data
Exclusivity Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
019785	001	4885100	SEP 11, 2007			
019785	001	4894445	JAN 16, 2007			U-337
019785	001	4988827	JAN 29, 2008			
019785	001	5324824	JAN 16, 2007			

Code	Definition
U-337	USE OF CARDIOLITE/MIRALUMA KIT FOR THE PREPARATION OF TC99M SESTAMIBI

There is no unexpired exclusivity for this product.

The applicant has made a Paragraph III certification to the unexpired patents. The O-Book lists Cardiolite and Miraluma as two separate products under the same NDA. Patents and Use codes are the same for both products. Although the applicant references Cardiolite, all information regarding the indication for Miraluma is retained in the applicant's labeling (as it appears in Cardiolite labeling). However, whereas Cardiolite labeling refers to "Miraluma" for breast imaging, the applicant has used the established name of the product, implying that the proposed product may be used for either indication.

However, although the two products are listed separately on the BMS web site, the link to Miraluma takes the reader to the Cardiolite web site:

Cardiolite® (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

Catalog Numbers	
CA2D	2-vial kit
CAKD	5-vial kit

Call **1-800-299-3431** to place an order.

miraluma® (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

Catalog Numbers	
CA2D	2-vial kit
CAKD	5-vial kit

Call **1-800-299-3431** to place an order.

I called the BMS phone number and asked the representative what product I would get if I ordered Miraluma and she said that I would get Cardiolite. Therefore, in reality, there is only one product, Cardiolite (not 2 as listed in the O-Book).

O-Book:

Active Ingredient:	TECHNETIUM TC-99M SESTAMIBI KIT
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	CARDIOLITE
Applicant:	BRISTOL MYERS SQUIBB
Strength:	N/A
Application Number:	019785
Product Number:	001
Approval Date:	Dec 21, 1990
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	TECHNETIUM TC-99M SESTAMIBI KIT
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MIRALUMA
Applicant:	BRISTOL MYERS SQUIBB
Strength:	N/A
Application Number:	019785
Product Number:	003
Approval Date:	May 23, 1997

Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

It is my understanding that an ANDA can not reference two products. However, since in reality there is only one RLD product, I have asked O-Book person, Harvey Greenberg, whether the O-Book can be revised to reflect one product number for Cardiolite/Miraluma.

At present, the applicant's product is labeled for indications from two different products.

PACKAGE INSERT LABELING MAY DEPEND ON THE ANSWER TO THIS QUESTION.

3. **INACTIVE INGREDIENTS;** The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section appearing in the chemistry review. Each 10 mL vial contains a lyophilized powder of:

1.0 mg $[Cu(MIBI)_4]BF_4$ (active where MIBI=2-methoxy isobutyl isonitrile)
0.025-0.75 mg Stannous Chloride Dihydrate
1.0 mg L-Cysteine Hyrochloride Monohydrate
2.6 mg Sodium Citrate Dihydrate
20 mg D-Mannitol
Prior to lyophilization, the pH of the aqueous bulk dispensing solution is adjusted with sodium hydroxide and/or hydrochloric acid to pH = 5.6.

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON:**

- **USP:**

Packaging and storage—Preserve in single-dose or multiple-dose containers.

Labeling—Label it to include the following, in addition to the information specified for *Labeling* under

Injections ⟨ 1 ⟩: the time and date of constitution; the volume of constitution; the amount of ^{99m}Tc as labeled sestamibi expressed as total megabecquerels (or millicuries) per mL at the time of constitution; the expiration date and time; the lot number; and the statement "Caution—Radioactive Material." The labeling indicates that in making dosage calculations, correction is to be made for radioactive decay, and also indicates that the radioactive half-life of ^{99m}Tc is 6.0 hours.

- **RLD:** Store at 15-25°C before and after reconstitution. …and, under Instructions, "Technetium Tc 99m Sestamibi should be used within 6 hours of preparation", and "Product should be used within 6 hours after preparation. "

- **ANDA:** Same as RLD, however, ANDA is additionally labeled, "Protect from light prior to reconstitution" (insert). From the "Summary of Chemistry Assessments" in the chemist's review: "Vials should be protected from light prior to reconstitution and contains no preservatives. "

5. **PACKAGING CONFIGURATIONS**

RLD: Made available in kits consisting of 2, 5, or 20 reaction vials.
ANDA: Made available in kits consisting of 5 or 30 reaction vials.

See FTR below regarding the use of this product in the themal cycler:

We note that you have deleted all information regarding the use of your product with a thermal cycler. Annotated labeling provided with your application fails to adequately address, justify, and explain why your product labeling limits the method for preparation to the water bath procedure while the RLD product may be prepared using either method. Please provide a full explanation.

The Recon-O-Stat (thermal cycler) was designed for use with the Cardiolite® vial, which is a 5 mL vial. A tungsten vial shield is an integral part of the device, as the tungsten shield is specially designed for the heat pump effect

and to provide shielding from radiation exposure. The Mallinckrodt vial, a 10 mL vial, will not completely fit in the tungsten lead shield. The lid cannot be put in place with the 10 mL vial, adversely affecting the heating profile and the radiation protection.

A second reason for not providing instructions for use of the Recon-O-Stat in the package insert is that the Recon-O-Stat thermal cycler is no longer available from Bristol-Myers Squibb. The units were custom-made for Bristol-Myers Squibb, and Bristol-Myers Squibb discontinued distributing the Recon-O-Stat units approximately one year ago. Even if a customer had a Recon-O-Stat thermal cycler and purchased a Mallinckrodt TechneScan Sestamibi kit, the Recon-O-Stat should not be used to heat the ^{99m}Tc Sestamibi because of the height difference in the 10 mL vial, as explained in the previous paragraph.

The sponsor was requested to add a statement in the Directions section that this product may not be used with the thermal cycler.

6. A proprietary name consult for "TechneScan Sestamibi" was sent to DMETS in the ODS on 4/18/2007 (see DFS). DMETS was also requested to address established name confusion between Tc99m products. DMETS was also notified that a consult for a similar name for ANDA 77-328 was also sent for review, TechneScan MDP. With the October 6, amendment, Mallinckrodt proposes deleting the "TechneScan" part of the name. We sent the new proposal over to DMETS who has assigned the consult the number, 07-892.

Other products listed in O-Book with the TechneScan name:

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
017842	BS	No	TECHNETIUM TC-99M ALBUMIN AGGREGATED KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN MAA	MALLINCKRODT
018272		No	TECHNETIUM TC-99M GLUCEPTATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN GLUCEPTATE	DRAXIMAGE
019882		No	TECHNETIUM TC-99M MERTIATIDE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN MAG3	MALLINCKRODT
018321		Yes	TECHNETIUM TC-99M OXIDRONATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN	MALLINCKRODT
017538	AP	No	TECHNETIUM TC-99M PYROPHOSPHATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN PYP KIT	MALLINCKRODT

7. CONTAINER/CLOSURE

The lyophilized nonradioactive drug product Techne Scan Sestamibi, is contained in a 10 mL glass tubing vial sealed with a 20 mm gray butyl rubber lyophilization stopper and an aluminum crimp cap seal.

8. FINISHED DOSAGE MANUFACTURING FACILITY

This product is manufactured at the Mallinckrodt facility in Maryland Heights, Missouri (below address). The Manufactured by statement lists the corporate address, Mallinckrodt Inc., in St. Louis, MO.

Mallinckrodt Inc
2703 Wagner Place,
Maryland Heights, MO 63043

9. NOTE REGARDING LABELING FROM CHEMISTRY REVIEW

Reviewer's Assessment:
PI and container labels are conform to CMC as reviewed in this ANDA and are consistent with the innovator's PI and container labels; however, all sections of the PI and container labels should add the manufacturer's name to appropriate sections where the distributor's name are denoted. The PI and container labels are otherwise adequate from a CMC prospective.

10. FIRST GENERIC?

Marty,

The following appears on the filing checklist for this application:

First Generic Product Received? NO PER MARTY 3/9/06
SEE MARTY FOR MORE DETAILS

Could you explain why this is not a first generic? The filing sheet refers to related ANDA (b) (4) a (b) (4) product. But that is a *completely* different and chemically unrelated product, similar only by virtue of the fact that (b) (4).

Additionally, the CIS-USA imaging agent (which also employs Tc imaging) filed under ANDA 78-242 did get first generic status.

Charlie,

This ANDA was not designated as a first generic for the following reasons. First as an injectable drug product the DBE does not need to initially evaluate any studies as the product is an injectable solution that is eligible for a waiver of BE. Second the reviews for these drug products actually take place outside of OGD as OGD does not have anyone with the technical background to review these ANDAs. The first submission (b) (4) from (b) (4) was probably designated as a first generic which would have been the error. It's true that these ANDAs will represent First Generic approvals for purposes of bringing generics to the market but RSB uses the first generic designation to trigger additional reviews within OGD. In this case it wasn't necessary.

Thanks,

Marty

Date of Review: November 26, 2007 **Date of Submission: October 6, 2007**

Primary Reviewer: Charlie Hoppes **Date:**

Team Leader: John Grace **Date:**

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

/s/

Charles Hoppes
11/27/2007 11:13:16 AM
LABELING REVIEWER

John Grace
11/28/2007 12:31:57 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-098 Dates of Submission: January 31, 2006

Applicant's Name: Mallinckrodt Inc.

Established Name: TechneScan® Sestamibi (Kit for Preparation of Technetium Tc 99m Sestamibi Injection)

Labeling Deficiencies:

A. GENERAL COMMENTS

1. The Office of Generic Drugs contacted the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety regarding the proposed proprietary name for this product. We will inform you of their comments when they become available to us.

2. Through searches of the FDA Adverse Event Reporting System database, we have become aware of reports of medication errors resulting from confusion between different Tc 99m imaging/diagnostic products, including confusion involving Technetium Tc 99m Sestamibi Injection.

   For this reason, we have consulted the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety regarding possible means of differentiating Technetium Tc 99m Sestamibi Injection from other Tc 99m products.

   At this time, we request that you forward a proposal to reduce risk of confusion.

3. Revise your storage statement where it appears on labels and in labeling to include the Fahrenheit equivalent and well as Celsius.

4. Revise labels and labeling to delete the terminal zero where it appears associated with the ingredient strength, e.g., revise to read, "…1 mg", rather than "…1.0 mg".

B. CONTAINER LABEL

1. See GENERAL COMMENTS 3 and 4.

2. Include the active ingredients with strengths for this drug product.

3. Include the route of administration as it appears on your proposed 30-Vial Carton labeling.

C. CARTON LABELING (5 Vial Kits and 30 Vial Kits)

1. See GENERAL COMMENTS 3 and 4.

2. Add "protect from light" statement. You may add the statement, "Retain in Carton until time of use."

3. We note that you have offered the following explanation for differences between your outer carton labeling for your 30 Vial Kit product compared with that of the RLD:

   Cardiolite is not offered in a 30-vial packaging configuration; therefore no annotated comparison can be made. The text for Mallinckrodt's proposed 30-vial carton configuration

is listed in the column on the left.

We do not believe that this is an adequate explanation for the omission of labeling statements present on the carton labeling of the RLD. Please comment especially regarding omission of the Warning statement regarding radiopharmaceuticals and the statement with the heading "License", which appears on the labeling of the RLD. Revise your labeling accordingly.

4. Regarding your 5 vial carton, please offer further comment regarding the omission of the statement with the heading "License" appearing on the 5 Vial carton of the RLD. We believe that this statement may serve to heighten awareness of the necessity and responsibility for proper disposal of this product. We believe that your product should provide a statement that has the same effect.

5. We note that the 30-Vial carton that you propose bears the statement, " (b) (4) ". However, your package insert labeling indicates that your product may be used for breast imaging. Please comment.

6. For the 5-Vial Carton, include the route of administration as it appears on your proposed 30-Vial Carton labeling.

D. PHYSICIAN INSERT

1. GENERAL COMMENTS

Distinguish section headings from subsection headings by use of differential prominence (greater prominence for section headings). Make consistent use of formatting for headings, for example, the heading "DESCRIPTION" should be of the same format and prominence as "CLINICAL PHARMACOLOGY", but the subsection, "CLINICAL TRIALS", should appear with lesser prominence. See 21 CFR 201.56 for listing of the section headings.

2. TITLE

a. Include the following text to appear immediately before the, "FOR DIAGNOSTIC USE", statement, "For Intravenous Use".

b. Delete the corporate address information from this section as it appears in the HOW SUPPLIED section. We refer you to 21 CFR 201.56(d)(4), for guidance.

c. Include the following text to appear immediately before the DESCRIPTION section, "Rx Only".

3. DESCRIPTION

a. Include the molecular formula, structural formula, and molecular weight (602.98) of $C_{24}H_{44}N_4O_4BF_4Cu$ in this section.

b. We acknowledge comments that, prior to lyophilization, the pH of the aqueous bulk dispensing solution is adjusted with sodium hydroxide and/or hydrochloric acid to pH = 5.6. Please include this information in this section.

4. DIRECTIONS

a. We note that you have deleted all information regarding the use of your product with a thermal cycler. Annotated labeling provided with your application fails to adequately address, justify, and explain why your product labeling limits the

method for preparation to the water bath procedure while the RLD product may be prepared using either method. Please provide a full explanation.

b. Please adequately explain why you have not provided vial shield labels with your application as referenced in this section. This is part of the approved labeling of the RLD and therefore we believe that it should be provided for in your application. We refer you to 21 CFR 314.94(a)(8)(iv), for guidance.

5. HOW SUPPLIED

Regarding the following sentence which appears immediately after the DIRECTIONS, "This reagent kit is approved by the U.S. Nuclear Regulatory Commission for distribution to persons…"

a. Is your kit being reviewed by the U.S. Nuclear Regulatory Commission?

b. If so, please describe exactly who is reviewing the kit (include contact information) and what has been forwarded for review.

E. RADIOASSAY INFORMATION LABEL WITH RADIATION WARNING SYMBOL

Please ensure that the number of labels provided in each kit is equal to the number of vials.

Submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission and except where requested otherwise, please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling?

Container Label:
See Comments above

Carton Labeling: (5 Vials and 30 Vials)
See Comments above

Professional Package Insert Labeling:
See Comments above

Radioassay Label:

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cardiolite

NDA Number: NDA 19-785

NDA Drug Name: Cardiolite (Technetium Tc 99m Sestamibi Kit)

NDA Firm**:** Bristol Myers Squibb

Date of Approval of NDA Insert and supplement #: NDA 19-785/ S-012, (approved 1/22/2002).

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD

1. MODELING LABELING

Labeling review based on the reference listed drug, by Bristol Myers Squibb, "Cardiolite (Technitium Tc 99m Sestamibi Kit)", approved January 22, 2002, (NDA 19-785/S-012). BMS also markets the product "Miraluma" under NDA 19-785. Although the labeling from S-012 is not available electronically, there are no PN labeling supplements for the RLD. Therefore, last labeling available electronically in Y-015 (dated 2/8/2006), may be used as a model. This labeling agrees with RLD labeling (rev. May 2003), submitted by the applicant.

Note *** The Orange Book does not capture a potency for this product due to degradation.

2. PATENTS/ EXCLUSIVITIES:

Patent Data
Exclusivity Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
019785	001	4885100	SEP 11, 2007			
019785	001	4894445	JAN 16, 2007			U-337
019785	001	4988827	JAN 29, 2008			
019785	001	5324824	JAN 16, 2007			

Code	Definition
U-337	USE OF CARDIOLITE/MIRALUMA KIT FOR THE PREPARATION OF TC99M SESTAMIBI

There is no unexpired exclusivity for this product.

The applicant has made a Paragraph III certification to the unexpired patents. The O-Book lists Cardiolite and Miraluma as two separate products under the same NDA. Patents and Use codes are the same for both products. Although the applicant references Cardiolite, all information regarding the indication for Miraluma is retained in the applicant's labeling (as it appears in Cardiolite labeling). However, whereas Cardiolite labeling refers to "Miraluma" for breast imaging, the applicant has used the established name of the product, implying that the proposed product may be used for either indication. However, although the two products are listed separately on the BMS web site, the link to Miraluma takes the reader to the Cardiolite web site:

Cardiolite® (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

Catalog Numbers	
CA2D	2-vial kit
CAKD	5-vial kit

Call **1-800-299-3431** to place an order.

miraluma® (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

Catalog Numbers	
CA2D	2-vial kit
CAKD	5-vial kit

Call **1-800-299-3431** to place an order.

I called the BMS phone number and asked the representative what product I would get if I ordered Miraluma and she said that I would get Cardiolite. Therefore, in reality, there is only one product, Cardiolite (not 2 as listed in the O-Book).

O-Book:

Active Ingredient:	TECHNETIUM TC-99M SESTAMIBI KIT
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	CARDIOLITE
Applicant:	BRISTOL MYERS SQUIBB
Strength:	N/A
Application Number:	019785
Product Number:	001
Approval Date:	Dec 21, 1990
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	TECHNETIUM TC-99M SESTAMIBI KIT
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MIRALUMA
Applicant:	BRISTOL MYERS SQUIBB
Strength:	N/A
Application Number:	019785
Product Number:	003
Approval Date:	May 23, 1997
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

It is my understanding that an ANDA can not reference two products. However, since in reality there is only one RLD product, I have asked O-Book person, Harvey Greenberg, whether the O-Book can be revised to reflect one product number for Cardiolite/Miraluma.

At present, the applicant's product is labeled for indications from two different products.

PACKAGE INSERT LABELING MAY DEPEND ON THE ANSWER TO THIS QUESTION.

