CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202207Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	January 31, 2013
Reviewer:	Kevin Wright, PharmD Division of Medication Error and Prevention Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Error and Prevention Analysis
Division Director:	Carol A. Holquist, RPh Division of Medication Error and Prevention Analysis
Drug Name and Strength:	Lymphoseek (Kit for Preparation of Technetium Tc 99m Tilmanocept Injection), 250 mcg per vial
Application Type/Number:	NDA 202207
Applicant/sponsor:	Navidea Biopharmaceuticals, Inc.
OSE RCM #:	2012-2720

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed vial labels, carton, package insert and Instructions for Use for Lymphoseek, NDA 202207, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The original Application for this product was submitted to the FDA on August 10, 2011. The container labels and carton labeling were previously reviewed in OSE Review #2011-3173, dated June 22, 2012. On September 10, 2012 the Division of Medical Imaging Products issued a Complete Response to the Applicant based on manufacturing deficiencies. On October 30, 2012, the Applicant submitted class 2 resubmission. As part of the resubmission, in addition to previous vial labels, carton and package insert labeling, the Applicant submitted preparation instructions (i.e., Instructions for Use) of Lymphoseek.

1.2 PRODUCT INFORMATION

The following product information is provided in the October 30, 2012 resubmission.

- Active Ingredient: Technetium Tc 99m Tilmanocept for Injection
- Indication of Use: radioactive diagnostic agent used in the (b) (4) localization of lymph nodes in patients with breast cancer or melanoma. (b) (4)
- Route of Administration: Intradermal or Subareolar
- Dosage Form: Powder for Injection
- Strength: 18.5 MBq (0.5 mCi in 50 mcg)
- Dose and Frequency:
- How Supplied: Kit (each kit contains)
    - five 0.25 mg Tilmanocept vials
    - five Diluent vials
    - five radiolabeled product shield labels (b) (4)
- Storage: Store Lymphoseek in original packaging at USP controlled room temperature 25°C (77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store technetium Tc 99m tilmanocept radiolabeled product in radiation shielding at room temperature.

  Use radiolabeled Lymphoseek (technetium Tc 99m tilmanocept) injection within 6 hours of preparation.
- Container and Closure System:

- Tilmanocept and diluent are individually packaged in glass vials

2 METHODS AND MATERIALS REVIEWED

We reviewed the Lymphoseek's vial labels, carton and package insert labeling, as well as preparation instructions submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Instructions for Use submitted September 21, 2012 (Appendix A)
- Tilmanocept Container Label submitted August 31, 2012 (Appendix B)
- Diluent Container Label submitted August 31, 2012 (Appendix C)
- Carton Labeling submitted August 31, 2012 (Appendix D)
- Radioassay Information Label submitted August 31, 2012 (Appendix E)

(b) (4)

- Insert Labeling submitted September 6, 2012 (no image)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed OSE Review 2011-3173 and we evaluated the review to ensure all our recommendations were implemented.

3 CONCLUSIONS

DMEPA reviewed that the proposed container labels, carton and package insert labeling and determined that these labels and labeling are acceptable based on the revisions that have been implemented after OSE Review 2011-3173. Thus, we have no additional revisions regarding these labels and labeling.

However, DMEPA concludes that the proposed instructions for use (IFU) can be improved to increase the readability and prominence of important information in the IFU to promote the safe use of the product to mitigate any confusion.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

A. Preparation Instructions for Lymphoseek

1. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert.[2] As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:

   - Revise all instances of trailing zeroes appearing in the text or tables of the preparation instructions. Trailing zeros are dangerous dose designations that could be misinterpreted as a 10 fold dose if the trailing zero is not seen (e.g., 1.0 mL as the final injection volume may be misinterpreted as 10 mL final injection volume).

   - Revise the '>' and '≥'symbols appearing in the instructions for use to read "greater than" or "greater than or equal" respectively. The "greater than" and "less than" signs have been misinterpreted to have the opposite meaning. For example, the "greater than" sign has been misinterpreted to mean "less than".

2. Before Step 1 of the preparation instructions, instruct the end user to carefully read the instructions prior to attempting to prepare this product.