3. **INACTIVE INGREDIENTS;** The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section appearing in the chemistry review. Each 10 mL vial contains a lyophilized powder of:

1.0 mg $[Cu(MIBI)_4]BF_4$ (active where MIBI=2-methoxy isobutyl isonitrile)
0.025-0.75 mg Stannous Chloride Dihydrate
1.0 mg L-Cysteine Hyrochloride Monohydrate
2.6 mg Sodium Citrate Dihydrate
20 mg D-Mannitol
Prior to lyophilization, the pH of the aqueous bulk dispensing solution is adjusted with sodium hydroxide and/or hydrochloric acid to pH = 5.6.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON:

- **USP:**

Packaging and storage—Preserve in single-dose or multiple-dose containers.

Labeling—Label it to include the following, in addition to the information specified for *Labeling* under *Injections* ⟨ 1 ⟩ : the time and date of constitution; the volume of constitution; the amount of ^{99m}Tc as labeled sestamibi expressed as total megabecquerels (or millicuries) per mL at the time of constitution; the expiration date and time; the lot number; and the statement "Caution—Radioactive Material." The labeling indicates that in making dosage calculations, correction is to be made for radioactive decay, and also indicates that the radioactive half-life of ^{99m}Tc is 6.0 hours.

- **RLD:** Store at 15-25°C before and after reconstitution. …and, under Instructions, "Technetium Tc 99m Sestamibi should be used within 6 hours of preparation", and "Product should be used within 6 hours after preparation. "

- **ANDA:** Same as RLD, however, ANDA is additionally labeled, "Protect from light prior to reconstitution" (insert). From the "Summary of Chemistry Assessments" in the chemist's review: "Vials should be protected from light prior to reconstitution and contains no preservatives. "

5. PACKAGING CONFIGURATIONS

RLD: Made available in kits consisting of 2, 5, or 20 reaction vials.
ANDA: Made available in kits consisting of 5 or 30 reaction vials.

6. A proprietary name consult for "TechneScan Sestamibi" was sent to DMETS in the ODS on 4/18/2007 (see DFS). DMETS was also requested to address established name confusion between Tc99m products. DMETS was also notified that a consult for a similar name for ANDA 77-328 was also sent for review, TechneScan MDP.

Other products listed in O-Book with the TechneScan name:

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
017842	BS	No	TECHNETIUM TC-99M ALBUMIN AGGREGATED KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN MAA	MALLINCKRODT
018272		No	TECHNETIUM TC-99M GLUCEPTATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN GLUCEPTATE	DRAXIMAGE
019882		No	TECHNETIUM TC-99M MERTIATIDE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN MAG3	MALLINCKRODT
018321		Yes	TECHNETIUM TC-99M OXIDRONATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN	MALLINCKRODT
017538	AP	No	TECHNETIUM TC-99M PYROPHOSPHATE KIT	INJECTABLE; INJECTION	N/A	TECHNESCAN PYP KIT	MALLINCKRODT

7. CONTAINER/CLOSURE

The lyophilized nonradioactive drug product Techne Scan Sestamibi, is contained in a 10 mL glass tubing vial sealed with a 20 mm gray butyl rubber lyophilization stopper and an aluminum crimp cap seal.

8. FINISHED DOSAGE MANUFACTURING FACILITY

This product is manufactured at the Mallinckrodt facility in Maryland Heights, Missouri (below address). The Manufactured by statement lists the corporate address, Mallinckrodt Inc., in St. Louis, MO.

Mallinckrodt Inc
2703 Wagner Place,
Maryland Heights, MO 63043

9. NOTE REGARDING LABELING FROM CHEMISTRY REVIEW

Reviewer's Assessment:
PI and container labels are conform to CMC as reviewed in this ANDA and are consistent with the innovator's PI and container labels; however, all sections of the PI and container labels should add the manufacturer's name to appropriate sections where the distributor's name are denoted. The PI and container labels are otherwise adequate from a CMC prospective.

10. FIRST GENERIC?

Marty,

The following appears on the filing checklist for this application:

First Generic Product Received? NO PER MARTY 3/9/06
SEE MARTY FOR MORE DETAILS

Could you explain why this is not a first generic? The filing sheet refers to related ANDA (b) (4) a (b) (4) product. But that is a *completely* different and chemically unrelated product, similar only by virtue of the fact that (b) (4)

Additionally, the CIS-USA imaging agent (which also employs Tc imaging) filed under ANDA 78-242 did get first generic status.

Charlie,

This ANDA was not designated as a first generic for the following reasons. First as an injectable drug product the DBE does not need to initially evaluate any studies as the product is an injectable solution that is eligible for a waiver of BE. Second the reviews for these drug products actually take place outside of OGD as OGD does not have anyone with the technical background to review these ANDAs. The first submission (b) (4) from (b) (4) was probably designated as a first generic which would have been the error. It's true that these ANDAs will represent First Generic approvals for purposes of bringing generics to the market but RSB uses the first generic designation to trigger additional reviews within OGD. In this case it wasn't necessary.

Thanks,

Marty

Date of Review: April 18, 2007 **Date of Submission: January 31, 2006**

Primary Reviewer: Charlie Hoppes **Date:**

Team Leader: John Grace **Date:**

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

/s/

Charles Hoppes
4/20/2007 02:22:52 PM
MEDICAL OFFICER

John Grace
4/22/2007 07:05:45 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-098

CHEMISTRY REVIEWS

ANDA 78-098

Technetium TC- 99M Sestamibi Injection

(Kit for the Preparation of Technetium Tc 99m Sestamibi Injection)

MALLINCKRODT, Inc.

Yusuf Amin
Chemistry Division I

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Chemistry Review Data Sheet

1. ANDA: 78-098

2. REVIEW #: 2

3. REVIEW DATE: 03-SEP-2008

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	31-JAN-2006
Amendment	06-OCT-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment N-000-AM	12-MAY-2008
Amendment N-000-AM	23-JUN-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Mallinckrodt Inc.
Address:	P. O. Box 5840 675 McDonnell Blvd. St. Louis, MO 63134
Representative:	James W. Brodack, Ph. D.
Telephone:	314 654-3045
Facsimile:	314 654-3344

8. DRUG PRODUCT NAME/CODE/TYPE: Technetium Tc 99m Sestamibi Injection.
Proprietary name: TechneScan Sestamibi

9. LEGAL BASIS FOR SUBMISSION: Technetium Tc 99m Sestamibi Injection (Kit for the Preparation of Technetium Tc 99m Sestamibi Injection) is based on NDA Cardiolite, NDA 19-785 owned by Bristol-Myers Squibb.

The applicant makes the following certifications in connection with its Abbreviated New Drug Application identified above. These certifications are based on information found in the current edition of *Approved Drug Products with Therapeutic Equivalence Evaluations.*

Paragraph II Certification
[21 USC 355(j)(2)(A)(vii)(II) and 21 CFR 314.94(a)(12)(i)(A)(2)]

In the opinion of the applicant and to the best of its knowledge, the following listed patent has expired:

US 4,452,774 expired 2004 Dec 21

Paragraph III Certification
[21 USC 355(j)(2)(A)(vii)(III) and 21 CFR 314.94(a)(12)(i)(A)(3)]

In the opinion of the applicant and to the best of its knowledge, the following listed patent(s) are unexpired:

US 4,885,100 expires 2007 Sep 11
US 4,894,445 expires 2007 Jan 16
US 4,988,827 expires 2008 Jan 29
US 5,324,824 expires 2007 Jan 16

Exclusivity Statement
[21 CFR 314.94(a)(3)(ii)]

According to information published in the list, the reference listed drug is not entitled to a period of marketing exclusivity (or any such periods have expired).

10. PHARMACOL. CATEGORY: A myocardial perfusion agent

11. DOSAGE FORM: : Injection, Powder, Lyophilized, for Solution

STRENGTH/POTENCY: 10-30 mCi after reconstitution

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

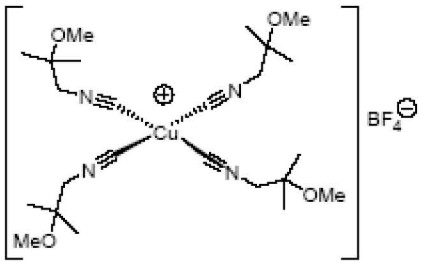
SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

$[Cu(MIBI)_4]BF_4$ (Cu MIBI; where MIBI is 2-methoxy-isobutyl-isonitrile) is the nonradioactive drug substance in the nonradioactive drug product TechneScan® Sestamibi (Kit for the Preparation of Technetium Tc-99m Sestamibi Injection). Section 3.2.S.1 includes all nomenclature, molecular and structural information, and general physicochemical properties of the $[Cu(MIBI)_4]BF_4$ drug substance. The general structure of the complex is given below. The X-ray data show a (b) (4) arrangement of MIBI ligands around the central copper atom.

Chemical name: Tetrakis (2-methoxyisobutylisonitrile) Copper(I) Tetrafluoroborate
Formula: $[Cu(MIBI)_4]BF_4$
Molecular weight: 602.99



$[Cu(MIBI)_4]BF_4$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)							

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: See Attachment document

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cardiolite/ Miraluma (Technetium TC-99M Sestamibi KIT) Bristol Myers Squibb	19-785	RLD

18. STATUS: CMC APPROVABLE (See attached Review)

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	20-DEC-2006	S. Ferguson
Pharm/Tox	Not Consulted	N/A	N/A
Biopharm	Not Consulted	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
OPDRA	DMETS comments Pending	05-OCT-2006	L. Epps
Labeling	Acceptable	17-SEP-2008	C. Hoppes
EA	Categorical exclusion justified	17-AUG-2006	L. Epps
Microbiology	Acceptable	12-AUG-2008	B. Pillari

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-098

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is approvable. The review was performed by Dr. E. Leutzinger of the division of New Drug Chemistry. **See File V:\FIRMSAM\MALLINCKRODT\LTRS&REV\78098.REV2b.DOC**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

TechneScan® Sestamibi and the Reference Listed Drug, Cardiolite®, are sterile, nonpyrogenic and non-radioactive kits that contain lyophilized mixtures of inactive components that, upon reconstitution with up to 5550 megabecquerels (150 mCi) Sodium Pertechnetate Tc-99m Injection, produce the radioactive drug product Technetium Tc-99m Sestamibi Injection. The amount of the radioactive drug substance, Technetium Tc-99m Sestamibi, that is formed is commensurate with the amount of radioactivity used to reconstitute each kit.

Table below lists the ingredients of the TechneScan Sestamibi kit in comparison to that in Cardiolite.

TechneScan® Sestamibi	Cardiolite®
Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0 mg	Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0 mg
Sodium Citrate Dihydrate - 2.6 mg	Sodium Citrate Dihydrate - 2.6 mg
L-Cysteine Hydrochloride Monohydrate - 1.0 mg	L-Cysteine Hydrochloride Monohydrate - 1.0 mg
Mannitol - 20 mg	Mannitol - 20 mg
Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) - 0.025 mg Stannous Chloride, Dihydrate ($SnCl_2 \cdot 2H_2O$) - 0.075 mg Tin Chloride (stannous and stannic) Dihydrate, maximum (as $SnCl_2 \cdot 2H_2O$) - 0.086 mg	Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) - 0.025 mg Stannous Chloride, Dihydrate ($SnCl_2 \cdot 2H_2O$) - 0.075 mg Tin Chloride (stannous and stannic) Dihydrate, maximum (as $SnCl_2 \cdot 2H_2O$) - 0.086 mg
pH reconstituted product is 5.0 – 6.0	pH reconstituted product is 5.0 – 6.0

B. Description of How the Drug Product is Intended to be Used

Route of Administration dosage form and strength:

The route of administration, dosage form, and strength of Mallinckrodt's TechneScan® Sestamibi (Kit for the Preparation of Technetium Tc-99m Sestamibi Injection) are the same as those of the reference listed drug, Cardiolite® (Kit for the Preparation of Technetium Tc-99m Sestamibi for Injection). Both Mallinckrodt's drug product and the reference listed drug are provided as reaction vials containing a nonradioactive lyophilized mixture of inactive components, which upon reconstitution with Sodium Pertechnetate Tc-99m Injection, produce the radioactive drug product, Technetium Tc-99m Sestamibi Injection. The radioactive drug product produced from either kit is a sterile, nonpyrogenic solution that may contain up to 5550 megabecquerels (150 mCi) of the radioactive drug substance Technetium Tc-99m Sestamibi in a volume of up to 3 mL and is intended solely for intravenous injection into humans. The recommended adult (70 kg) dose for administration of either radioactive drug product is 370 to 1110 megabecquerels (10 to 30 millicuries).

C. Basis for Approval Recommendation:

The CMC is approvable. The review was performed by Dr. E. Leutzinger of the division of New Drug Chemistry. See File

V:\FIRMSAM\MALLINCKRODT\LTRS&REV\78098.REV2b.DOC

ANDA 78-098
(Technetium Tc-99m Sestamibi Injection)

Eldon E. Leutzinger, Ph.D.
Pharmaceutical Assessment Lead

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION OF PREMARKETING ASSESSMENT AND MANUFACTURING SCIENCE (BRANCH V)

CMC REVIEW OF NDA 78-098

FOR THE OFFICE OF GENERIC DRUGS

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Chemistry Assessment **9**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data ..... N/A

S DRUG SUBSTANCE [Name, Manufacturer] ..... ……N/A

P DRUG PRODUCT [Name, Dosage form] ..... N/A

A APPENDICES ..... N/A

R REGIONAL INFORMATION ..... N/A

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 ..... N/A

A. Labeling & Package Insert ..... N/A

B. Environmental Assessment Or Claim Of Categorical Exclusion ..... N/A

III. List Of Deficiencies To Be Communicated ..... N/A

Chemistry Review Data Sheet

1. ANDA 78-098

2. REVIEW # 2

3. REVIEW DATE: 08/27/2008

4. REVIEWER: Eldon E. Leutzinger, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	February 1, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment N-000-AM	12-MAY-2008
Amendment N-000-AM	23-JUN-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Mallinckrodt Inc.
Address:	P.O. Box 5840 675 McDonnell Blvd. St. Louis, MO 63134
Representative:	James W. Brodack, ph.D. Regulatory Affairs Manager
Telephone:	314-654-3045 Facsmile (314-654-3344)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: TechneScan Sestamibi

b) Non-Proprietary (Established Name): Technetium Tc 99m Sestamibi Injection
c) Code Name/# (ONDQA only): 092
d) Chem. Type/Submission Priority (ONDQA only): N/A

9. LEGAL BASIS FOR SUBMISSION: ANDA, CFR 314.94

10. PHARMACOL. CATEGORY: Diagnostic radiopharmaceutical

11. DOSAGE FORM: Lyophilized powder for the Preparation of Technetium Tc 99m Sestamibi Injection

12. STRENGTH/POTENCY: 10 – 30 mCi (370 – 1110 MBq) after reconstitution

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: X__Rx ___OTC

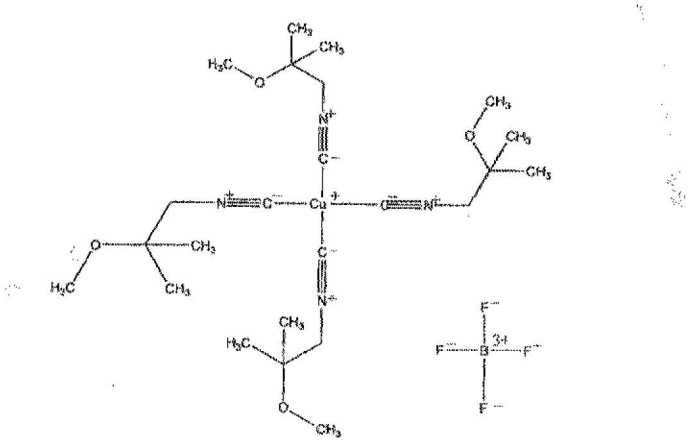
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

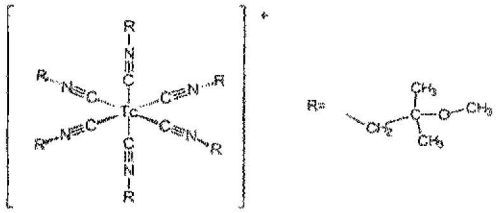
Chemical Name:
The kit consists of a lyophilized vial containing a Final Intermediate, $[Cu(MIBI)_4]BF_4$ and inactive ingredients. $[Cu(MIBI)_4]BF_4$ has a molecular weight of 602.98 and has the following chemical structure. See the next review page.



On reconstitution of the kit, pertechnetate ($^{99m}TcO_4^-$) (b) (4) [redacted] (b) (4) The latter reacts with the above intermediate to form the active ingredient (Drug Substance), in accordance to the following chemical reaction.

(b) (4) [redacted]

The structure of the Drug Substance (far right side of the above reaction) is shown below:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:
See Review #1 (Leon A. Epps, PhD., 12/12/2006, ONDQA/DPAMS).

B. Other Documents:
See Review #1

18. STATUS:

ONDQA:
See Review #1

OGD: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 78-098

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

A recommendation of APPROVAL is made for ANDA 78-098.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Reference is made to the Review #1 of the original ANDA (Leon A. Epps, Ph.D., former CMC reviewer in Branch V, 12/12/2006).

B. Description of How the Drug Product is Intended to be Used

See Review #1 (Leon A. Epps, Ph.D.).

C. Basis for Approvability or Not-Approval Recommendation

(Basis for Approval).

From a CMC standpoint, I have no concerns regarding the information provided where tests are added for residual solvents (drug substance and excipients). Also, there are no concerns regarding any of the updates containing changes made to CMC, except for those parts that involve changes to microbiological parameters.

The following changes to microbiological parameters for 78-098 has been approved in a comparability protocol. The firm has agreed to submit testing data via supplement submission. Brenda Pillari granted micro review acceptable as of 8/12/2008 (please see TCON note on 8/12/08 in DFS).

Amendment #4

(b) (4)

III. Administrative

A. Reviewer's Signature

Eldon E. Leutzinger, Ph.D.

B. Endorsement Block

CMC Reviewer's Name / Eldon E. Leutzinger, PhD.