3. In Table 1, reorganize the order of the columns as follows: 1) Desired Number of Injections, 2) Volume per Syringe, and 3) Total Injection Volume (mL). This presentation is more consistent with the insert labeling and may mitigate possible confusion between the instructions for use and insert labeling.

4. In step 2, revise the second bullet, so the end user can easily determine the radioactive concentration needed based on the reconstituted volume of the vial.

5. Move Table 2 to appear adjacent to Step 2 and Step 3, so the end user can easily find reference to the Table.

6. (b) (4)

If you have further questions or need clarifications, please contact Sandra Rimmel, project manager, at 301-796-2445.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[2] http://www.ismp.org/Tools/errorproneabbreviations.pdf, Last accessed 10/28/2009.

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/s/

KEVIN WRIGHT
01/31/2013

YELENA L MASLOV
01/31/2013

CAROL A HOLQUIST
02/03/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	June 22, 2012
Reviewer:	Jibril Abdus-Samad, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Lymphoseek (Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection) 250 mcg/vial
Application Type/Number:	NDA 202207
Applicant:	Navidea Biopharmaceuticals, Inc.
OSE RCM #:	2011-3173

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Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Lymphoseek NDA 202207 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted the original labels and labeling on August 10, 2011. The Applicants submitted updated container label and carton labeling on February 13, 2012 and updated insert labeling on April 5, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission.

- Active Ingredient: Technetium Tc 99m Tilmanocept for Injection
- Indication of Use: radioactive diagnostic agent used in the (b) (4) localization of lymph nodes in patients with breast cancer or melanoma. (b) (4)
- Route of Administration: intradermal or subareolar
- Dosage Form: for injection
- Strength: 0.25 mg
- Dose and Frequency: 18.5 MBq (0.5 mCi in 50 mcg)
- How Supplied: Each Kit contains
    - five 0.25 mg Tilmanocept vials
    - five Diluent vials
    - five radiolabeled product shield labels

    (b) (4)
- Storage: Store Lymphoseek in original packaging at USP controlled room temperature 25°C (77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store technetium Tc 99m tilmanocept radiolabeled product in radiation shielding at room temperature.

  Use radiolabeled Lymphoseek (technetium Tc 99m tilmanocept) injection within 6 hours of preparation.
- Container and Closure System:
    - Tilmanocept is packaged in a glass vial
    - Diluent is packaged in a glass vial

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Lymphoseek label and labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Tilmanocept Container Label submitted February 13, 2012 (Appendix B)
- Diluent Container Label submitted February 13, 2012 (Appendix C)
- Carton Labeling submitted February 13, 2012 (Appendix D)
- Radioassay Information Label submitted August 10, 2011 (Appendix E)

(b) (4)

- Insert Labeling submitted April 5, 2012

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Lymphoseek can be administered in one to five injections depending on the administering physicians' preference and injection technique. This affects the preparation because there are limits to the volume of solution, radioactivity, and mass of Tilmanocept injected into the patient. The preparation instructions involve determining the number of injections to be given, the total injection volume, and the total reconstitution volume. There are numerous steps in this process, however, this product is prepared by nuclear pharmacists that are certified to prepare products with numerous steps. Additionally, the nuclear pharmacist must perform quality control check for each preparation, which minimizes the risk of incorrect preparation of this Lymphoseek.

Lymphoseek will be prepared by a nuclear pharmacist with the end product being drawn up in a syringe. Currently, the Lymphoseek Kit does not contain syringe labels to ensure proper identification and prevent wrong drug errors. Inclusion of these labels in the packaging may prevent wrong drug errors.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling are unacceptable because the labels lack standard labeling requirements such as NDC number and manufacturer information. Additionally, the Dosage and Administration section of the insert labeling contains dangerous abbreviations that have led to medication errors with other products.

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[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

If you have further questions or need clarifications, please contact Sandra Griffith, OSE project manager, at 301-796-2445.

4.1 COMMENTS TO THE DIVISION

A. General Comments for the Insert Labeling

1. Replace the punctuation, - , with the word, *to*, in all areas of the labeling.
2. Revise the abbreviation, *µg*, to read, *mcg*. The abbreviation, *µg* , has been misinterpreted as milligram. Additionally, this abbreviation appears on the Institute of Safe Medication Practices' List of Error-Prone Abbreviations, Symbols and Dose Designations.[2] FDA agreed to not use error-prone abbreviations in approved labeling.
3. Remove trailing zeros as they have been misinterpreted and resulted in ten fold overdose. Additionally, trailing zeros are considered dangerous dose designations and appear on the Institute of Safe Medication Practices' List of Error-Prone Abbreviations, Symbols and Dose Designations' FDA agreed to not use error-prone dose designations in approved labeling.
4. Revise the abbreviation, *µL*, to read *microliters*.

B. Dosage and Administration - section 2

(b) (4)

4.2 COMMENTS TO THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. General Comments

Include twenty-five syringe labels for the nuclear pharmacists to label the syringes once they are prepared. The syringe labels should include the product name and a space for the preparer to note the radioactivity amount, date and time of assay, and expiration date.

B. Container Label – Tilmanocept (Appendix B)

1. Add a NDC number on the upper third portion of the principal display panel.
2. Relocate the company logo, Navidea, and decrease its prominence. Currently, Navidea appears on the left side of the proprietary and established names. While reading left to right, it appears the name of the product is Navidea. Additionally this label is rather small and the space

[2] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations.

http://www.ismp.org/tools/errorproneabbreviations.pdf . Last accessed June 19, 2012

should be used to display important information needed for nuclear pharmacist to prepare the product safely.

3. Revise the presentation of the proprietary and established name to read as follows:

   Tilmanocept Powder for preparation of Lymphoseek (technetium Tc 99m tilmanocept) injection

4. Revise the strength from 0.25 mg to 250 mcg so the strength statement and dosing information utilize the identical units of measure. The strength should appears as follows:

   250 mcg per vial

5. Add the statements:

   For Use with Lymphoseek Kit Only
   Administer only after radiolabeling with technetium Tc 99m
   See insert for preparation and administration instructions

6. Revise the statement, [redacted] (b) (4) to read as follows

   Store at 25°C (77 °F) (USP controlled room temperature); excursions permitted to 15°C to 30°C (59°F to 86°F) in original package.

C. Container Label – Diluent (Appendix C)

1. Include a NDC number on the upper third portion of the principal display panel and the statement, Rx Only.

2. Include the following statements:

   For diluting radiolabeled Lymphoseek only
   Not for direct administration
   See package insert for preparation and administration instructions
   Single Use Vial - Discard unused portion

3. Revise the statement [redacted] (b) (4) to read as follows

   Store at 25°C (77 °F) (USP controlled room temperature); excursions permitted to 15°C to 30°C (59°F to 86°F) in original package.

4. Add the lot and expiration date to the side panel.

5. Relocate the distributor information toward the lower portion of the label so that nuclear pharmacists can easily read the important information on the label to safely use the product.

D. Carton Labeling (Appendix D)

1. Relocate the list of kit contents from the side panel to the principal display panel.

2. Revise the strength statement, *0.25 mg*, to read, *250 mcg*, so the strength statement and dosing information utilize the identical units of measure.
3. Decrease the prominence of the strength statement by decreasing the width of the background.
4. Relocate the statement, Rx Only toward the bottom of the principal display panel
5. Revise the statement, *Store at* (b) (4) to read as follows

   Store at 25°C (77 °F) (USP controlled room temperature); excursions permitted to 15°C to 30°C (59°F to 86°F) in original package.
6. Relocate the company logo/graphic from the principal display panel to the rear panel.
7. Remove the (b) (4), at the top of the rear panel. These numbers do not provide useful information to nuclear pharmacists.

E. Radioassay Information Label (Appendix E)

1. Revise the strength statement, *Tilmanocept 50 g*, to read *Tilmanocept 50 mcg*.
2. Revise the vertical lines for writing the MBq, volume, time/date and expiration time to a horizontal presentation.
3. Revise the statement, (b) (4) to read as follows

   Store at 25°C (77 °F) (USP controlled room temperature); excursions permitted to 15°C to 30°C (59°F to 86°F) in original package.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Appendix B: Tilmanocept Container Label

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/s/

JIBRIL ABDUS-SAMAD
06/22/2012

TODD D BRIDGES
06/22/2012

CAROL A HOLQUIST
06/22/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 4/3/2012

To: Alberta Davis-Warren, Regulatory Project Manager
Division of Medical Imaging Products

From: James Dvorsky, Regulatory Reviewer
Division of Professional Promotion

Subject: Comments on draft labeling (Package Insert) for NDA 202207, Lymphoseek (technetium Tc 99m tilmanocept) Injection

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In response to your labeling consult request on August 19, 2011, we have reviewed the draft Package Insert for Lymphoseek and offer the following comments. Note that these comments are based upon the March 26, 2012 version of the label.