CMC Branch Chief (Acting) Name / Sarah Pope, Ph.D.

C. CC Block

ONDQA Project Manager Name / D.Mesmer

8 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

Yusuf A. Amin
9/22/2008 01:56:43 PM
CHEMIST

Albert Mueller
9/22/2008 02:51:22 PM
CHEMIST

Dat Doan
9/22/2008 03:03:00 PM
CSO

ANDA 78-098
(Technetium Tc-99m Sestamibi Injection)

Eldon E. Leutzinger, Ph.D.
Pharmaceutical Assessment Lead

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION OF PREMARKETING ASSESSMENT AND MANUFACTURING SCIENCE (BRANCH V)

CMC REVIEW OF NDA 78-098

FOR THE OFFICE OF GENERIC DRUGS

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II. Summary of Chemistry Assessments.....7

A. Description of the Drug Product(s) and Drug Substance(s).....7

B. Description of How the Drug Product is Intended to be Used.....7

C. Basis for Approvability or Not-Approval Recommendation.....7

III. Administrative.....8

A. Reviewer's Signature.....8

B. Endorsement Block88

C. CC Block 8

Chemistry Assessment **9**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data....N/A

S DRUG SUBSTANCE [Name, Manufacturer] ..... ……N/A

P DRUG PRODUCT [Name, Dosage form].....N/A

A APPENDICES .....N/A

R REGIONAL INFORMATION .....N/A

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....N/A

A. Labeling & Package Insert .....N/A

B. Environmental Assessment Or Claim Of Categorical Exclusion .....N/A

III. List Of Deficiencies To Be Communicated.....N/A

Chemistry Review Data Sheet

1. ANDA 78-098

2. REVIEW # 2

3. REVIEW DATE: 08/27/2008

4. REVIEWER: Eldon E. Leutzinger, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	February 1, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment N-000-AM	12-MAY-2008
Amendment N-000-AM	23-JUN-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Mallinckrodt Inc.
Address:	P.O. Box 5840 675 McDonnell Blvd. St. Louis, MO 63134
Representative:	James W. Brodack, ph.D. Regulatory Affairs Manager
Telephone:	314-654-3045 Facsmile (314-654-3344)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: TechneScan Sestamibi

b) Non-Proprietary (Established Name): Technetium Tc 99m Sestamibi Injection
c) Code Name/# (ONDQA only): 092
d) Chem. Type/Submission Priority (ONDQA only): N/A

9. LEGAL BASIS FOR SUBMISSION: ANDA, CFR 314.94

10. PHARMACOL. CATEGORY: Diagnostic radiopharmaceutical

11. DOSAGE FORM: Lyophilized powder for the Preparation of Technetium Tc 99m Sestamibi Injection

12. STRENGTH/POTENCY: 10 – 30 mCi (370 – 1110 MBq) after reconstitution

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: X__Rx ___OTC

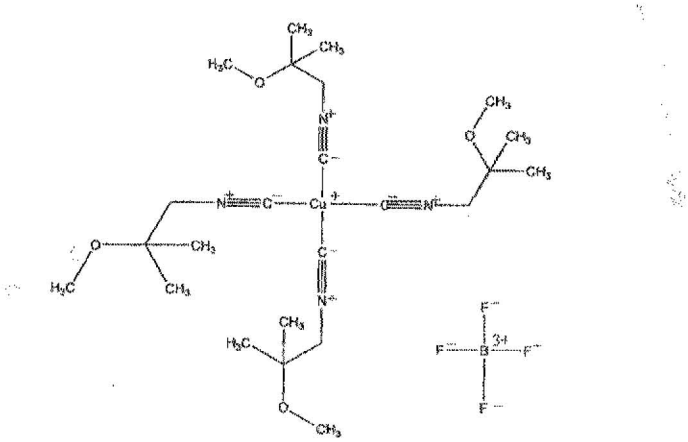
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

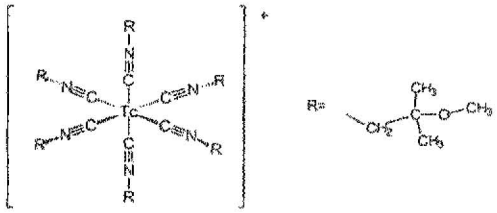
Chemical Name:
The kit consists of a lyophilized vial containing a Final Intermediate, $[Cu(MIBI)_4]BF_4$ and inactive ingredients. $[Cu(MIBI)_4]BF_4$ has a molecular weight of 602.98 and has the following chemical structure. See the next review page.



On reconstitution of the kit, pertechnetate ($^{99m}TcO_4^-$) [redacted] (b) (4) [redacted] (b) (4) The latter reacts with the above intermediate to form the active ingredient (Drug Substance), in accordance to the following chemical reaction.

[redacted] (b) (4)

The structure of the Drug Substance (far right side of the above reaction) is shown below:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:
See Review #1 (Leon A. Epps, PhD., 12/12/2006, ONDQA/DPAMS).

B. Other Documents:
See Review #1

18. STATUS:

ONDQA:
See Review #1

OGD: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-090

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

A recommendation of APPROVAL is made for ANDA 78-098, pending a satisfactory Microbiology assessment. See Part II.C. for a list of those sections of the amendment that need review by a microbiologist.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Reference is made to the Review #1 of the original ANDA (Leon A. Epps, Ph.D., former CMC reviewer in Branch V, 12/12/2006).

B. Description of How the Drug Product is Intended to be Used

See Review #1 (Leon A. Epps, Ph.D.).

C. Basis for Approvability or Not-Approval Recommendation

(Basis for Approval).

From a CMC standpoint, I have no concerns regarding the information provided where tests are added for residual solvents (drug substance and excipients). Also, there are no concerns regarding any of the updates containing changes made to CMC, except for those parts that involve changes to microbiological parameters. The latter changes need to be assessed by a Microbiologist for their acceptability. Those parts of Amendment 4 and 5 that need microbiology assessment are listed as follows:

Amendment #4

(b) (4)

III. Administrative

A. Reviewer's Signature

Eldon E. Leutzinger, Ph.D.

B. Endorsement Block

CMC Reviewer's Name / Eldon E. Leutzinger, PhD.

CMC Branch Chief (Acting) Name / Sarah Pope, Ph.D.

C. CC Block

ONDQA Project Manager Name / D.Mesmer

7 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

Eldon Leutzinger
8/28/2008 03:18:30 PM
CHEMIST

Sarah Pope
8/29/2008 01:50:19 PM
CHEMIST
Concur

ANDA 78-098

Technetium TC- 99M Sestamibi Injection

(Kit for the Preparation of Technetium Tc 99m Sestamibi Injection)

MALLINCKRODT, Inc.

Yusuf Amin
Chemistry Division I

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B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

Chemistry Review Data Sheet

1. ANDA: 78-098

2. REVIEW #: 1

3. REVIEW DATE: 08-NOV-2006

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	31-JAN-2006
Amendment	06-OCT-2007
Amendment (labeling)	14-DEC-2007
Amendment (labeling)	17-JAN-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Mallinckrodt Inc.
Address:	P. O. Box 5840 675 McDonnell Blvd. St. Louis, MO 63134
Representative:	James W. Brodack, Ph. D.
Telephone:	314 654-3045
Facsimile:	314 654-3344

8. DRUG PRODUCT NAME/CODE/TYPE: Technetium Tc 99m Sestamibi Injection.
Proprietary name: TechneScan Sestamibi

9. LEGAL BASIS FOR SUBMISSION: Technetium Tc 99m Sestamibi Injection (Kit for the Preparation of Technetium Tc 99m Sestamibi Injection) is based on NDA Cardiolite, NDA 19-785 owned by Bristol-Myers Squibb.

The applicant makes the following certifications in connection with its Abbreviated New Drug Application identified above. These certifications are based on information found in the current edition of *Approved Drug Products with Therapeutic Equivalence Evaluations.*

Paragraph II Certification
[21 USC 355(j)(2)(A)(vii)(II) and 21 CFR 314.94(a)(12)(i)(A)(2)]

In the opinion of the applicant and to the best of its knowledge, the following listed patent has expired:

US 4,452,774 expired 2004 Dec 21

Paragraph III Certification
[21 USC 355(j)(2)(A)(vii)(III) and 21 CFR 314.94(a)(12)(i)(A)(3)]

In the opinion of the applicant and to the best of its knowledge, the following listed patent(s) are unexpired:

US 4,885,100 expires 2007 Sep 11
US 4,894,445 expires 2007 Jan 16
US 4,988,827 expires 2008 Jan 29
US 5,324,824 expires 2007 Jan 16

Exclusivity Statement
[21 CFR 314.94(a)(3)(ii)]

According to information published in the list, the reference listed drug is not entitled to a period of marketing exclusivity (or any such periods have expired).

10. PHARMACOL. CATEGORY: A myocardial perfusion agent

11. DOSAGE FORM: : Injection, Powder, Lyophilized, for Solution

STRENGTH/POTENCY: 10-30 mCi after reconstitution

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

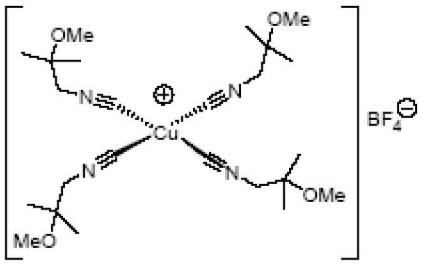
SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

$[Cu(MIBI)_4]BF_4$ (Cu MIBI; where MIBI is 2-methoxy-isobutyl-isonitrile) is the nonradioactive drug substance in the nonradioactive drug product TechneScan® Sestamibi (Kit for the Preparation of Technetium Tc-99m Sestamibi Injection). Section 3.2.S.1 includes all nomenclature, molecular and structural information, and general physicochemical properties of the $[Cu(MIBI)_4]BF_4$ drug substance. The general structure of the complex is given below. The X-ray data show a (b) (4) arrangement of MIBI ligands around the central copper atom.

Chemical name: Tetrakis (2-methoxyisobutylisonitrile) Copper(I) Tetrafluoroborate
Formula: $[Cu(MIBI)_4]BF_4$
Molecular weight: 602.99



$[Cu(MIBI)_4]BF_4$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)							

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: See Attachment document

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cardiolite/ Miraluma (Technetium TC-99M Sestamibi KIT) Bristol Myers Squibb	19-785	RLD

18. STATUS: CMC APPROVABLE (See attached Review)

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	20-DEC-2006	S. Ferguson
Pharm/Tox	Not Consulted	N/A	N/A
Biopharm	Not Consulted	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
OPDRA	DMETS comments Pending	05-OCT-2006	L. Epps
Labeling	Acceptable	06-FEB-2008	C. Hoppes
EA	Categorical exclusion justified	17-AUG-2006	L. Epps
Microbiology	Acceptable	28-NOV-2007	B. Pilari

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-098

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is approvable. The review was performed by Dr. Leon A. Epps of the division of New Drug Chemistry. **See File V:\FIRMSAM\MALLINCKRODT\LTRS&REV\78098.REV1.DOC**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

TechneScan® Sestamibi and the Reference Listed Drug, Cardiolite®, are sterile, nonpyrogenic and non-radioactive kits that contain lyophilized mixtures of inactive components that, upon reconstitution with up to 5550 megabecquerels (150 mCi) Sodium Pertechnetate Tc-99m Injection, produce the radioactive drug product Technetium Tc-99m Sestamibi Injection. The amount of the radioactive drug substance, Technetium Tc-99m Sestamibi, that is formed is commensurate with the amount of radioactivity used to reconstitute each kit.

Table below lists the ingredients of the TechneScan Sestamibi kit in comparison to that in Cardiolite.

TechneScan® Sestamibi	Cardiolite®
Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0 mg	Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0 mg
Sodium Citrate Dihydrate - 2.6 mg	Sodium Citrate Dihydrate - 2.6 mg
L-Cysteine Hydrochloride Monohydrate - 1.0 mg	L-Cysteine Hydrochloride Monohydrate - 1.0 mg
Mannitol - 20 mg	Mannitol - 20 mg
Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) - 0.025 mg Stannous Chloride, Dihydrate ($SnCl_2 \cdot 2H_2O$) - 0.075 mg Tin Chloride (stannous and stannic) Dihydrate, maximum (as $SnCl_2 \cdot 2H_2O$) - 0.086 mg	Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) - 0.025 mg Stannous Chloride, Dihydrate ($SnCl_2 \cdot 2H_2O$) - 0.075 mg Tin Chloride (stannous and stannic) Dihydrate, maximum (as $SnCl_2 \cdot 2H_2O$) - 0.086 mg
pH reconstituted product is 5.0 – 6.0	pH reconstituted product is 5.0 – 6.0

B. Description of How the Drug Product is Intended to be Used

Route of Administration dosage form and strength:

The route of administration, dosage form, and strength of Mallinckrodt's TechneScan√ Sestamibi (Kit for the Preparation of Technetium Tc-99m Sestamibi Injection) are the same as those of the reference listed drug, Cardiolite√ (Kit for the Preparation of Technetium Tc-99m Sestamibi for Injection). Both Mallinckrodt's drug product and the reference listed drug are provided as reaction vials containing a nonradioactive lyophilized mixture of inactive components, which upon reconstitution with Sodium Pertechnetate Tc-99m Injection, produce the radioactive drug product, Technetium Tc-99m Sestamibi Injection. The radioactive drug product produced from either kit is a sterile, nonpyrogenic solution that may contain up to 5550 megabecquerels (150 mCi) of the radioactive drug substance Technetium Tc-99m Sestamibi in a volume of up to 3 mL and is intended solely for intravenous injection into humans. The recommended adult (70 kg) dose for administration of either radioactive drug product is 370 to 1110 megabecquerels (10 to 30 millicuries).

C. Basis for Approval Recommendation:

The CMC is approvable. The review was performed by Dr. Leon A. Epps of the division of New Drug Chemistry. See File

V:\FIRMSAM\MALLINCKRODT\LTRS&REV\78098.REV1.DOC

ANDA 78-098

TechneScan Sestamibi (Kit for the Preparation of Tc 99m Sestamibi Injection)

Tyco/Mallinckrodt

Leon A. Epps, Ph.D.

Office of New Drug Quality Assessment (DPAMS/Branch V)

CMC Review of ANDA 78-098 for the Office of Generic Drugs

The Executive Summary..... **16**

I. Recommendations 16

A. Recommendation and Conclusion on Approvability..... 16

Pending overall acceptable cGMP compliance, the ANDA is recommended for approval action from CMC perspective pending..... 16

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 16

None..... 16

III. Administrative.....17

A. Reviewer's Signature 17

B. Endorsement Block 18

C. CC Block..... 18

CHEMISTRY ASSESSMENT..... **18**

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....18

S DRUG SUBSTANCE [Cu(MIBI)4BF4, (b) (4) 18

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A APPENDICES..... 60

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A. Labeling & Package Insert..... 64

B. Environmental Assessment Or Claim Of Categorical Exclusion..... 65

Chemistry Review Data Sheet

1. ANDA 78-098

2. REVIEW 01

3. REVIEW DATE: August 17, 2006

4. REVIEWER: Leon A. Epps, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 19-785 for Cardiolite by Bristol-Myers Squibb	December 21, 1990

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original ANDA	February 1, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Tyco/Mallinckrodt Inc
Address:	675 McDonnell Boulevard P.O. Box 5840 St. Louis, MO 63134
Representative:	James W. Brodack, Ph.D. Regulatory Affairs Manager
Telephone:	314 654-3045

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Prorprietary Name: TechneScan Sestamibi

b) Non-Prorprietary Name: Technetium Tc-99m Sestamibi Injection
c) Code Name/#: 092
d) Chem. Type/Submission Priority (ONDQA only):

9. LEGAL BASIS FOR SUBMISSION: ANDA, 21 CFR 314.94

10. PHARMACOL. CATEGORY: Myocardial imaging agent

11. DOSAGE FORM: Lyophilized Powder for the Preparation of Technetium Tc99m Sestamibi Injection

12. STRENGTHS/POTENCIES: 10-30 mCi (370-1110 MBq).

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

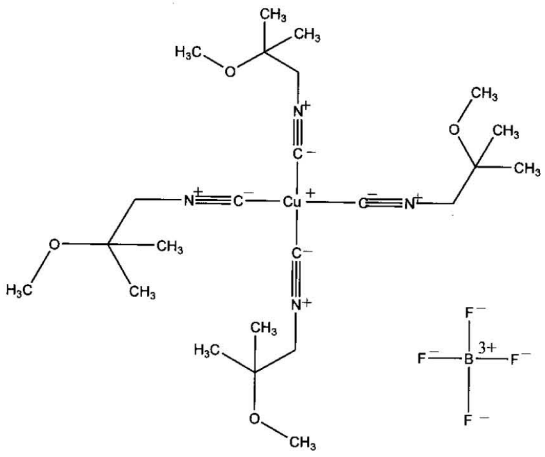
SPOTS product – Form Completed

x Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

The $[Cu(MIBI)_4]BF_4$ (where MIBI corresponds to 2-methoxyisobutylisonitrile) is the Final Intermediate that has a molecular formula of $C_{24}H_{44}N_4O_4BF_4Cu$ and a molecular weight of 602.98.

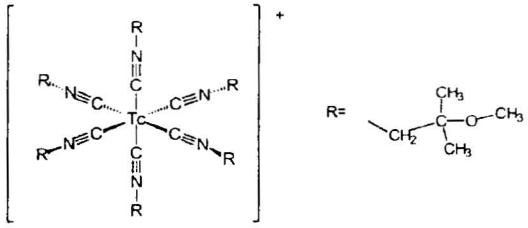
$[Cu(MIBI)_4]BF_4$ has the following chemical structure:



The Final Intermediate is the key ingredient used to form the radioactive drug substance "Technetium Tc-99m Sestamibi" in situ upon reconstitution of the kit with Sodium Pertechnetate Tc-99m as shown below.