(b) (4)

[redacted]

See attached label sections for grammatical changes.

[redacted]

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/s/

JAMES S DVORSKY
04/03/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Addendum Pediatric and Maternal Health Staff Memorandum

Date: April 2, 2011 **Date Consulted:** November 22, 2011

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Team Leader – Pediatric Team
Pediatric and Maternal Health Staff

Lisa Mathis, MD, OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Medical Imaging Products (DMIP)

Drug: Lymphoseek Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection, NDA 202207

Subject: PREA Studies and Pediatric Use Labeling

DISCUSSION AND CONCLUSIONS

This memorandum is an addendum to the Pediatric and Maternal Health Memorandum dated December 20, 2011, regarding the Sponsor's failure to adequately address PREA study requirements in their initial new drug application submission. The Sponsor subsequently submitted a revised Pediatric Plan on February 2, 201 (b) (4)

Since the re-submission of the Pediatric Plan for Lymphoseek, DMIP has revised the proposed indication for Lymphoseek, and is limiting the indication to include only breast cancers and melanomas. These cancers are considered adult indications and qualify products for a full waiver of pediatric studies under PREA because studies would be impossible or impractacable in the pediatric population. PMHS agrees that a waiver of pediatric studies is appropriate for the revised Lymphoseek indication. DMIP could consider issuing a Written Request for Lymphoseek if they believe there is a public health benefit of obtaining studies in children.

Lymphoseek pediatric use labeling should reflect that safety and effectiveness have not been established. (b) (4)

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/s/

JEANINE A BEST
04/02/2012

LISA L MATHIS
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Maternal Health Team Review

Date: March 28, 2012 **Date Consulted:** October 13, 2011

From: Upasana Bhatnagar, M.D.
Medical Officer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa S. Tassinari, Ph.D.
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Lisa Mathis, M.D.
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Medical Imaging Products (DMIP)

Drug: **Lymphoseek (Technetium Tc99m Tilmanocept for Injection)-NDA 202207**

Sponsor: Neoprobe Corporation

Subject: Pregnancy and Nursing Mothers Labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Lymphoseek labeling, PubMed literature search

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of Lymphoseek

INTRODUCTION

On August 10, 2011, Neoprobe Corporation submitted a New Drug Application (NDA) to the Division of Medical Imaging (DMIP) for a radiopharmaceutical called Lymphoseek (Technetium Tc99m Tilmanocept for Injection). The Sponsor proposed indication is for the use of Lymphoseek as a diagnostic agent to be used to (b) (4) localize lymph nodes intraoperatively. DMIP consulted the Pediatric and Maternal Health Staff's Maternal Health Team (PMHS-MHT) on October 13, 2011 to review the Pregnancy and Nursing Mothers subsections of the Sponsor proposed labeling. This review includes PMHS-MHT recommendations for revisions to the proposed labeling for Lymphoseek.

BACKGROUND

Lymphoseek (Technetium Tc99m Tilmanocept for Injection) is a diagnostic agent to be used intraoperatively to image tumor-draining lymph nodes. Tilmanocept has multiple units of diethylenetriaminepentacetic acid (DTPA) and mannose attached to a dextran core. DTPA is a chelating agent for Tc99m. The mannose component of the molecule interacts with mannose binding receptors on macrophages and dentritic cells in lymphatic tissue.

Lymphoseek has a half-life of 3 hours, and is cleared from the injection site with <1% of the drug entering systemic circulation.[1] The proposed dose for same day surgery to be administered within 15 hours of surgery is 50 µg Lymphoseek radiolabeled with 18.5 MBq (Megabequerals) or 0.5 mCi (millicuries) of Technetium Tc99m. (b) (4)

In pregnant women, breast cancer is the most common cancer occurring in an estimated 1:3000 women.[2] Because regional lymph node metastasis is a vital prognostic factor in breast cancer, lymphatic mapping and sentinel lymph node biopsy procedures are central to staging breast cancer. In comparison to traditional lymph node dissection, the minimally invasive nature of the procedure make lymphatic mapping a preferable option for patients with breast cancer. The pregnant and post-partum patient population would particularly benefit from a minimally invasive diagnostic procedure. Therefore, it is likely that Lymphoseek could be administered to pregnant and lactating women who require lymphatic mapping.