(b) (4)

(b) (4) is the drug substance in reconstituted TechneScan Sestambi (as also in Cardiolite), the structure of which is shown as follows:



17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLET	COMMENTS
(b) (4)							

(b) (4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63, 243	Original IND

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	20-DEC-2006	S. Ferguson
Pharm/Tox	Not consulted N/A	N/A	N/A
Biopharm	Not consulted N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A (USP methods used)
OPDRA	DMETS comments pending	October 5, 2006	L. Epps
EA	Categorical exclusion justified	August 17, 2006	L. Epps
Microbiology	Acceptable	28-NOV-2007	N/A

THE CHEMISTRY REVIEW FOR ANDA 78-098

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

As of September 13, 2006, there is an overall recommendation of withhold on the CGMP inspection by the Office of Compliance. Pending resolution of the CGMP issues and an overall acceptable CGMP inspection status, the ANDA is recommended for approval action from CMC perspective. Note that item 2 on list of CMC deficiencies relates to a minor labeling change recommendation and does not affect the approvability recommendation.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance(s)

Tetrakis (2-methoxy isobutyl isonitrile) Copper (+1) tetrafluoroborate, [Cu(MIBI)$_4$]BF_4, is the Final Intermediate in the TechneScan Sestamibi (Kit for the Preparation of Technetium Tc-99m Sestamibi Injection). (b) (4) [Cu(MIBI)$_4$]BF_4 in the lyophilized kit formulation.

[Cu(MIBI)$_4$]BF_4 is isolated as a white, crystalline solid that melts at 104.2 °C with limited solubility in water. It has a molecular formula of $C_{24}H_{44}N_4O_4BF_4Cu$, molecular weight of 602.98 and its structure was elucidated from X-ray data on a single crystal and powder X-ray diffraction studies.

Each 10 mL vial of the TechneScan Sestamibi kit contains a sterile , non-pyrogenic, lyophilized mixture of 1.0 mg [Cu(MIBI)$_4$]BF_4, 0.025-0.75 mg Stannous Chloride Dihydrate, 1.0 mg L-Cysteine Hyrochloride Monohydrate, 2.6 mg Sodium Citrate Dihydrate and 20 mg D-Mannitol dissolved in an aqueous solution between pH 5.6-5.7. The lyophilized contents of the vial are stored under nitrogen at 15-25°C before and after reconstitution. Vials should be protected from light prior to reconstitution and contains no preservatives.

TechneScan Sestamibi can be reconstituted with up to 5550 MBq (150 mCi) of Sodium Pertechnetate Tc 99m Injection in a volume up to 3 mL. On reconstitution of a reaction vial with Sodium Pertechnetate Tc 99m Injection, (b) (4) .

B. Description of How the Drug Product is Intended to be Used:

TechneScan Sestamibi (Kit for the Preparation of Tc 99m Sestamibi Injection) is based on the listed drug, Cardiolite (NDA 19-785 by Bristol-Myers Squibb approved on December 21, 1990) and is indicated for diagnostic imaging of myocardial perfusion after a prescribed intravenous administration of a recommended adult (70 kg) dose of 370-1110 MBq (10-30 mCi).

The TechneScan Sestamibi kit is designed to be used by and distributed to persons licensed by the U.S. Nuclear Regulatory Commission to use byproduct material identified in Section 3 5.200 or under an equivalent license of an Agreement State.

C. Basis for Approvability or Not-Approval Recommendation:
Based upon the Initial Quality Assessment, results from the two studies that Mallinckrodt designated as "key" or critical variables were evaluated and they include: (1) order of addition of components during manufacture and (2) lyophilization parameters. In the first case, the applicant effectively demonstrates that the optimum order of addition of components during manufacture of the bulk drug substance formulation is: (b) (4)

In the second case, the applicant adequately qualified lyophilization parameters (i.e., vacuum temperature and time) to consistently produce TechneScan Sestamibi at low moisture levels of < (b) (4)% , and RCP values similar to the innovators Cardiolite.

Overall, the applicant submitted sufficient data and information to demonstrate satisfactory control over components, production processes, and the identity, strength, purity, quality of the finished drug product. However, Establishment Evaluation Requests were submitted to the Office of Compliance on March 28, 2006 for evaluation of cGMP compliance status but an overall compliance recommendation is still pending.

Overall recommendation:
From a CMC perspective, I recommend that the ANDA be approved after an overall acceptable compliance recommendation is received from Office of Compliance.

III. Administrative

A. Reviewer's Signature

Leon A. Epps, Ph.D., Reviewer ONDQA

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/s/

Yusuf A. Amin
2/25/2008 03:33:36 PM
CHEMIST

Albert Mueller
2/25/2008 03:45:00 PM
CHEMIST

Dat Doan
2/27/2008 12:21:00 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-098

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW-ADDENDUM

ANDA No.	78-098
Drug Product Name	Technetium TC-99M Sestamibi Injection Kit
Strength(s)	1.0 mg per vial
Applicant Name	Mallinckrodt, Inc
Address	672 McDonnell Boulevard, PO Box 5840, St. Louis, MO 63134
Applicant's Point of Contact	James W. Brodack, PhD, Regulatory Affairs Mgr.
Contact's Telephone Number	314-654-3045
Contact's Fax Number	314-654-8905
Original Submission Date(s)	31 January 2006
Submission Date(s) of Amendment(s) Under Review	N/A
Reviewer	Zakia R. Williams, Ph.D.
OUTCOME DECISION	**ACCEPTABLE**

ADDENDUM OF AN ABBREVIATED NEW DRUG APPLICATION (ANDA)

1. EXECUTIVE SUMMARY

This is an addendum to the Bioequivalence Review (DFS N078098 N 000 31-Jan-2006). The purpose of the addendum is to correct the provision of the CFR regulation used in the original DBE recommendations, from 21 CFR 320.22(b)(1) to 21 CFR 320.24 (b)(6).

In the original review, the firm (Mallinckrodt, Inc) submitted a waiver request of *in vivo* BE study requirements for its Technetium Tc99m Sestamibi Injection Kit, 1.0 mg per vial, comparing it to Cardiolite® Kit for the Preparation of Technetium Tc99m Sestamibi injection, manufactured by Bristol-Myers Squibb Medical Imaging, Inc.

The submission was reviewed and the waiver request was granted by the Division of Bioequivalence citing **21 CFR 320.22(b) (1)**.

Upon further review, the DBE now recommends the application be approved based on **21 CFR 320.24 (b) (6)**. The waiver citation of 21 CFR 320.22(b)(1) is considered not appropriate for this drug product.

The DBE recommendations for the test product should now read:

2. Recommendations

The Division of Bioequivalence (DBE) recommends the test product, Mallinckrodt's, Technetium Tc99m Sestamibi Injection Kit, 1.0 mg per vial, be approved based on 21 CFR § 320.24(b)(6).

ANDAs : 78-098

Reviewer: Williams, Zakia **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Technetium Tc99m Sestamibi Injection Mallinckrodt, Inc

---

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
6205	1/31/2006	Other	Addendum	0	0
				Bean Total:	0

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/s/

Zakia R Williams
8/12/2008 03:37:40 PM
BIOPHARMACEUTICS

Yih Chain Huang
8/12/2008 04:10:05 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
8/12/2008 04:38:22 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-098
Drug Product Name	Technetium TC-99M Sestamibi Injection Kit[1]
Strengths	N/A (10-30 mCi, depending upon body weight)
Applicant	Mallinckrodt, Inc.
US Contact	James W. Brodack, PhD, Regulatory Affairs Mgr.
Address	672 McDonnell Boulevard, PO Box 5840, St. Louis, MO 63134
Telephone & Facsimile	Tel.: 314-654-3045; Fax.: 314-654-8905
Clinical Site	N/A
Analytical Site	N/A
Submission Date	31 January 2006
Amendment Date(s)	N/A
Reviewer	Kristopher Bough, PhD
First Generic	Potential 1st generic

REVIEW OF AN ABBREVIATED NEW DRUG APPLICATION (ANDA)

1. EXECUTIVE SUMMARY

This is a review of a wavier request.

The firm has submitted a waiver request of in vivo bioequivalence (BE) study requirements for its Technetium TC-99M Sestamibi Injection kit, 10-30 mCi based upon 21 CFR §320.22(b)(1).

The active and inactive ingredients of the test Technetium TC-99m Sestamibi Injection kit are Q_1 and Q_2 similar to the RLD. The waiver of in vivo BE study requirements for the firm's Technetium TC-99m Sestamibi Injection kit is granted.

The application is **acceptable** without deficiencies.

[1] The kit contains a lyophilized powder for solution to be reconstituted by the patient prior to injection

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3. SUBMISSION SUMMARY

3.1. Contents of Submission

BIOEQUIVALENCE STUDY TYPE		INCLUDED	QUANTITY	COMMENTS
Waiver request		☒	1	Kit = parenteral solution reconstituted from lyophilized powder prior to injection; to be used no >6 hours before diagnostic testing
In vivo	Fasted	☐		
	Fed	☐		
In vitro dissolution		☐		
Vasoconstrictor		☐		
Pharmacodynamic		☐		
Prior Failures		☐		
Amendments		☐		

3.2. Product Information[2,3,4]

Test Product	Technetium TC-99m sestamibi injection kit, strength = N/A (10-30 mCi after reconstitution depending upon body weight)
RLD	Cardiolite® (technetium TC-99m sestamibi kit) injection, strength N/A[5]
RLD Manufacturer	Bristol Myers-Squibb
ANDA No.	19-785
ANDA Approval Date	21 December 1990
Indications	(1) Radiopharmaceutical diagnostic agent used to diagnose coronary heart disease & myocardial function; and, (2) Cancer
Adverse Effects	Taste perversion (7%), Hypotension, bradycardia, chest pain/angina (2.1%), flushing & rash, vomiting (0.1%), hypersensitivity, headache (0.2%)
Warnings	Hypersensitivity, caution with pharmacological stress
Recommended Dosing	Single i.v. injection of entire contents; strength will vary depending upon body weight between 10-30 mCi
Mechanisms of action	(1) Technetium TC-99m is a cationic complex which binds irreversibly to myocardial tissue in proportion to blood flow. (2) In addition, TC-99m is extracted from circulating blood into such areas of elevated cellular metabolism as neoplasms; accordingly, it is also indicated in the diagnosis of breast cancer and approved under the same NDA as Miraluma® (see also history below).

[2] Electronic Orange Book
[3] csi micromedix.com, Technetium TC-99M Sestamibi
[4] http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/203502.html
[5] The firm correctly references Cardiolite® and not Miraluma® as the RLD, as per the controlled correspondence with OGD as indicated in the history below

3.3. PK/PD Information[6]

Absorption	N/A (i.v. injection)
T_{max}	1 hour resting; 30 min following stress testing
Food Effect	N/A
Distribution	< 1% protein binding; uptake by spleen, gallbladder & bowel may interfere with imaging; transient uptake into liver; binds irreversibly to myocardial tissue
Metabolism	No evidence that technetium TC-99m is metabolized
Elimination	Renal = > 27%; Feces = ~33% within 48 hours; over 60% of a dose is recovered in urine/bile within 24 hours
Half-life	~6 hours

3.4. Relevant OGD History

The DBE has reviewed no ANDAs or protocols for this drug product. However, OGD did review four controls related to Technetium TC-99m Sestamibi Injection kit, including one pertaining to the present submission (control #04-715).

The OGD responded to the firm's three DBE-related questions as follows:

Question 1: It is our understanding, based on discussions with M. Shimer, that a Citizen's Petition is not necessary to have Cardiolite listed as the RLD. Please confirm the FDA will review the Orange Book and list Cardiolite as the RLD without the need for a Citizen's Petition.

Response: Though there has not yet been an RLD designated for Technetium TC-99M Sestamibi Kit, it would not be necessary for you to submit a citizen petition requesting such a designation. FDA would independently designate Cardiolite as an RLD in the next Orange Book Supplement.

Question 2: Regarding the Cardinal Health product, please confirm an ANDA is acceptable to the Agency, considering the label claim would not be altered from the RLD.

Response: An ANDA is the appropriate type of application to use in seeking approval for a generic version of Cardiolite injection. We remind you that an ANDA for Cardiolite injection must be complete before it can be received (filed). An application should contain information to show that the active ingredient is the same, the labeling is the same, that the proposed drug is bioequivalent, and other information as detailed in Section 505(j)(2)(A) of the Act and 21 CFR 314.94 regarding content and format of an abbreviated application.

[6] csi micromedix.com, Technetium TC-99M Sestamibi

Question 3: If it is agreed that the Cardinal Health product can be submitted as an ANDA and as the product will be administered intravenously, containing the same active and inactive ingredients, and in the same concentration as the RLD, the Sponsor plans to request a biowaiver in lieu of a bioequivalence study. Please confirm that this approach is acceptable to the Agency.

Response: Cardinal Health may request a waiver of the in vivo determination of bioequivalence. See 21 CFR 320.22(b)(1). If such a waiver is granted, bioequivalence would be determined through evaluation of other data in the application (e.g., comparison of active and inactive ingredients), but the in vivo assessment would not be required.

Both Cardiolite® and Miraluma® (technetium TC-99m sestamibi) Injection kit were approved under the same NDA #19-875. Both have identical formulations (see formulation below). Cardiolite® was approved 21 Dec 1990 and is indicated for cardiovascular imaging in the diagnosis of coronary heart disease. In contrast, Miraluma® was approved 23 May 1997 and is approved as a radiopharmaceutical diagnostic agent for breast cancer imaging.

3.5. Pre-Study Bioanalytical Method Validation

N/A

3.6. In Vivo Bioequivalence Studies

N/A

3.7. Formulation

Strength	10-30 mCi
Are active ingredients Q_2 identical?	Yes
Are inactive ingredients Q_1 & Q_2 identical?	Yes
If a tablet, is the product scored?	N/A
If yes, which strengths are scored?	-----
Is scoring of RLD the same as test?	-----
Is the formulation acceptable?	**ACCEPTABLE**
If not acceptable, why?	-----
Location in Appendix	Please see 5.2. Formulation below

3.8. In Vitro Dissolution

N/A

3.9. Waiver Requests

Strength	10-30 mCi
Regulation cited	21 CFR § 320.22(b)(1)
Proportional to strength tested in vivo?	N/A
Is formulation acceptable?	Yes (as above)
Is dissolution acceptable?	N/A
Waivers granted?	**WAIVER IS GRANTED**
If not granted, why?	-----

4. GENERAL REMARKS

4.1. Deficiency Comments

None.

4.2. Recommendations

The firm's test formulation for Technetium TC-99m Sestamibi Injection, 10-30 mCi (final strength is weight dependent), meets the criteria set forth in 21 CFR § 320.22 (b)(1) and is therefore bioequivalent to Cardiolite®, the RLD (NDA 19-785, 21 Dec 1990).

The waiver of the in vivo BE study for Technetium TC-99m Sestamibi Injection kit is granted.

The firm should be informed of the above recommendations.

5. APPENDICES

5.1. Individual In Vivo BE Study Review

N/A

5.2. Formulation

TechneScan® Sestamibi	**Cardiolite®**
Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0 mg	Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0 mg
Sodium Citrate Dihydrate - 2.6 mg	Sodium Citrate Dihydrate - 2.6 mg
L-Cysteine Hydrochloride Monohydrate - 1.0 mg	L-Cysteine Hydrochloride Monohydrate - 1.0 mg
Mannitol - 20 mg	Mannitol - 20 mg
Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) - 0.025 mg Stannous Chloride, Dihydrate ($SnCl_2 \cdot 2H_2O$) - 0.075 mg Tin Chloride (stannous and stannic) Dihydrate, maximum (as $SnCl_2 \cdot 2H_2O$) - 0.086 mg	Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) - 0.025 mg Stannous Chloride, Dihydrate ($SnCl_2 \cdot 2H_2O$) - 0.075 mg Tin Chloride (stannous and stannic) Dihydrate, maximum (as $SnCl_2 \cdot 2H_2O$) - 0.086 mg
pH reconstituted product is 5.0 – 6.0	pH reconstituted product is 5.0 – 6.0

Reviewer's Comments: *Both Mallinckrodt's TechneScan® Sestamibi formulation and Cardiolite®, the RLD, are supplied as reaction vials containing a non-radioactive, lyophilized mixture of excipients which upon reconstitution with sodium pertechnetate TC-99m injection solution react to produce the radioactive drug product.*

It is important to note that both Cardiolite® and Miraluma® (Technetium TC-99m Sestamibi) Injection kit were approved under the same NDA #19-875. Both have identical formulations (see formulation below). Cardiolite®, the RLD, was approved 21 Dec 1990 and is indicated for cardiovascular imaging in the diagnosis of ***coronary heart disease****. In contrast, Miraluma® was approved 23 May 1997 and is approved as a radiopharmaceutical diagnostic agent for* ***breast cancer*** *imaging. The firm references correctly Cardiolite® as the RLD.*

As per 21 CFR §320.22 (b)(1), the active and inactive ingredients of the test product are Q_1 and Q_2 the same as the RLD. All inactive ingredients are within IIG limits.

The proposed formulation is acceptable.

5.3. Dissolution Data

N/A

5.4. Consult Reviews

N/A

5.5. SAS Output

N/A

5.6. Additional Attachments

None.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDAs: 78-098 APPLICANT: Mallinckrodt, Inc.