[1] March 14, 2012, personal communication with Christy John of Clinical Pharmacology
[2] National Cancer Institute, http://www.cancer.gov/cancertopics/pdq/treatment/breast-cancer-and-pregnancy/HealthProfessional/page1, website accessed 3/21/2012.

REVIEWED MATERIALS

Sponsors Proposed Pregnancy and Nursing Mothers Labeling

(b) (4)

REVIEW OF LITERATURE AND PRACTICE GUIDELINES

The likelihood of fetal harm is related to the dose of the radiopharmaceutical and the stage of fetal development when the exposure occurs. Ionizing radiation from radiopharmaceuticals can result in harmful fetal effects such as cell death and teratogenic effects, carcinogenesis, and genetic effects or mutations in germ cells.[3] For the period two weeks after conception,

[3] ACOG Committee Opinion. Sept 2004. Guidelines for Imaging During Pregnancy

exposure to a radiopharmaceutical will have an "all or none" impact on the fetus, causing no effect or causing fetal demise. Organogenesis starts three to five weeks post conception.[4] Throughout gestation, doses less than 0.05 gray (50mGy) have no measurable noncancer risk to the embryo/fetus at any stage. The threshold for the absorbed dose resulting in adverse fetal effects during early embryogenesis is >0.1 gray but during major organogenesis likely lies between 0.1-0.2 gray.[5,6] In doses from 0.05-0.5 gray, exposure from 2-15 weeks gestation may result in growth retardation, reduction of IQ, and increased incidence of severe mental retardation. Radiation exposures greater than 0.5 gray have multiple implications for both the mother and the fetus. The lifetime risk of cancer due to perinatal exposure is estimated to be 0.3-1% with less than 0.05 gray exposure or 0.4% per 10mGy dose to the fetus.[4, 7]

Most of the data available regarding placental transfer of radiopharmaceuticals during pregnancy is based on estimates derived from animal studies. In a study of free technetium by Gilbert et al in 1996, 19 fetal sheep were studied after maternal injection with free technetium.[8] Although the mechanism of transport through the placenta was uncertain, technetium was detected in the fetal circulation and peaked at one hour post maternal injection.

Reviewer comment: Because free technetium does cross the placenta, exposure in utero to technetium based radiopharmaceuticals such as Lymphoseek can potentially cause fetal harm. To minimize fetal exposure especially in early gestation, imaging studies using radiopharmaceuticals should be performed early in the menstrual cycle, within the first 10 days. Patients who are unsure of their menses should be tested for pregnancy.

Technetium Tc99m DTPA and Pregnancy

No studies were found in a PubMed literature search performed to obtain data regarding Lymphoseek use during pregnancy and lactation. However, because Tilmanocept is a composed of multiple units of DTPA and mannose, guidelines and studies regarding Tc99m DTPA, a renal imaging agent, were reviewed.

In 1997, Russell et al published a study to estimate the fetal radiation exposure from maternal administered doses by surveying 26 medical institutions regarding the most commonly used diagnostic nuclear medicine procedures used in women of childbearing age.[9] The study used the Medical Internal Radiation Dosimetry (MIRD) program to estimate the absorbed

[4] Pregnancy and Medical Radiation, ICRP Publication 84, Annals ICRP 2000, 30(1). 9-12.
[5] Centers for Disease Control and Prevention, Radiation and Pregnancy: A Fact Sheet for Clinicians, www.bt.cdc.gov/radiation/prenatalphysician.asp, accessed, 2/28/2011
[6] National Council of Radiation Protection and Measurement Report 128: Radionuclide Exposure of the Embryo/Fetus, 41-48.
[7] American College of Radiology, Practice Guideline for Imaging Pregnant or Potentially Pregnant Adolescents and Women with Ionizing Radiation, 2008
[8] Gilbert WM, Newman PS, et al. Technetium Tc99m rapidly crosses the ovine placenta and intermembranous pathway. *Am J Obstet Gynecol*. 1996; 175:1557-62.
[9] Russell JR, Stabin MG, et al. Radiation Absorbed dose to the Embryo/Fetus from Radiopharmaceuticals. *Health Phys*.1997. 73(5): 756-769