DRUG PRODUCT: Technetium TC-99m Sestamibi Injection Kit, 10-30 mCi

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation & Research

ANDAs : 78-098

BIOEQUIVALENCE - **ACCEPTABLE** Submission Dates: 31 January 2006

1. Waiver (WAI) Outcome: **AC**
Strength: N/A (10-30 mCi, depending upon weight)

Outcome Decision: AC - Acceptable

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/s/

Kristopher Bough
11/22/2006 12:14:37 PM
BIOPHARMACEUTICS

Moheb H. Makary
11/22/2006 12:47:22 PM
BIOPHARMACEUTICS

Barbara Davit
11/22/2006 04:43:07 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-098

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review
Review for HFD-620

October 25, 2007

ANDA: 78-098

Drug Product Name
Proprietary: N/A
Non-proprietary: TechneScan Sestamibi Kit
Drug Product Classification: N/A

Review Number: #2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
10/6/2007	10/9/2007	N/A	10/19/2007

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
January 31, 2006	1	March 29, 2007

Applicant/Sponsor
Name: Mallinckrodt Inc.
Address: 675 McDonnel Blvd, St. Louis, MO 63134
Representative: James W. Brodack, Ph.D. Regulatory Affairs Manager
Telephone: 314-654-3045

Name of Reviewer: Brenda Pillari

Conclusion: The submission is **recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Minor Amendment

2. SUBMISSION PROVIDES FOR: Response to microbiology deficiencies

3. MANUFACTURING SITE:
Mallinckrodt Facility
2703 Wagner Place,
Maryland Heights, MO 63043

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Lyophilized powder in single dose 10mL glass vials, IV, 10-30mCi after reconstitution with radioactive Sodium Pertecchnetate Tc99m Injection.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: A myocardial perfusion agent.

B. SUPPORTING/RELATED DOCUMENTS:

(b) (4)

C. REMARKS:

File name: 78-098a1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –
N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –
The subject drug product is provided as a kit consisting of a 10mL reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients as lyophilized powder, closed with rubber stopper and sealed with aluminum caps.

B. Brief Description of Microbiology Deficiencies –
none identified.

C. Assessment of Risk Due to Microbiology Deficiencies –
none identified.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiology Reviewer, Brenda Pillari, Ph.D.
Microbiology Team Leader, Neal J. Sweeney, Ph.D.

C. CC Block
cc:
Field Copy

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/s/

Brenda Pillari
11/28/2007 10:35:29 AM
MICROBIOLOGIST

Bonnie McNeal
11/28/2007 10:42:55 AM
MICROBIOLOGIST
Checked for submission link only.

Neal Sweeney
11/28/2007 11:45:34 AM
MICROBIOLOGIST

Product Quality Microbiology Review
Review for HFD-620

March 29, 2007

ANDA: 78-098

Drug Product Name
Proprietary: N/A
Non-proprietary: TechneScan Sestamibi Kit
Drug Product Classification: N/A

Review Number: #1

Subject of this Review
Submission Date: January 31, 2006
Receipt Date: February 1, 2006
Consult Date: N/A
Date Assigned for Review: March 21, 2007

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: Mallinckrodt Inc.
Address: 675 McDonnel Blvd, St. Louis, MO 63134
Representative: James W. Brodack, Ph.D. Regulatory Affairs Manager
Telephone: 314-654-3045

Name of Reviewer: Brenda Pillari

Conclusion: The submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:**
Mallinckrodt Facility
2703 Wagner Place,
Maryland Heights, MO 63043

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Lyophilized powder in single dose 10mL glass vials, IV, 10-30mCi after reconstitution with radioactive Sodium Pertecchnetate Tc99m Injection.

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** A myocardial perfusion agent.

B. **SUPPORTING/RELATED DOCUMENTS:** (b) (4)

05.

C. **REMARKS:** The subject drug product consists of a non-radioactive solution as a lyophilized powder in the form of a kit, which when mixed with radioactive Sodium Pertecchnetate Tc99m Injection, produces imaging medium for use in patients.

This application is similar to ANDA (b) (4) (b) (4) .

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Executive Summary

I. Recommendations

A. Recommendation on Approvability –

The submission is **not recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –

N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –

The subject drug product is provided as a kit consisting of a 10mL reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients as lyophilized powder, closed with rubber stopper and sealed with aluminum caps.

B. Brief Description of Microbiology Deficiencies –

Incomplete Comparability protocol.

C. Assessment of Risk Due to Microbiology Deficiencies –

moderate

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiology Reviewer, Brenda Pillari, Ph.D.
Microbiology Team Leader, Neal J. Sweeney, Ph.D.

C. CC Block

cc:
Field Copy

13 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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

/s/

Brenda Pillari
4/9/2007 12:42:13 PM
MICROBIOLOGIST

Mark Anderson
4/9/2007 05:02:09 PM
MICROBIOLOGIST

Checked for correct linking

Neal Sweeney
4/10/2007 09:46:39 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-098

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-098 Applicant MALLINCKRODT, Inc.
Drug Technetium TC- 99M Sestamibi Injection Strength(s)

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 13 Aug 2008 Initials MHS	Date 9/21/08 Initials rlw

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = _____ NDA# 19-785
Patent/Exclusivity Certification: Yes ☒ No ☐
Date Checked Previously granted
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 2/1/2006, BOS=Cardiolite NDA 19-875, PIII to '100, '445, '827 and '824. ANDA ack for filing on 2/1/2006(LO dated 3/30/2006). Firm acknowledged pediatric exclusivity that attached to the '827 patent in their 5/12/08 submission. CP 08-0323 remains pending with the Agency. All patents and exclusivities have expired for the RLD. ANDA is eligible for Full Approval once the Agency responds to the pending CP.

Note: C.P. response issued 8/13/08 (FDA 2008-P-0122).

2. Project Manager, Dat Doan Team1 Review Support Branch	Date 8/8/08 Initials dd	Date _____ Initials _____

Original Rec'd date 1/31/06
Date Acceptable for Filing 2/1/06
Patent Certification (type) III
Date Patent/Exclus.expires 7/29/08
Citizens' Petition/Legal Case Yes ☒ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 12/20/06
Date of Office Bio Review 11/22/06
Date of Labeling Approv. Sum
Date of Sterility Assur. App. 11/28/07
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☒ Date 2/26/08
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement

Reviewer:	Labeling Team Leader:
Date _____	Date 9/21/08
Name/Initials _____	Name/Initials rlw/for

Comments:
Final-printed labeling (FPL) found acceptable for approval (Approval Summary dated 9/18/08).

From: Doan, Dat
Sent: Thursday, September 18, 2008 11:23 AM

To: Barlow, James T; Grace, John F
Subject: 78-098/Technetium/Mallinckrodt

Hi Jim, John:

Can I please get your endorsement for 78-098/Technetium/Mallinckrodt?

<< File: 78098.ap.labeling.summary.pdf >>

<< File: 78098.ap.letter.DOC >>

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 9/21/08
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments:N/A. There are no patents listed in the current "Orange Book" for this drug product.

5. Div. Dir./Deputy Dir. Date9/4/08
Chemistry Div. I II OR III Initials RMP
Comments:The CMC section is satisfactory based on ONDQA review.

6. Frank Holcombe **First Generics Only** Date 9/21/08
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. This ANDA was granted tentative approval on February 26, 2008.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Cardiolite Injection
Bristool Myers Squibb Pharma Company NDA 19-785

8. Peter Rickman Date 9/21/08
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐
Comments: ThisANDA was granted tentative approval on February 26, 2008. Final approval at that time was blocked by Mallinckrodt's paragraph III certification to the 827 patent that was to expire on July 29, 2008 (with the pediatric exclusivity extension). Refer to the administrative sign-off form completed at that time.

On May 12, 2008, Mallinckrodt submitted a "minor" amendment to request final aproval of this ANDA effective upon the expiration of the '827 patent on July 29, 2008 (with pediatric exclusivity extension). Minor CMC changes were also submitted at that time. Mallinckrodt's June 23, 2008 amendment addresses issues related to the USP chapter in residual solvents. Updated final-printed labeling (FPL) was submitted on July 3, and September 9, 2008 in response to a template forwarded by OGD's labeling team in response to BPCA. All CMC issues were reviewed on consult in OPS.

Final-printed lableing found acceptable for approval (Approval Summary #2) 9/18/08.

Microbiology/Sterility Assurance remains acceptable for approval per t-con in DFS dated 7/28/08.

CMC found acceptable for approval Chemistry Review #2) based upon review performed in OPS by Eldon Leutzinger, Ph.D.) 9/3/08.

OR

8. Robert L. West — Date 9/21/08
Deputy Director, OGD — Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 12/20/06 (Verified 9/21/08). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product. The agency issued a response to a Citizen Petition submitted by Bristol Myers Squibb Medical Imaging on August 13, 2008.

This first-generic ANDA is recommended for approval.

Mallinckrodt has addressed the M-54 labeling exclusivity under BPCA. This is Acceptable.

9. Gary Buehler — Date 9/21/08
Director, OGD — Initials rlw/for
Comments:First-generic approval for this drug product.
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Dat Doan — Date9/22/08
Review Support Branch — Initials dd

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
1:20pm Time notified of approval by phone
1:23pm Time approval letter faxed

FDA Notification:
9/22/08 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
9/22/08 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

EES Data for: 078098

*** Compliance Recommendations ***

App No	Doc Seq No	Date	OC Recommendation
078098	000	12/20/2006	ACCEPTABLE
078098	000	9/13/2006	WITHHOLD

*** EER Table ***

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert/ Effective Date
(b) (4)			OC RECOMMENDATION	12/20/2006	AC	12/20/2006	None
			REQUEST CANCELLED	4/7/2006	PN	3/28/2006	None
			OC RECOMMENDATION	4/7/2006	AC	4/7/2006	None
			OC RECOMMENDATION	4/7/2006	AC	4/7/2006	None
			OC RECOMMENDATION	3/28/2006	AC	3/28/2006	None
			OC RECOMMENDATION	3/28/2006	AC	3/28/2006	None
			OC RECOMMENDATION	3/28/2006	AC	3/28/2006	None

COMIS TABLE:

Comis Application Table Data for Application No: 078098

***** Note: For Enterprise Search Files you may have to click and close the new window on first use***

Back to Search Form ***COMIS Pool Reviewers*** **ES DFS Files Only** **ES - All Files** **EDR** **Additions**

Drug Name: TECHNETIUM TC -99M SESTAMIBI KIT

Potency: 10-30 M CI Dosage Form: FIJ APPL Type: N

Applicant: MALLINCKRODT

Status Code: PN Status Date: 6/24/2008 Clock Date: 2/1/2006 USP: N Org: 600

Therapeutic Drug Class: RADIOACTIVE DIAGNOSTIC AGENTS

Patent Certification: 3 Patent Expiration Date: PEPFAR:

Incom Doc Type		*Supp Mod Type*			*Decision Code*						
N *Volume Locator*	000		1/31/2006	2/1/2006	TA	2/26/2008	PN	6/24/2008	1	2789094	5/14/2008
N *Volume Locator*	000	AC	10/6/2007	10/9/2007	TA	2/26/2008				3167291	
N *Volume Locator*	000	AF	12/14/2007	12/17/2007	TA	2/26/2008				3882091	
N *Volume Locator*	000	AF	1/17/2008	1/18/2008	TA	2/26/2008				3895853	
N *Volume Locator*	000	AM	5/12/2008	5/14/2008	OP	5/14/2008				3954549	

N ***Volume Locator***	000	AM	6/23/2008	6/24/2008	OP	6/24/2008	3973327
N ***Volume Locator***	000	AF	7/3/2008	7/8/2008	OP	7/8/2008	3980051
N ***Volume Locator***	000	AF	9/9/2008	9/10/2008	OP	9/10/2008	4012076
N ***Volume Locator***	000	XP	9/9/2008	9/10/2008	CL	9/10/2008	4012079

Comis Document Table Data

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 019785 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
019785	001	4885100	Sep 11, 2007				
019785	001	4988827	Jan 29, 2008				
019785	001	4988827*PED	Jul 29, 2008				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
019785	**001**	**PED**	**Oct 30, 2011**
019785	**001**	**M-54**	**Apr 30, 2011**

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page

Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through August, 2008

Patent and Generic Drug Product Data Last Updated: September 19, 2008

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

/s/

Dat Doan

9/22/2008 01:48:28 PM

9/12 final label print / exclusivity statement update

COVIDIEN

September 9, 2008

ORIG AMENDMENT

N- 000-AF

N- 000- XP

OFFICE OF GENERIC DRUGS
CDER/FDA (HFD-600)
Attn: Document Room E-150
7500 Standish Place
Rockville, MD 20855

Re: MINOR AMENDMENT – LABELING & PATENT CERTIFICATION UPDATE; Amendment 7 to Original Abbreviated New Drug Application # 078098 for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection

Dear Sir/Madam:

On January 31, 2006, Mallinckrodt Inc. submitted an original Abbreviated New Drug Application (ANDA) in electronic format pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.

Mallinckrodt received two deficiency letters during the review of ANDA 78-098, one with Microbiology deficiencies received by fax on April 19, 2007, and the second with labeling deficiencies received by fax on April 23, 2007. Responses to these deficiencies were submitted on October 6, 2007, as Amendment 1 to this application.

On November 29, 2007, Mallinckrodt received a second Labeling Deficiency letter by fax dated November 28, 2007. The response to this deficiency letter was submitted on December 14, 2007, as Amendment 2 to this application.

On January 15, 2008, Mallinckrodt received a third Labeling Deficiency letter by fax. The response to this deficiency letter was submitted on January 17, 2008, as Amendment 3 to this application.

On February 26, 2008, the Agency completed their review and issued a tentative approval for this application. Final approval was not issued due to a period of pediatric exclusivity that was granted to the Reference Listed Drug, Cardiolite, in January 2008. The patent listed in Mallinckrodt's Paragraph III certification in ANDA 78-098, U.S. Patent No. 4,988,827, received an additional six-month period of marketing exclusivity which is scheduled to expire on July 29, 2008.

On May 12, 2008, Mallinckrodt Inc. submitted Amendment 4 to this application to request the Agency to reactivate the application and issue final approval on July 29, 2008, on the basis of the above tentative approval and the expiration of U.S. Patent No. 4,988,827 (with pediatric exclusivity) on July 29, 2008.

RECEIVED
SEP 10
OGD

675 McDonnell Boulevard
Hazelwood, MO
63042
314-654-2000 [T]

On June 23, 2008, Mallinckrodt Inc. submitted Amendment 5 to this application to provide information necessary to demonstrate control of residual solvents for the drug substance and excipients used in the manufacture of the drug product. This amendment was in response to the May 27, 2008, notification from the Office of Generic Drugs to industry regarding the compliance of all ANDAs with USP <467> Residual Solvents effective July 1, 2008.

On April 30, 2008, a labeling supplement to the Reference Listed Drug NDA was approved by the Agency. The updated labeling, which became available on the FDA web site on June 19, contained information relative to the pediatric population and was reformatted according to the Physician Labeling Rule. Mallinckrodt revised the labeling text in ANDA 78-098 to contain this information and submitted it as Amendment 6 on July 3, 2008.

The Agency notified Mallinckrodt on August 5, 2008, that additional revisions to our labeling text would be required due to marketing exclusivity granted to the innovator of the Reference Listed Drug on the basis of the pediatric trial information added to their approved labeling. On September 8, 2008, the Agency provided the labeling text changes to Mallinckrodt via e-mail. The revised labeling text for the Kit for the Preparation of Technetium Tc 99m Sestamibi Injection, including final printed labeling, is hereby submitted as Amendment 7 to this application.

An updated patent certification is also provided in this amendment to reflect the marketing exclusivity that was recently listed in the Orange Book for the Reference Listed Drug.

This Amendment is provided in electronic format in addition to the following paper documents which contain original signatures: FDA Form 356h, cover letter and patent certification statement. A printed copy of the contents of the index-md5.txt file is included as an appendix to this cover letter in accordance with the ICH eCTD specification. The electronic submission is being provided on one (1) CD-ROM disk and is approximately 3 megabytes (MB) in size. This application has been organized according to the International Conference on Harmonization (ICH) specification for the electronic Common Technical Document (eCTD), Version 3.2, and the April 2006 Guidance for Industry on *Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

Mallinckrodt Inc. certifies that the files contained in the above electronic submission are virus free and have been checked with McAfee VirusScan Enterprise, program version 8.5i.

The point of contact for this electronic application is James W. Brodack, Ph.D., Director, Imaging Solutions Regulatory Affairs, (314) 654-3045 (voice), (314) 654-3344 (fax).

Sincerely,

James W. Brodack

James W. Brodack, Ph.D.
Director, Imaging Solutions Regulatory Affairs

JEFFREY S. BOONE, J.D.
Vice President, Intellectual Property

COVIDIEN

2008 September 9

SECOND REVISED
PATENT AND EXCLUSIVITY CERTIFICATION
Kit for the Preparation of Technetium Tc99m Sestamibi Injection
ANDA 78-098

The applicant makes the following certifications in connection with its Abbreviated New Drug Application identified above. These certifications are based on information found in the current edition of *Approved Drug Products with Therapeutic Equivalence Evaluations.*

Paragraph II Certification
[21 USC 355(j)(2)(A)(vii)(II) and 21 CFR 314.94(a)(12)(i)(A)(2)]

In the opinion of the applicant and to the best of its knowledge, the following listed patent(s) have expired:

US 4,885,100 expired 2007 Sep 11
US 4,988,827 expired 2008 Jul 29 (including a pediatric extension)

Exclusivity Statement [21 CFR 314.94(a)(3)(ii)]

According to information published in the list, the reference listed drug is entitled to the following period of marketing exclusivity:

M-54 "INFORMATION FROM PEDIATRIC STUDIES ADDED TO LABEL", expires 2011 Oct 30 (including a pediatric extension)

Mallinckrodt Inc.

by:

Jeffrey S. Boone, J.D.
Vice President, Intellectual Property

675 MCDONNELL BLVD.
HAZELWOOD, MO
63042

314-654-8955 [T]
314-654-3156 [F]

RECORD OF TELEPHONE CONVERSATION

Background Information:
On July 10, 2008, Mallinckrodt provided a reformatted version of section 1.11.1 from amendment #4 originally submitted on June 23, 2008.