dose to the embryo/fetus per unit of activity of radiopharmaceutical administered to the mother in typical doses. The investigators estimated fetal radiation exposure at multiple times during gestation (early in the pregnancy, at six months, and at nine months) following use of Tc99m-DTPA in the mother for common procedures. Table 1 below includes the indicated procedures using Tc99m-DTPA, particularly those procedures requiring the highest administered doses, and the estimated exposure at these doses to a fetus.

Table 1. Estimated Fetal Absorbed Dose for Procedures using Tc99m DTPA					
	Administered Dose MBq (mCi)	**Early mGy**	**3 months mGy**	**6months mGy**	**9 months mGy**
Kidney imaging, Brain imaging	750 MBq (20 mCi)	9.0 mGy	6.5 mGy	3.1 mGy	3.5 mGy
Hypertension	800 MBq (22 mCi)	9.6 mGy	7.0 mGy	3.3 mGy	3.8 mGy
Residual urine determination	350 MBq (9.5 mCi)	4.2 mGy	3.0 mGy	1.4 mGy	0.16 mGy
Gastric Reflux	10 MBq (0.27 mCi)	0.12 mGy	0.087 mGy	0.041 mGy	0.047 mGy

Adapted from Table 4b. Russell et al. [7]

Reviewer comment: Even at the highest doses, the estimated fetal radiation exposure from maternal use of Tc 99m DTPA are substantially less than the threshold for teratogenic effects of 50 mGy.

Technetium Tc99m DTPA and Lactation

A review of literature and guidelines was performed to determine whether maternal radiation exposure from use of Tc99m DTPA affects lactation and whether infants exposed through human milk and/or close contact experience adverse effects. The annual background radiation at sea level is approximately 3.1 millisievert (mSv).[10] According to the Nuclear Regulatory Commission, the regulatory limit for the effective dose to an embryo, fetus, or nursing child is 5 mSv (0.5 rem).[11] If a lactating individual has received a radionuclide and the total effective dose equivalent (TEDE) to a nursing infant or child could exceed 0.1 rem (1mSv), instructions to the mother must be provided, assuming that breastfeeding is not interrupted.

[10] US Nuclear Regulatory Commission, Biologic Effects of Radiation, http://www nrc.gov/reading-rm/doc-collections/fact-sheets/bio-effects-radiation ,updated January 2011, accessed 3/2011

[11] Siegel, 2002, Guide for Diagnostic Nuclear Medicine, Nuclear Regulatory Commission Regulation of Nuclear Medicine, p 9-10.

In the United States Nuclear Regulatory Commission (NRC) guidelines, set forth in NUREG 1556, volume 9, Appendix U, no interruption of breastfeeding is necessary after maternal treatment with Tc 99m-DTPA for doses up to 1000 MBq (30mCi) to achieve an infant effective dose level below 1 mSv.[12] The LactMed Database was queried for Tc99m DTPA. The recommendation referred to the NRC guidelines for interruption of breastfeeding, and noted that some experts, applying the principle of as low as reasonably achievable (ALARA), recommended breastfeeding should be interrupted for 3 to 6 hours after a dose and that the milk be expressed and discarded.

Lactation Studies

Rubow et al studied the excretion of commonly used radiopharmaceuticals in human breast milk 60 patients.[13] The authors acknowledged the wide variation in data from patients receiving the same dose of a radiopharmaceutical, and this was particularly the case with Tc99m DTPA in this study. Using the worst case scenario of transfer of radiopharmaceuticals into human milk, the investigators obtained milk samples from patients after administration of radionuclides at regular intervals for at least 24 hours after administration. The calculation of activity ingested by the infant included variables such as the frequency of feeding, volume per feed, and the decay of the radiopharmaceutical. Among the five patients receiving a 600 MBq dose of Tc99m DTPA, the highest effective dose for the infant was 0.48 mSv in four patients, but one patient had an effective dose of 16.12 mSv. However, for all five of the patients, the average effective half life of Tc99mDTPA in the breast milk was 4.5 hours. The authors noted that radiochemical purity of the radiopharmaceutical could have affected the levels of drug in the patient who was the outlier.