On July 11, 2008, the OGD Microbiologist, Brenda Pillari, PhD, identified a number of changes in the batch record that would require a Microbiology review of (b) (4) Additionally, a change to their endotoxin testing procedure was mentioned. Although these changes were submitted and approved in a comparability protocol, a significant microbiology review of the data is still required (via supplement submission from the applicant).

Telephone Conversation:
On July 28, 2008, Dr. Brenda Pillari (Microbiology Team Leader at the FDA) and Kun Shen (Microbiology Project Manager at the FDA) called Dr. James Broadck (Director of Imaging Solution Regulatory Affair at Mallinckrodt) to discuss these changes. In the discussion, Dr. Brodack stated that the proposed changes were submitted earlier in a comparability protocol, which has been approved by the FDA. Reason to enlist the changes in the June 23 amendment is that Mallinckrodt has been utilizing this format in their documentation procedures (the new equipment must be listed in the batch record for future use). Dr. Brodack also committed that no changes will take place until the FDA fully approve the changes via supplement approval in the future. Dr. Pillari concurred with the firm's explanation, and confirmed the approval of the comparability protocol mentioned during the conversation. In conclusion, Dr. Pillari agrees that no action is indicated for the June 23 amendment from the microbiology team.

DATE
7/28/08

ANDA NUMBER
78-098

TELECON

INITIATED BY
MADE
_ APPLICANT/ _ BY
SPONSOR TELE.

X FDA _ IN
PERSON

PRODUCT NAME
Kit for the Preparation of Technetium Tc99m Sestamibi Injection

FIRM NAME
Mallinckrodt

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Dr. James Broadck, Director of Imaging Solution Regulatory Affairs

TELEPHONE NUMBER

SIGNATURE

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

/s/

Kun Shen

8/12/2008 11:40:40 AM

MICROBIOLOGIST

ANDA: 78-098
Firm: Mallinkrodt Inc.

Drug: Technetium TC -99M Sestamibi Kit
Classification of Drug: Radiopharmaceutical

Desired Completion Date: High Priority due to patent expiration July 23, 2008

Hi ONDQA Team:

I sent in a consult request in June concerning ANDA 78-098 asking for a review of submission dated May 12, 2008.

At this time, I'd like to request that you ALSO please review submission dated June 23, 2008.

Please cc Ben Danso (ben.danso@fda.hhs.gov) when checking the review into DFS.

Thank you very much for your help.

Dat Doan
Office of New Drugs
Project Manager, Chemistry Team 1
Dat.doan@fda.hhs.gov

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

/s/

Dat Doan
7/1/2008 12:47:50 PM
CSO

Benjamin Danso
7/8/2008 07:36:37 AM
CSO

COVIDIEN

July 3, 2008

OFFICE OF GENERIC DRUGS
CDER/FDA (HFD-600)
Attn: Document Room E-150
7500 Standish Place
Rockville, MD 20855

N/A
ORIG AMENDMENT

Re: MINOR AMENDMENT – LABELING UPDATE; Amendment 6 to Original Abbreviated New Drug Application # 078098 for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection

Dear Sir/Madam:

On January 31, 2006, Mallinckrodt Inc. submitted an original Abbreviated New Drug Application (ANDA) in electronic format pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.

Mallinckrodt received two deficiency letters during the review of ANDA 78-098, one with Microbiology deficiencies received by fax on April 19, 2007, and the second with labeling deficiencies received by fax on April 23, 2007. Responses to these deficiencies were submitted on October 6, 2007, as Amendment 1 to this application.

On November 29, 2007, Mallinckrodt received a second Labeling Deficiency letter by fax dated November 28, 2007. The response to this deficiency letter was submitted on December 14, 2007, as Amendment 2 to this application.

On January 15, 2008, Mallinckrodt received a third Labeling Deficiency letter by fax. The response to this deficiency letter was submitted on January 17, 2008, as Amendment 3 to this application.

On February 26, 2008, the Agency completed their review and issued a tentative approval for this application. Final approval was not issued due to a period of pediatric exclusivity that was granted to the Reference Listed Drug, Cardiolite, in January 2008. The patent listed in Mallinckrodt's Paragraph III certification in ANDA 78-098, U.S. Patent No. 4,988,827, received an additional six-month period of marketing exclusivity which is scheduled to expire on July 29, 2008.

On May 12, 2008, Mallinckrodt Inc. submitted Amendment 4 to this application to request the Agency to reactivate the application and issue final approval on July 29, 2008, on the

675 McDonnell Boulevard
Hazelwood, MO
63042

314-654-2000 [T]

basis of the above tentative approval and the expiration of U.S. Patent No. 4,988,827 (with pediatric exclusivity) on July 29, 2008.

On June 23, 2008, Mallinckrodt Inc. submitted Amendment 5 to this application to provide information necessary to demonstrate control of residual solvents for the drug substance and excipients used in the manufacture of the drug product. This amendment was in response to the May 27, 2008, notification from the Office of Generic Drugs to industry regarding the compliance of all ANDAs with USP <467> Residual Solvents effective July 1, 2008.

On April 30, 2008, a labeling supplement to the Reference Listed Drug NDA was approved by the Agency. The updated labeling, which became available on the FDA web site on June 19, contained information relative to the pediatric population and was reformatted according to the Physician Labeling Rule. Mallinckrodt has revised the labeling text in ANDA 78-098 according to the approved RLD labeling and is hereby submitting the updated information as Amendment 6 to this application.

This Amendment is provided in electronic format in addition to the following paper documents which contain original signatures: FDA Form 356h and the cover letter. A printed copy of the contents of the index-md5.txt file is included as an appendix to this cover letter in accordance with the ICH eCTD specification. The electronic submission is being provided on one (1) CD-ROM disk and is approximately 36 megabytes (MB) in size. This application has been organized according to the International Conference on Harmonization (ICH) specification for the electronic Common Technical Document (eCTD), Version 3.2, and the April 2006 Guidance for Industry on *Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

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Sincerely,

James W. Brodack

James W. Brodack, Ph.D.
Director, Imaging Solutions Regulatory Affairs

enc.

COVIDIEN

June 23, 2008

OFFICE OF GENERIC DRUGS
CDER/FDA (HFD-600)
Attn: Document Room E-150
7500 Standish Place
Rockville, MD 20855

N-000-AM

Re: MINOR AMENDMENT – COMPLIANCE WITH USP <467> RESIDUAL SOLVENT REQUIREMENT; Amendment 5 to Original Abbreviated New Drug Application # 078098 for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection

Dear Sir/Madam:

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675 McDonnell Boulevard
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63042
314-654-2000 [T]

On May 12, 2008, Mallinckrodt Inc. submitted Amendment 4 to this application to request the Agency to reactivate the application and issue final approval on July 29, 2008, on the basis of the above tentative approval and the expiration of U.S. Patent No. 4,988,827 (with pediatric exclusivity) on July 29, 2008.

On May 27, 2008, the Office of Generic Drugs issued notification to industry regarding the compliance with USP <467> Residual Solvents for all ANDAs starting July 1, 2008. Mallinckrodt Inc. hereby submits Amendment 5 to this application to contain the information necessary to demonstrate control of residual solvents for the drug substance and excipients used in the manufacture of the drug product. Mallinckrodt Inc. notes that at the time of tentative approval, the drug substance and several excipients described in the application already met the requirement for the control of residual solvents. This amendment provides information to demonstrate the control of residual solvents for the remaining excipients used in the drug product manufacture. In addition to the above documentation, this amendment also includes chemistry, manufacturing and control information that has been updated relative to that provided in the application by the time of tentative approval. Section 1.11.1 contains a list of the sections containing updated information in Module 3.

This Amendment is provided in electronic format in addition to the following paper documents which contain original signatures: FDA Form 356h, cover letter and field copy certification. A printed copy of the contents of the index-md5.txt file is included as an appendix to this cover letter in accordance with the ICH eCTD specification. The electronic submission is being provided on one (1) CD-ROM disk and is approximately 6 megabytes (MB) in size. This application has been organized according to the International Conference on Harmonization (ICH) specification for the electronic Common Technical Document (eCTD), Version 3.2, and the April 2006 Guidance for Industry on *Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

Mallinckrodt Inc. certifies that the files contained in the above electronic submission are virus free and have been checked with McAfee VirusScan Enterprise, program version 8.5i.

The point of contact for this electronic application is James W. Brodack, Ph.D., Director, Imaging Solutions Regulatory Affairs, (314) 654-3045 (voice), (314) 654-3344 (fax).

Sincerely,

James W. Brodack

James W. Brodack, Ph.D.
Director, Imaging Solutions Regulatory Affairs

enc.

COVIDIEN

July 3, 2008

OFFICE OF GENERIC DRUGS
CDER/FDA (HFD-600)
Attn: Document Room E-150
7500 Standish Place
Rockville, MD 20855

N/A
ORIG AMENDMENT

Re: MINOR AMENDMENT – LABELING UPDATE; Amendment 6 to Original Abbreviated New Drug Application # 078098 for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection

Dear Sir/Madam:

On January 31, 2006, Mallinckrodt Inc. submitted an original Abbreviated New Drug Application (ANDA) in electronic format pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.

Mallinckrodt received two deficiency letters during the review of ANDA 78-098, one with Microbiology deficiencies received by fax on April 19, 2007, and the second with labeling deficiencies received by fax on April 23, 2007. Responses to these deficiencies were submitted on October 6, 2007, as Amendment 1 to this application.

On November 29, 2007, Mallinckrodt received a second Labeling Deficiency letter by fax dated November 28, 2007. The response to this deficiency letter was submitted on December 14, 2007, as Amendment 2 to this application.

On January 15, 2008, Mallinckrodt received a third Labeling Deficiency letter by fax. The response to this deficiency letter was submitted on January 17, 2008, as Amendment 3 to this application.

On February 26, 2008, the Agency completed their review and issued a tentative approval for this application. Final approval was not issued due to a period of pediatric exclusivity that was granted to the Reference Listed Drug, Cardiolite, in January 2008. The patent listed in Mallinckrodt's Paragraph III certification in ANDA 78-098, U.S. Patent No. 4,988,827, received an additional six-month period of marketing exclusivity which is scheduled to expire on July 29, 2008.

On May 12, 2008, Mallinckrodt Inc. submitted Amendment 4 to this application to request the Agency to reactivate the application and issue final approval on July 29, 2008, on the

675 McDonnell Boulevard
Hazelwood, MO
63042

314-654-2000 [T]

COVIDIEN

May 12, 2008

ORIG AMENDMENT

U/Am

OFFICE OF GENERIC DRUGS
CDER/FDA (HFD-600)
Attn: Document Room E-150
7500 Standish Place
Rockville, MD 20855

Re: MINOR AMENDMENT – FINAL APPROVAL REQUESTED; Amendment 4 to Original Abbreviated New Drug Application # 078098 for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection

Dear Sir/Madam:

On January 31, 2006, Mallinckrodt Inc. submitted an original Abbreviated New Drug Application (ANDA) in electronic format pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.

Mallinckrodt received two deficiency letters during the review of ANDA 78-098, one with Microbiology deficiencies received by fax on April 19, 2007, and the second with labeling deficiencies received by fax on April 23, 2007. Responses to these deficiencies were submitted on October 6, 2007, as Amendment 1 to this application.

On November 29, 2007, Mallinckrodt received a second Labeling Deficiency letter by fax dated November 28, 2007. The response to this deficiency letter was submitted on December 14, 2007, as Amendment 2 to this application.

On January 15, 2008, Mallinckrodt received a third Labeling Deficiency letter by fax. The response to this deficiency letter was submitted on January 17, 2008, as Amendment 3 to this application.

On February 26, 2008, the Agency completed their review and issued a tentative approval for this application. Final approval was not issued due to a period of pediatric exclusivity that was granted to the Reference Listed Drug, Cardiolite, in January 2008. The patent listed in Mallinckrodt's Paragraph III certification in ANDA 78-098, U.S. Patent No. 4,988,827, received an additional six-month period of marketing exclusivity which is scheduled to expire on July 29, 2008.

Mallinckrodt Inc. hereby submits Amendment #4 to ANDA 78-098 per 21 CFR 314.120 to request that the Agency reactivate the application and issue final approval on July 29, 2008.

675 McDonnell Boulevard
Hazelwood, MO
63042

314-654-2000 [T]

The regulatory basis for this request is:

1. Tentative approval of ANDA 78-098 was issued on February 26, 2008. In this letter, the Agency indicated that they had completed the review of this application and based upon the information presented to date concluded that the drug is safe and effective for use as recommended in the submitted labeling. A copy of the tentative approval letter is provided as an attachment to this cover letter.

2. As a result of pediatric exclusivity being granted to the Reference Listed Drug, Cardiolite, U.S. Patent No. 4,988,827, subject of Mallinckrodt's Paragraph III certification in ANDA 78-098, is currently due to expire (with pediatric exclusivity) on July 29, 2008. An updated patent certification is provided in this application in Section 1.3.5.2.

In addition to the above documentation, this amendment also includes chemistry, manufacturing and control information that has been updated relative to that provided in the application by the time of tentative approval. Section 1.11.1 contains a list of the sections containing updated information in Module 3.

No changes have been made to the final printed labeling that was provided in Amendment 3 to ANDA 78-098. On May 7, 2008, the Agency provided notification on their web site that a labeling supplement was approved for the Reference Listed Drug (April 30, 2008) with an approval type "Patient Population Altered". Mallinckrodt presumes this labeling supplement is related to the pediatric exclusivity granted to Cardiolite in January 2008 and that any information relating to pediatric use may be restricted to the Cardiolite labeling for a period of time. Mallinckrodt therefore requests that the Agency grant final approval to Mallinckrodt's Kit for the Preparation of Technetium Tc 99m Sestamibi Injection on the basis of the labeling submitted to the tentatively approved application.

This Amendment is provided in electronic format in addition to the following paper documents which contain original signatures: FDA Form 356h, cover letter, field copy certification and patent certification. A printed copy of the contents of the index-md5.txt file is included as an appendix to this cover letter in accordance with the ICH eCTD specification. The electronic submission is being provided on one (1) CD-ROM disk and is approximately 20 megabytes (MB) in size. This application has been organized according to the International Conference on Harmonization (ICH) specification for the electronic Common Technical Document (eCTD), Version 3.2, and the April 2006 Guidance for Industry on *Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

Mallinckrodt Inc. certifies that the files contained in the above electronic submission are virus free and have been checked with McAfee VirusScan Enterprise, program version 8.5i.

The point of contact for this electronic application is James W. Brodack, Ph.D., Director, Imaging Solutions Regulatory Affairs, (314) 654-3045 (voice), (314) 654-3344 (fax).

Sincerely,

James W. Brodack

James W. Brodack, Ph.D.
Director, Imaging Solutions Regulatory Affairs

enc.

COVIDIEN

January 17, 2008

OFFICE OF GENERIC DRUGS
CDER/FDA (HFD-600)
Attn: Document Room E-150
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

Re: MINOR AMENDMENT – RESPONSE TO LABELING DEFICIENCIES; Amendment 3 to Original Abbreviated New Drug Application # 078098 for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection

Dear Sir/Madam:

On January 31, 2006, Mallinckrodt Inc. submitted an original Abbreviated New Drug Application (ANDA) in electronic format pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.

Mallinckrodt received two deficiency letters during the review of ANDA 78-098, one with Microbiology deficiencies received by fax on April 19, 2007, and the second with labeling deficiencies received by fax on April 23, 2007. Responses to these deficiencies were submitted on October 6, 2007, as Amendment 1 to this application.

On November 29, 2007, Mallinckrodt received a second Labeling Deficiency letter by fax dated November 28, 2007. The response to this deficiency letter was submitted on December 14, 2007, as Amendment 2 to this application.

On January 15, 2008, Mallinckrodt received a third Labeling Deficiency letter by fax. The deficiency observations are provided in Section 1.11.1 of this amendment followed by Mallinckrodt's response in bold. A copy of this deficiency letter is also included in that section.

Mallinckrodt Inc. herby submits Amendment #3 to ANDA 78-098 per 21 CFR 314.120 to provide the following documents in response to the above communication:

- Responses to the Labeling Deficiency letter dated January 15, 2008
- Electronic versions of Final Printed Labeling and Structured Product Labeling for the drug product

RECEIVED
JAN 18 2008
OGD

675 McDonnell Boulevard
Hazelwood, MO
63042
314-654-2000 [T]

This Amendment is provided in electronic format in addition to the following paper documents which contain original signatures: cover letter and the FDA Form 356h. A printed copy of the contents of the index-md5.txt file is included as an appendix to this cover letter in accordance with the ICH eCTD specification. The electronic submission is being provided on one (1) CD-ROM disk and is approximately 2 megabytes (MB) in size. This application has been organized according to the International Conference on Harmonization (ICH) specification for the electronic Common Technical Document (eCTD), Version 3.2, and the April 2006 Guidance for Industry on *Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

Mallinckrodt Inc. certifies that the files contained in the above electronic submission are virus free and have been checked with McAfee VirusScan Enterprise, program version 8.5i.

The point of contact for this electronic application is James W. Brodack, Ph.D., Regulatory Affairs Manager, (314) 654-3045 (voice), (314) 654-3344 (fax).

Sincerely,

James W. Brodack

James W. Brodack, Ph.D.
Director, Imaging Solutions Regulatory Affairs

enc.

COVIDIEN

May 12, 2008

ORIG AMENDMENT

U/Am

OFFICE OF GENERIC DRUGS
CDER/FDA (HFD-600)
Attn: Document Room E-150
7500 Standish Place
Rockville, MD 20855

Re: MINOR AMENDMENT – FINAL APPROVAL REQUESTED; Amendment 4 to Original Abbreviated New Drug Application # 078098 for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection

Dear Sir/Madam:

On January 31, 2006, Mallinckrodt Inc. submitted an original Abbreviated New Drug Application (ANDA) in electronic format pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.

Mallinckrodt received two deficiency letters during the review of ANDA 78-098, one with Microbiology deficiencies received by fax on April 19, 2007, and the second with labeling deficiencies received by fax on April 23, 2007. Responses to these deficiencies were submitted on October 6, 2007, as Amendment 1 to this application.

On November 29, 2007, Mallinckrodt received a second Labeling Deficiency letter by fax dated November 28, 2007. The response to this deficiency letter was submitted on December 14, 2007, as Amendment 2 to this application.

On January 15, 2008, Mallinckrodt received a third Labeling Deficiency letter by fax. The response to this deficiency letter was submitted on January 17, 2008, as Amendment 3 to this application.

On February 26, 2008, the Agency completed their review and issued a tentative approval for this application. Final approval was not issued due to a period of pediatric exclusivity that was granted to the Reference Listed Drug, Cardiolite, in January 2008. The patent listed in Mallinckrodt's Paragraph III certification in ANDA 78-098, U.S. Patent No. 4,988,827, received an additional six-month period of marketing exclusivity which is scheduled to expire on July 29, 2008.

Mallinckrodt Inc. hereby submits Amendment #4 to ANDA 78-098 per 21 CFR 314.120 to request that the Agency reactivate the application and issue final approval on July 29, 2008.

675 McDonnell Boulevard
Hazelwood, MO
63042

314-654-2000 [T]

Telephone Fax

ANDA 78-098

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8988)

TO: Mallinckrodt Inc. TEL: 314-654-3045

ATTN: James W. Brodack, Ph.D. FAX: 314-654-3344

FROM: Charlie Hoppes

:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Kit for Preparation of Technetium Tc 99m Sestamibi Injection.

Pages (including cover and signature pate): __3__

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING #3
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-098 Date of Submission: December 14, 2007

Applicant's Name: Mallinckrodt Inc.

Established Name: Kit for Preparation of Technetium Tc 99m Sestamibi Injection

---

Labeling Deficiencies:

A. GENERAL COMMENT

1. We acknowledge your comments that you withdrawal proposal of the proprietary name, "Sestamibi" and that you intend to market with the established name at this time. Although the Division of Medication Errors and Technical Support (DMETS) has been notified, we expect that they will finish their review and provide comments on labels and labeling as well as comments regarding mitigation of error potential with respect to the established name of this product. We will forward any DMETS comments when they become available to us.

2. We acknowledge your comment, following discussions with CDR Koung Lee, regarding a commitment to provide SPL labeling within 14 days post approval of this application.

B. CONTAINER LABEL

If space permits, add the statement, "Use within 6 hours of reconstitution."

Submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

John Grace
1/15/2008 12:24:31 PM
for Wm Peter Rickman

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-098 Applicant MALLINCKRODT, Inc.
Drug Technetium TC- 99M Sestamibi Injection Strength(s)

APPROVAL ☐ **TENTATIVE APPROVAL** ☒ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer**
Chief, Reg. Support Branch
Date 8 Jan 2008 Date 2/26/08
Initials mhs Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)
Pediatric Exclusivity System
RLD = _____ NDA# 19-785
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval
Comments: Firm provided PIII certs to the '100, '445, '827 and '824 patents. Only the '827 patent remains unexpired and it expires on 1/29/2008. On 10/18/2007 Debbie AVant of the Peds team sent an e-mail to members of OGD informing them that pediatric studies had been submitted. To date OGD has not been informed whether Pediatric exclusivity will be granted to the Cardiolite NDA. Therefore OGD will not be able to issue a full approval of this ANDA until such a time that pediatric exclusivity is denied. If pediatric exclusivity is granted to BMS then this ANDA will not be eligible for Full Approval until 7/29/2008. OGD must await the evaluation of the peds study before taking action. If on 1/29/2008 OGD has not been informed of the pediatric exclusivity determination then OGD may only TA this ANDA.

Update 2/21/08: Ped exclusivity granted to NDA 19-785. Ped exclusivity has attached to the '827 patent with the exclusivity expiring on 7/29/2008. ANDA is now eligible for TA only.

2. **Project Manager**, Dat Doan Team1
Review Support Branch
Date 1/8/08 Date _____
Initials dd Initials _____

Original Rec'd date 1/31/06
Date Acceptable for Filing 2/1/06
Patent Certification (type) III
Date Patent/Exclus.expires 7/29/08
Citizens' Petition/Legal Case Yes ☐ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☐
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 12/20/06
Date of Office Bio Review 11/22/06
Date of Labeling Approv. Sum
Date of Sterility Assur. App. 11/28/07
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Acceptable Bio review tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer:
Date _____
Name/Initials _____

Labeling Team Leader:
Date 2/26/08
Name/Initials rlw/for

Comments:

From: Grace, John F
Sent: Wednesday, February 20, 2008 10:36 AM
To: Hoppes, Charles V; Doan, Dat
Cc: Barlow, James T
Subject: RE: 78098/Mallinckrodt/Technetium

concur

From: Hoppes, Charles V
Sent: Wednesday, February 20, 2008 6:55 AM
To: Doan, Dat
Cc: Grace, John F; Barlow, James T
Subject: RE: 78098/Mallinckrodt/Technetium

Dat,

Labeling still OK for TA…no changes for the RLD since the approval summary.

Charlie

From: Doan, Dat
Sent: Tuesday, February 19, 2008 3:00 PM
To: Hoppes, Charles V
Cc: Grace, John F
Subject: 78098/Mallinckrodt/Technetium

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 2/26/08
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments:N/A. Mallinckrodt has made a paragraph III certification to the '827 patent due to expire on July 29, 2008 (with pediatric exclusivity extension).

5. Div. Dir./Deputy Dir. Date 2/25/08
Chemistry Div. I II OR III Initials RMP
Comments:An administrative review done by Yusuf is satisfactory for TA. However, before the AP a follow-up will needed for consult on OPDRA because the DMETS comments are still pending. However, Mallinckrodt is not pursuing a proprietary name at this time.

6. Frank Holcombe **First Generics Only** Date 2/26/08
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
Waived - Application was reviewed in ONDQA.

7. Vacant Date _____
Deputy Dir., DLPS Initials _____
RLD = Cardiolite (Kit for the Preparation of Technetium Tc 99m Sestamibi for Injection
Bristol Myers Squibb Pharma Co. NDA 19-785

8. Peter Rickman Date 2/26/08
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐
Comments:Bioequivalence waiver granted under 21 CFR 320.22(b)(1). Drug product is "Q&Q" to the RLD. Office-level bio endorsed 11/22/06.

Microbiology/Sterility Assurance found acceptable (Micro Review #2) 11/28/07.

Labeling found acceptable for tentative approval 2/6/08. DMETS consult for a proprietary name is pending at this time. However, Mallinckrodt is not seeking the proprietary name for approval.

CMC found acceptable for approval. CMC reviewed in ONDQA by Leon Epps, Ph.D. Chemistry Review #1.

OR

8. Robert L. West Date 2/26/08
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments:Acceptable EES dated 12/20/06 (Verified 2/26/08). No "OAI" Alerts noted.

Mallinckrodt made a paragraph III certification to the '827 patent due to expire on July 29, 2008 (with pediatric extension). There are no other patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for tentative approval.

9. Gary Buehler Date 2/26/08
Director, OGD Initials rlw/for
Comments:First-generic tentative approval.
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Dat Doan Date_____
Review Support Branch Initials _____

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
2:30 pm Time notified of approval by phone
2:35 pm Time approval letter faxed

FDA Notification:
2/26/08 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
2/26/08 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

EES Data for: 078098

*** Compliance Recommendations ***

App No	Doc Seq No	Date	OC Recommendation
078098	000	12/20/2006	ACCEPTABLE
078098	000	9/13/2006	WITHHOLD

*** EER Table ***

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert/ Effective Date
(b) (4)			OC RECOMMENDATION	12/20/2006	AC	12/20/2006	None
			REQUEST CANCELLED	4/7/2006	PN	3/28/2006	None
			OC RECOMMENDATION	4/7/2006	AC	4/7/2006	None
			OC RECOMMENDATION	4/7/2006	AC	4/7/2006	None
			OC RECOMMENDATION	3/28/2006	AC	3/28/2006	None
			OC RECOMMENDATION	3/28/2006	AC	3/28/2006	None
			OC RECOMMENDATION	3/28/2006	AC	3/28/2006	None

COMIS TABLE:

Comis Application Table Data for Application No: 078098

***** Note: For Enterprise Search Files you may have to click and close the new window on first use***

Back to Search Form ***COMIS Pool Reviewers*** **ES DFS Files Only** **ES - All Files** **EDR**

Drug Name: TECHNETIUM TC -99M SESTAMIBI KIT

Potency: 10-30 M CI Dosage Form: INJ APPL Type: N

Applicant: MALLINCKRODT

Status Code: PN Status Date: 10/9/2007 Clock Date: 2/1/2006 USP: N Org: 600

Therapeutic Drug Class: RADIOACTIVE DIAGNOSTIC AGENTS

Patent Certification: 3 Patent Expiration Date: PEPFAR:

Incom Doc Type		*Supp Mod Type*			*Decision Code*		*Status code*				
N *Volume Locator*	000		1/31/2006	2/1/2006	OP	2/1/2006	PN	10/9/2007	10	2789094	2/1/2006
N *Volume Locator*	000	AC	10/6/2007	10/9/2007	OP	10/9/2007				3167291	
N *Volume Locator*	000	AF	12/14/2007	12/17/2007	OP	12/17/2007				3882091	
N *Volume Locator*	000	AF	1/17/2008	1/18/2008	OP	1/18/2008				3895853	

Comis Document Table Data

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 019785 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
019785	001	4885100	SEP 11,2007			
019785	001	4988827	JAN 29,2008			
019785	001	4988827*PED	JUL 29,2008			

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).

2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.

3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply

4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

5. U.S. Patent Nos. RE 36481 and RE 36520 were relisted for Zocor (NDA 19-766) pursuant to the decision and related order in Ranbaxy Labs. v.Leavitt, No. 05-1838 (D.D.C. April 30, 2006). The '481 and '520 patents remained listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act were triggered and run. For additional information on this matter, please refer to Docket Nos. 2005P-0008 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.

6. Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under Section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through January, 2008
Patent and Generic Drug Product Data Last Updated: February 25, 2008

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

/s/

Dat Doan

2/26/2008 03:08:26 PM

COVIDIEN

December 14, 2007

OFFICE OF GENERIC DRUGS
CDER/FDA (HFD-600)
Attn: Document Room E-150
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
NAF

Re: MINOR AMENDMENT – RESPONSE TO LABELING DEFICIENCIES; Amendment 2 to Original Abbreviated New Drug Application # 078098 for TechneScan® Sestamibi (Kit for the Preparation of Technetium Tc 99m Sestamibi Injection)

Dear Sir/Madam:

On January 31, 2006, Mallinckrodt Inc. submitted an original Abbreviated New Drug Application (ANDA) in electronic format pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for TechneScan® Sestamibi (Kit for the Preparation of Technetium Tc 99m Sestamibi Injection).

Mallinckrodt received two deficiency letters during the review of ANDA 78-098, one with Microbiology deficiencies received by fax on April 19, 2007, and the second with labeling deficiencies received by fax on April 23, 2007. Responses to these deficiencies were submitted on October 6, 2007, as Amendment 1 to this application.

On November 29, 2007, Mallinckrodt received a second Labeling Deficiency letter by fax dated November 28, 2007. These deficiency observations are repeated in leaf document 1.11.1 of Module 1 of this amendment, followed by Mallinckrodt's response in bold. A copy of this deficiency letter is also included in that section.

Mallinckrodt Inc. herby submits Amendment #2 to ANDA 78-098 per 21 CFR 314.120 to provide the following documents in response to the above communication:

- Responses to the Labeling Deficiency letter dated November 28, 2007
- Updated draft labeling for the drug product

With this amendment, Mallinckrodt is withdrawing its previous proposals to market the drug product under one of the two proprietary names submitted for the drug product, i.e., TechneScan Sestamibi and Sestamibi. At this time, Mallinckrodt intends to use only the

RECEIVED
DEC 17 2007
OGD

675 McDonnell Boulevard
Hazelwood, MO
63042

314-654-2000 [T]

established name to market the drug product upon approval, i.e., Kit for the Preparation of Technetium Tc 99m Sestamibi Injection. The draft labeling included in this amendment reflects the use of this established name, and prior labeling text using the previously proposed brand names have been withdrawn from the application.

During the preparation of this amendment, Mallinckrodt discovered that certain Word documents previously submitted with the January 31, 2006, original submission were inadvertently omitted from the XML backbone file. These files are Word documents containing the labeling text for the reference listed drug under Module section 1.14.3.2 Approved Labeling Text for Listed Drug. These files are being resubmitted in this amendment in their original form in order to make them available in the eCTD backbone for the entire application.

In the November 28, 2007, labeling deficiency letter, the Agency made note of the requirement to submit SPL labeling per 21 CFR 314.94(d)(ii). On December 4, 2007, Mallinckrodt contacted Mr. Koung Lee in the Office of Generic Drugs to clarify the SPL submission requirements for an eCTD submission. As a result of this discussion with Mr. Lee, Mallinckrodt will commit to the submission of SPL labeling within fourteen (14) days post approval of this application.

This Amendment is provided in electronic format in addition to the following paper documents which contain original signatures: cover letter and the FDA Form 356h. A printed copy of the contents of the index-md5.txt file is included as an appendix to this cover letter in accordance with the ICH eCTD specification. The electronic submission is being provided on one (1) CD-ROM disk and is approximately 36 megabytes (MB) in size. This application has been organized according to the International Conference on Harmonization (ICH) specification for the electronic Common Technical Document (eCTD), Version 3.2, and the April 2006 Guidance for Industry on *Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

Mallinckrodt Inc. certifies that the files contained in the above electronic submission are virus free and have been checked with McAfee VirusScan Enterprise, program version 8.5i.

The point of contact for this electronic application is James W. Brodack, Ph.D., Regulatory Affairs Manager, (314) 654-3045 (voice), (314) 654-3344 (fax).

Sincerely,

James W. Brodack

James W. Brodack, Ph.D.
Regulatory Affairs Manager

enc.

Telephone Fax

ANDA 78-098

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8988)

TO: Mallinckrodt Inc. TEL: 314-654-3045

ATTN: James W. Brodack FAX: 314-654-3344

FROM: Charlie Hoppes

:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for TechneScan® Sestamibi (Kit for Preparation of Technetium Tc 99m Sestamibi Injection).

Pages (including cover): __4__

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-098 Date of Submission: October 6, 2007

Applicant's Name: Mallinckrodt Inc.

Established Name: TechneScan® Sestamibi (Kit for Preparation of Technetium Tc 99m Sestamibi Injection)

Labeling Deficiencies:

A. GENERAL COMMENT

We acknowledge your comments that you propose to drop "TechneScan" for your line of Tc 99m radiopharmaceuticals. However, labeling submitted retains that nomenclature. Please delete. Additionally, we acknowledge your proposal to retain "Sestamibi" as a proprietary name to differentiate this product from other Tc-containing radiopharmaceuticals. We have contacted the Division of Medication Errors and Technical Support (DMETS), regarding this proposal and will forward their comments to you when they become available to us.

B. CONTAINER LABEL

See GENERAL COMMENT

C. CARTON LABELING (5 Vial Kits and 30 Vial Kits)

1. See GENERAL COMMENT

2. Add the statement, "Use within 6 hours of reconstitution."

3. Combine the statements, "Diagnostic Agent for Intravenous Use.", and "FOR INTRAVENOUS USE AFTER LABELING WITH ADDITIVE-FREE TECHNETIUM Tc 99m.", to read, "DIAGNOSTIC AGENT FOR INTRAVENOUS USE AFTER LABELING WITH ADDITIVE-FREE TECHNETIUM Tc 99m."

D. PHYSICIAN INSERT

1. GENERAL

Please note that you are required to submit SPL labeling from which we will review the data elements. For additional information, please refer to 21 CFR 314.94(d)(ii), the SPL Implementation Guide for FDA Content of Labeling Submissions at:
http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf
…and Docket 92S-0251, Memorandum 32.

2. PRECAUTIONS (Information for Patients)

Revise this section to read as follows:

CARDIOLITE® and MIRALUMA® are different names for the same drug, (Kit for Preparation of Technetium Tc 99m Sestamibi Injection). Patients should be advised to inform their health care provider if they had an allergic reaction to either drug or if they had an imaging study with either drug.

Include a disclaimer with the manufacturer's name for the products, CARDIOLITE® and

MIRALUMA®.

3. DOSAGE AND ADMINISTRATION

Bold the subsection heading, "**For Myocardial Imaging**".

4. DIRECTIONS

We acknowledge your comments regarding omission of text referencing the thermal cycler. Please make a comment in this section that your product is not for use with that device.

5. HOW SUPPLIED

a. Revise such that your storage statement appears as a distinct labeling statement.

b. We acknowledge comments that your kit will not be reviewed by the Nuclear Regulatory Commission. Please revise to add the following statement appearing on marketed radio-diagnostic products:

> This reagent kit is approved by the U.S. Nuclear Regulatory Commission for distribution to persons licensed to use by-product material identified in §35.200 to 10 CFR Part 35, to persons who have a similar authorization issued by an Agreement State, and, outside the United States, to persons authorized by the appropriate authority.

Alternatively, comment as to why the above statement should not appear on labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission and except where requested otherwise, please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

John Grace
11/28/2007 12:31:09 PM
for Wm Peter Rickman

COVIDIEN

October 6, 2007

N-000-AC

OFFICE OF GENERIC DRUGS
CDER/FDA (HFD-600)
Attn: Document Room E-150
7500 Standish Place
Rockville, MD 20855

Re: MINOR AMENDMENT – RESPONSE TO MICROBIOLOGY DEFICIENCIES and LABELING DEFICIENCIES; Amendment 1 to Original Abbreviated New Drug Application # 078098 for TechneScan® Sestamibi (Kit for the Preparation of Technetium Tc 99m Sestamibi Injection)

Dear Sir/Madam:

On January 31, 2006, Mallinckrodt Inc. submitted an original Abbreviated New Drug Application (ANDA) in electronic format pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for TechneScan® Sestamibi (Kit for the Preparation of Technetium Tc 99m Sestamibi Injection).