In 2000, Stabin and Breitz calculated the possible radiation dose to an infant from ingestion of common radiopharmaceuticals including Tc99m DTPA.[14] Because individual concentration into breast milk varies, they used typical doses, the lowest doses, and highest doses in literature to estimate the exposure of an infant through human milk. The investigators assumed that the drug reached peak concentration three hours after administration and that the infant breastfed starting at three hours after administration of the radiopharmaceutical and every breastfed every four hours subsequently. The total amount of milk with radiopharmaceutical present was calculated by summing all of the dose until the concentration dropped to negligible values. They also assumed that the dose ingested by the infant would be absorbed in the gastrointestinal tract and behave pharmacologically as it would in an adult. In their discussion, the authors noted that the highest concentration into breast milk of most radiopharmaceuticals was seen within fours hours of administration. The data regarding Tc99m DTPA from three studies of seven total patients indicated that no

[12] US Nuclear Regulatory Commission NUREG 1556, Volume 9, Appendix U, October 2002
[13] Rubow S, Klopper J, et al. The excretion of radiopharmaceuticals in human breast milk: additional data and dosimetry. Eur J of Nuc Med. 1994:21(2):144-153.
[14] Stabin MG, Breitz HB. Breast milk excretion of Radiopharmaceuticals:Mechanisms, Findings, & Radiation Dosimetry. J Nucl Med. 2000; 41:863-873.

interruption of breast feeding was necessary to limit the estimated dose to an infant to less than 1 mSv.

Reviewer comment: *The majority of patients had similar levels of Tc DTPA in breast milk with the concentration in milk decreasing exponentially with a half-life of approximately four hours. Therefore, to interrupt breastfeeding for four hours and to discard the milk would be appropriate after administration of Tc99m DTPA.*

Close contact infant exposure

Theoretically, exposure of a mother to a radioactive compound may pose a risk to her infant from proximity to the mother who is emitting radioactivity. This exposure occurs through close contact with the mother during cuddling even if the mother interrupts breastfeeding or is not currently breastfeeding but caring for an infant. The dose to the infant should not exceed 1mSv, the annual public dose limit.[19]

Mountford et al. estimated the close contact dose to infants from technetium based compounds by multiplying the dose rate measured on or near the surface of the patient by an effective exposure time. For their calculation of effective exposure time, they assumed that contact between parent and infant occurred as follows: the first 20 minutes of each hour for eight hours post injection, the first 20 min of every fourth hour for the next 12 hours, and the first 20 min of each hour for the remaining 4 hours.[15] The authors grouped all of the technetium based compounds, and noted that interruption of close contact was not essential but could be recommended for maternal reassurance.

Reviewer comment: The Mountford study included technetium based compounds that are used at doses that are much higher than the proposed dose for Lymphoseek. Therefore, it is unlikely that close contact between an infant and mother needs to be limited after Lymphoseek administration. In a communication with Brenda Ye, M.D., medical officer from DMIP, she noted that based on the dosimetry of Lymphoseek, an interruption in close contact would not be needed.

DISCUSSION

Lymphoseek (Technetium Tc99m Tilmanocept for Injection) is a diagnostic agent to be used intraoperatively to image tumor-draining lymph nodes mostly likely for staging of breast cancer and melanoma. The Division of Medical Imaging (DMIP) consulted the Pediatric and Maternal Health Staff's Maternal Health Team (PMHS-MHT) to review the Sponsor proposed labeling for the pregnancy and nursing mothers subsections.

Because no studies during pregnancy have been conducted in humans and animal reproduction studies were not conducted, PMHS-MHT recommends labeling Lymphoseek

[15] Mountford PJ. Estimation of close contact doses to young infants from surface dose rates on radioactive adults. *Nuclear Medicine Communications*. 1987;8:857-863.

pregnancy category C. Placental studies indicate that free technetium, such as that in technetium based radiopharmaceuticals, crosses the placenta.