Mallinckrodt received two deficiency letters during the review of ANDA 78-098, one with Microbiology deficiencies received by fax on April 19, 2007, and the second with labeling deficiencies received by fax on April 23, 2007. The deficiency observations are repeated in leaf document 1.11.1 of Module 1 of this amendment, followed by Mallinckrodt's response in bold. Copies of the deficiency letters are also included in that section.

Mallinckrodt Inc. herby submits Amendment #1 to ANDA 78-098 per 21 CFR 314.120 to provide the following documents in response to the above communication:

- A revised Comparability Protocol (CP) as an appended document to Section 3.2.R Regional Information – Drug Product
- Responses to Labeling Deficiencies

Additionally Mallinckrodt is providing an amended Module 3 with chemistry, manufacturing and control documentation from (b) (4) and Mallinckrodt's Maryland Heights facility which reflect minor editorial and/or language changes, minor changes in format, minor changes to how a procedure is performed or corrections to documents included in the original submission.

675 McDonnell Boulevard
Hazelwood, MO
63042

314-654-2000 [T]

This Amendment is provided in electronic format in addition to the following paper documents which contain original signatures: cover letter, FDA Form 356h and the field copy certification. The electronic submission is being provided on one (1) CD-ROM disk and is approximately 85 megabytes (MB) in size. This application has been organized according to the International Conference on Harmonization (ICH) specification for the electronic Common Technical Document (eCTD), Version 3.2, and the April 2006 Guidance for Industry on *Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

Mallinckrodt Inc. certifies that the files contained in the above electronic submission are virus free and have been checked with Networks Associates Technology, Inc.'s McAfee VirusScan Enterprise, program version 8.0.0.

The point of contact for this electronic application is James W. Brodack, Ph.D., Regulatory Affairs Manager, (314) 654-3045 (voice), (314) 654-3344 (fax).

Sincerely,

James W. Brodack

James W. Brodack, Ph.D.
Regulatory Affairs Manager

Telephone Fax

ANDA 78-098

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8988)

TO: Mallinckrodt

TEL: 314-654-3045

ATTN: James W. Brodack

FAX: 314-654-8905

FROM: Charlie Hoppes

:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for TechneScan® Sestamibi (Kit for Preparation of Technetium Tc 99m Sestamibi Injection).

Pages (including cover): __4__

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-098 Dates of Submission: January 31, 2006

Applicant's Name: Mallinckrodt Inc.

Established Name: TechneScan® Sestamibi (Kit for Preparation of Technetium Tc 99m Sestamibi Injection)

Labeling Deficiencies:

A. GENERAL COMMENTS

1. The Office of Generic Drugs contacted the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety regarding the proposed proprietary name for this product. We will inform you of their comments when they become available to us.

2. Through searches of the FDA Adverse Event Reporting System database, we have become aware of reports of medication errors resulting from confusion between different Tc 99m imaging/diagnostic products, including confusion involving Technetium Tc 99m Sestamibi Injection.

   For this reason, we have consulted the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety regarding possible means of differentiating Technetium Tc 99m Sestamibi Injection from other Tc 99m products.

   At this time, we request that you forward a proposal to reduce risk of confusion.

3. Revise your storage statement where it appears on labels and in labeling to include the Fahrenheit equivalent and well as Celsius.

4. Revise labels and labeling to delete the terminal zero where it appears associated with the ingredient strength, e.g., revise to read, "…1 mg", rather than "…1.0 mg".

B. CONTAINER LABEL

1. See GENERAL COMMENTS 3 and 4.

2. Include the active ingredients with strengths for this drug product.

3. Include the route of administration as it appears on your proposed 30-Vial Carton labeling.

C. CARTON LABELING (5 Vial Kits and 30 Vial Kits)

1. See GENERAL COMMENTS 3 and 4.

2. Add "protect from light" statement. You may add the statement, "Retain in Carton until time of use."

3. We note that you have offered the following explanation for differences between your outer carton labeling for your 30 Vial Kit product compared with that of the RLD:

   Cardiolite is not offered in a 30-vial packaging configuration; therefore no annotated comparison can be made. The text for Mallinckrodt's proposed 30-vial carton configuration

is listed in the column on the left.

We do not believe that this is an adequate explanation for the omission of labeling statements present on the carton labeling of the RLD. Please comment especially regarding omission of the Warning statement regarding radiopharmaceuticals and the statement with the heading "License", which appears on the labeling of the RLD. Revise your labeling accordingly.

4. Regarding your 5 vial carton, please offer further comment regarding the omission of the statement with the heading "License" appearing on the 5 Vial carton of the RLD. We believe that this statement may serve to heighten awareness of the necessity and responsibility for proper disposal of this product. We believe that your product should provide a statement that has the same effect.

5. We note that the 30-Vial carton that you propose bears the statement, ' (b) (4) . However, your package insert labeling indicates that your product may be used for breast imaging. Please comment.

6. For the 5-Vial Carton, include the route of administration as it appears on your proposed 30-Vial Carton labeling.

D. PHYSICIAN INSERT

1. GENERAL COMMENTS

Distinguish section headings from subsection headings by use of differential prominence (greater prominence for section headings). Make consistent use of formatting for headings, for example, the heading "DESCRIPTION" should be of the same format and prominence as "CLINICAL PHARMACOLOGY", but the subsection, "CLINICAL TRIALS", should appear with lesser prominence. See 21 CFR 201.56 for listing of the section headings.

2. TITLE

a. Include the following text to appear immediately before the, "FOR DIAGNOSTIC USE", statement, "For Intravenous Use".

b. Delete the corporate address information from this section as it appears in the HOW SUPPLIED section. We refer you to 21 CFR 201.56(d)(4), for guidance.

c. Include the following text to appear immediately before the DESCRIPTION section, "Rx Only".

3. DESCRIPTION

a. Include the molecular formula, structural formula, and molecular weight (602.98) of $C_{24}H_{44}N_4O_4BF_4Cu$ in this section.

b. We acknowledge comments that, prior to lyophilization, the pH of the aqueous bulk dispensing solution is adjusted with sodium hydroxide and/or hydrochloric acid to pH = 5.6. Please include this information in this section.

4. DIRECTIONS

a. We note that you have deleted all information regarding the use of your product with a thermal cycler. Annotated labeling provided with your application fails to adequately address, justify, and explain why your product labeling limits the

method for preparation to the water bath procedure while the RLD product may be prepared using either method. Please provide a full explanation.

b. Please adequately explain why you have not provided vial shield labels with your application as referenced in this section. This is part of the approved labeling of the RLD and therefore we believe that it should be provided for in your application. We refer you to 21 CFR 314.94(a)(8)(iv), for guidance.

5. HOW SUPPLIED

Regarding the following sentence which appears immediately after the DIRECTIONS, "This reagent kit is approved by the U.S. Nuclear Regulatory Commission for distribution to persons…"

a. Is your kit being reviewed by the U.S. Nuclear Regulatory Commission?

b. If so, please describe exactly who is reviewing the kit (include contact information) and what has been forwarded for review.

E. RADIOASSAY INFORMATION LABEL WITH RADIATION WARNING SYMBOL

Please ensure that the number of labels provided in each kit is equal to the number of vials.

Submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission and except where requested otherwise, please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

John Grace
4/22/2007 07:04:18 AM
for Wm Peter Rickman

FAX – Microbiology Deficiencies Enclosed

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773 (301-594-0320)

TO: James W. Brodack, Ph.D.
Mallinckrodt Inc.
PHONE: 314-654-3045
FAX: 314-654-8905

FROM: Mark Anderson
Microbiology Project Manager
PHONE: (301) 827-0530
FAX: (301) 827-5911

Total number of pages, excluding this cover sheet: __1__

Date: April 17, 2007

Microbiology Deficiencies:

Enclosed are the microbiology deficiencies for ANDA 78-098 for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection. The submission reviewed was submitted on January 31, 2006. Please respond to this communication as quickly as possible. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this communication will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter.

Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

If you have questions, feel free to call Bonnie McNeal or Mark Anderson.

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 78-098 APPLICANT: Mallinckrodt Inc.

DRUG PRODUCT: TechneScan Sestamibi Kit

A. Microbiology Deficiencies:

1. The reviewer notes that a Comparability Protocol (CP) providing

(b) (4)

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Neal J. Sweeney, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Neal Sweeney
4/19/2007 03:19:46 PM

ANDA 78-098

MAR 30 2006

Mallinckrodt Inc.
Attention: James W. Brodack, Ph.D.
P.O. Box 5840
675 McDonnell Boulevard
St. Louis, MO 63134

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Technetium Tc 99m Sestamibi for Injection

DATE OF APPLICATION: January 31, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 1, 2006

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Simon Eng
Project Manager
301-827-5765

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 78-098

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/
HFD-143/OIM/DRM

Endorsement:
HFD-615/M.Shimer, Chief, RSB _____ date 30 March 2006
HFD-615/S.Shepperson, CSO _____ date 03-30-2006

Word File
V:\CDSNAS\OGDS11\FIRMSAM\MALLINCKRODT\LTRS&REV\78098.ACK.DOC

F/T sms 3-30-2006

ANDA Acknowledgment Letter!

ANDA ~~78-098~~ Final Check List for Branch Chief

FAX (314) 654-3344

- ✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.
- ✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.
- ✓ 3) Check for gross errors in letter.
- ✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)
- ✓ 5) Check address and contact person on letter vs. 356h.
- ✓ 6) Check for any t-cons and verify date and correspondence date.
- ✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.
- ✓ 8) Check for any comments or problems raised by reviewer on Check List.
- N/A 9) If first generic, copy BE review and file.
- ✓ 10) Sign Check List.
- ___ 11) Check electronic Orange Book to verify current patent information and correct RLD.
- ✓ 12) Check for MOU patents
- ✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.
- ✓ 14) Review Basis for Submission. Cardiolite Kit 19-785
- ✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

  PIII → 100 exp 9/11/07
  PIII → 445 exp 1/16/07
  PIII → 827 exp 1/29/08
  PIII → 829 exp 1/16/07
- ✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.
- ✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.
- ✓ 18) Pull USP information. (USP ___yes ✓ no)
- ✓ 19) Final Grammar review on letter.
- ✓ 20) Verify information in OGD Patent Tracking System.
- ✓ 21) EES slip.
- ✓ 22) Document in record book.

Signature Martin H. Raw date 30 March 2006

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 78-098 **FIRM NAME:** MALLINCKRODT INC.

RELATED APPLICATION(S): SEE (b) (4) (b) (4) (b) (4)

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☒ **Micro Review !!!Yes, MICRO Review NEEDED!!!**
☐ **BST**	☐ **BDI**	

First Generic Product Received? NO PER MARTY 3/9/06

SEE MARTY FOR MORE DETAILS

DRUG NAME: TECHNETIUM TC- 99M SESTAMIBI
DOSAGE FORM: INJECTION, 10-30 M CI (KIT)

Random Queue: 1
Chem Team Leader: Mueller, Albert PM: Simon Eng Labeling Reviewer: James Barlow

Letter Date: JANUARY 31, 2006	**Received Date:** FEBRUARY 1, 2006
Comments: EC- 1 YES	**On Cards:** YES
Therapeutic Code: 5020100 RADIOACTIVE DIAGNOSTIC AGENTS	
Archival Format: PAPER	**Sections** I **(356H Sections per EDR Email)**
Review copy: YES Not applicable to electronic sections	E-Media Disposition: YES SENT TO EDR
Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) (Required for Non-USP drugs)	**NO**
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category (Must be completed for ALL Original Applications)	N Not a Part3 Combo Product Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Stanly Shepperson

Date 28-March-2006

Recommendation:

☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: Martin Shimer **Date:** 30 March 2006

ADDITIONAL COMMENTS REGARDING THE ANDA:
30 March 2006: Martin spoke to Dr. Broderick re difference in vial size (10mL) used by Mallinckrodt vs the RLD (5mL). Dr. Broderick confirmed that the volume fill of the proposed Generic is equivalent to that of the RLD. As a matter of practice Mallinckrodt uses 10mL vials for all radiopharmaceuticals for ease of packaging across different product lines

Top 200 Drug Product:

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☒
Sec. II	**Basis for Submission** **NDA# : 19-785** Ref Listed Drug: CARDIOLITE Firm: BRISTOL MYERS SQUIBB ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** 1. Paragraph: III 2. Expiration of Patent: 1-29-2008 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Route of administration SAME 4. Dosage Form SAME 5. Strength SAME	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL YES 2. 1 RLD label and 1 RLD container label YES 3. 1 side by side labeling comparison with all differences annotated and explained YES 4. Was a proprietary name request submitted? YES (If yes, send email to Labeling Rvwr indicating such.) Email to J. Barlow on 3-29-2006. **How Supplied:** 10 ml vial in a kit of 5 or carton of 30.	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) NO **2. Request for Waiver of In-Vivo Study(ies): YES** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) YES **4. Lot Numbers of Products used in BE Study(ies):** NA **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below) NA	☒

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation YES 2. Inactive ingredients as appropriate YES. Q1/Q2.	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers YES b. Type II DMF authorization letters or synthesis NO TYPE II DMF INVOLVED. c. COA(s) specifications and test results from drug substance mfgr(s) YES d. Applicant certificate of analysis YES e. Testing specifications and data from drug product manufacturer(s) YES f. Spectra and chromatograms for reference standards and test samples YES g. CFN numbers YES 2. **Inactive Ingredients** a. Source of inactive ingredients identified YES b. Testing specifications (including identification and characterization) YES c. Suppliers' COA (specifications and test results) YES d. Applicant certificate of analysis YES	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. CFN numbers YES	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address YES 2. Functions YES 3. CGMP Certification/GLP YES 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3.If sterile product: Aseptic fill / YES 4.Filter validation (if aseptic fill) NA- lyophilized powder 5. Reprocessing Statement YES **<u>Proposed Commercial Batch Sizes:</u>** 10L – 20 L	☒

Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES 2. In-process Controls - Specifications and data YES 3 lots produced: (b) (4)	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data (Type III DMF References) YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data YES 2. Certificate of Analysis for Finished Dosage Form YES	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted YES 2. Post Approval Commitments YES 3. Expiration Dating Period YES- 24 MONTHS 4. Stability Data Submitted YES a. 3 month accelerated stability data YES b. Batch numbers on stability records the same as the test batch YES	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance YES 2. Finished Dosage Form YES 3. Same lot numbers	☒
Sec. XVII	**Environmental Impact Analysis Statement** YES	☒

Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) YES	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe

tyco
Healthcare

Mallinckrodt

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505(j)(1)(A)(i)

January 31, 2006

OFFICE OF GENERIC DRUGS
CDER/FDA (HFD-600)
Attn: Document Room E-150
7500 Standish Place
Rockville, MD 20855

Re: Submission of Original Abbreviated New Drug Application # 078098 for TechneScan® Sestamibi (Kit for the Preparation of Technetium Tc 99m Sestamibi Injection)

Dear Sir/Madam:

Mallinckrodt Inc. hereby submits this original Abbreviated New Drug Application (ANDA) pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for TechneScan® Sestamibi (Kit for the Preparation of Technetium Tc 99m Sestamibi Injection). Per 21 CFR 314.92(a)(1), the Reference Listed Drug used for the basis of this submission is Cardiolite® (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection), described in NDA 19-785.

The above application contains information related to the manufacture of a technetium Tc 99m radiopharmaceutical kit reaction vial that contains a nonradioactive lyophilized mixture of components necessary for the preparation of the radioactive drug product, Technetium Tc 99m Sestamibi Injection. The radioactive drug product is prepared by the end user via reconstitution of the vial contents with Sodium Pertechnetate Tc 99m Injection obtained from a Technetium Tc 99m Generator. Since the radioactive drug product is only formed during reconstitution of the kit reaction vial contents, all components of the reaction vial would normally be viewed as inactive ingredients by the Agency. For the purposes of presenting information in this application, however, information pertaining to the chemistry, manufacture and control of the nonradioactive ligand component of the kit, i.e., tetrakis(2-methoxyisobutylisonitrile) copper(I) tetrafluoroborate, is presented in the drug substance section of the application, along with information related to the radioactive drug substance, Technetium Tc 99m Sestamibi. Likewise, the chemistry, manufacture and control information related to the nonradioactive kit reaction vial are presented in the drug product section of the application, along with information related to the radioactive drug product, Technetium Tc 99m Sestamibi Injection.

This ANDA submission is being provided in electronic format in addition to the following paper documents which contain original signatures: cover letter, FDA Form 356h, patent certification, debarment certification, field copy certification, a Claim of Categorical Exclusion from the requirement of an environmental assessment, cGMP certifications and copies of letters of authorization to review pertinent Drug Master Files. The electronic submission is being

provided on one (1) CD-ROM disk and is approximately two hundred twenty-seven (227) megabytes in size. This application has been organized according to the International Conference on Harmonization (ICH) specification for the electronic Common Technical Document (eCTD), Version 3.2, and the October 2005 Guidance for Industry on *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

Mallinckrodt Inc. certifies that the files contained in the above electronic submission are virus free and have been checked with Networks Associates Technology, Inc.'s McAfee VirusScan Enterprise, program version 8.0.0.

The point of contact for this electronic application is James W. Brodack, Ph.D., Regulatory Affairs Manager, (314) 654-3045 (voice), (314) 654-8905 (fax).

Sincerely,

James W. Brodack

James W. Brodack, Ph.D.
Regulatory Affairs Manager