In the Nursing Mothers subsection of labeling, PMHS-MHT recommends that nursing mothers pump and discard milk for the first four hours after receiving Lymphoseek. Based on the half life of Lymphoseek, its limited systemic absorption, and the limited nature of treatment needed to perform lymphatic mapping, the Sponsor proposed labeling recommendation for (b) (4). However, because multiple variables influence the degree of transfer of a radiopharmaceutical into breast milk and applying the principle of ALARA (as low as reasonably achievable), interruption for four hours would minimize risk to the infant without placing an undue burden on a nursing mother.

Additionally, including section 8.6 Females of Reproductive Potential in labeling for Lymphoseek will inform prescribers who must balance the benefits gained from the diagnostic procedure for pregnant women or female of reproductive potential against the impact of radiation exposure to a fetus. By conducting imaging studies early in the menstrual cycle, within the first 10 days, or testing patients for pregnancy who are unsure of their menses, providers can limit inadvertent exposures to Lymphoseek.

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

RECOMMENDATIONS

- Technetium Tc 99m Lymphoseek Injection should be labeled as pregnancy category C.

- Nursing mothers should be advised to pump and discard breast milk for the first four hours after administration of Technetium Tc 99m Lymphoseek Injection. Labeling for patient counseling regarding breast feeding should be included in section 17 as well.

- Section 8.6 Females of Reproductive Potential should be added to labeling. To prevent inadvertent exposures, Technetium Tc 99m Lymphoseek Injection should be given in the first ten days of the menstrual cycle or a pregnancy test should be done within the 48 hours prior to use of Technetium Tc 99m Lymphoseek Injection.

- MHT recommended revisions to the Sponsor's proposed labeling are below. A track changes version has been included in Appendix A.

PMHS – Maternal Health Labeling Recommendations

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

- Pregnancy Category C: Use only if clearly needed. (8.1)
- Nursing mothers: express and discard milk for the first 4 hours following administration of Technetium Tc 99m Lymphoseek. (8.3)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate or well-controlled studies of Technetium Tc99m Lymphoseek Injection in pregnant women. Unbound technetium crosses the placenta. All radiopharmaceuticals, including Technetium Tc 99m Lymphoseek Injection have a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development and the (b) (4) radiopharmaceutical dose. No reproduction and development studies in animals have been conducted with Technetium Tc 99m Lymphoseek Injection. Technetium Tc 99m Lymphoseek Injection should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether Technetium Tc 99m Lymphoseek Injection is (b) (4) in human milk. Based on the clearance of this drug, advise patients to express and discard milk during the first four hours after administration of Technetium 99m Lymphoseek Injection. Exercise caution when administering Technetium 99m Lymphoseek Injection to a nursing mother.

8.6 Females of Reproductive Potential

In females of reproductive potential, administration of Technetium Tc 99m Lymphoseek Injection should be performed within the ten days following the onset of menses or a pregnancy test should be performed within 48 hours prior to the administration.

17 PATIENT COUNSELING INFORMATION

- Instruct patients to inform their physician or healthcare provider if they:
  1. are pregnant or breast feeding.
  2. are sensitive to technetium-containing contrast agents.
  3. (b) (4)

- Inform nursing mothers to express and discard milk for the first four hours following administration of Technetium Tc 99m Lymphoseek Injection

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/s/

UPASANA BHATNAGAR
04/04/2012

MELISSA S TASSINARI
04/05/2012

LISA L MATHIS
04/10/2012

Clinical Consultation

FROM: Amir Shahlaee, M.D.
Medical Reviewer
Division of Oncology Products 2
OHOP/OND/CDER/FDA

Joseph Gootenberg, M.D.
Medical Team Leader and Deputy Division Director,
Division of Oncology Products 2
OHOP/OND/CDER/FDA

TO: Dr. Brenda Ye,
ODEIV/DMIP/CDER/FDA

SUBJECT: Use of Technetium Tc 99m Lymphoseek® Injection (abbreviated Tc 99m Lymphoseek) to for intra-operative lymph node mapping in pediatric oncology

IND 202,207

DATE CONSULT RECEIVED: February 27, 2012
DATE CONSULT COMPLETED: March 14, 2012

MATERIAL REVIEWED

1. Original NDA 202,207 application
2. The list of questions generated by DMIP and PMHS Review Teams
3. The formal consultation form
4. Previous consultation performed by PMHS
5. Denial of Pediatric Waiver Letter
6. Applicants proposed pediatric development plan

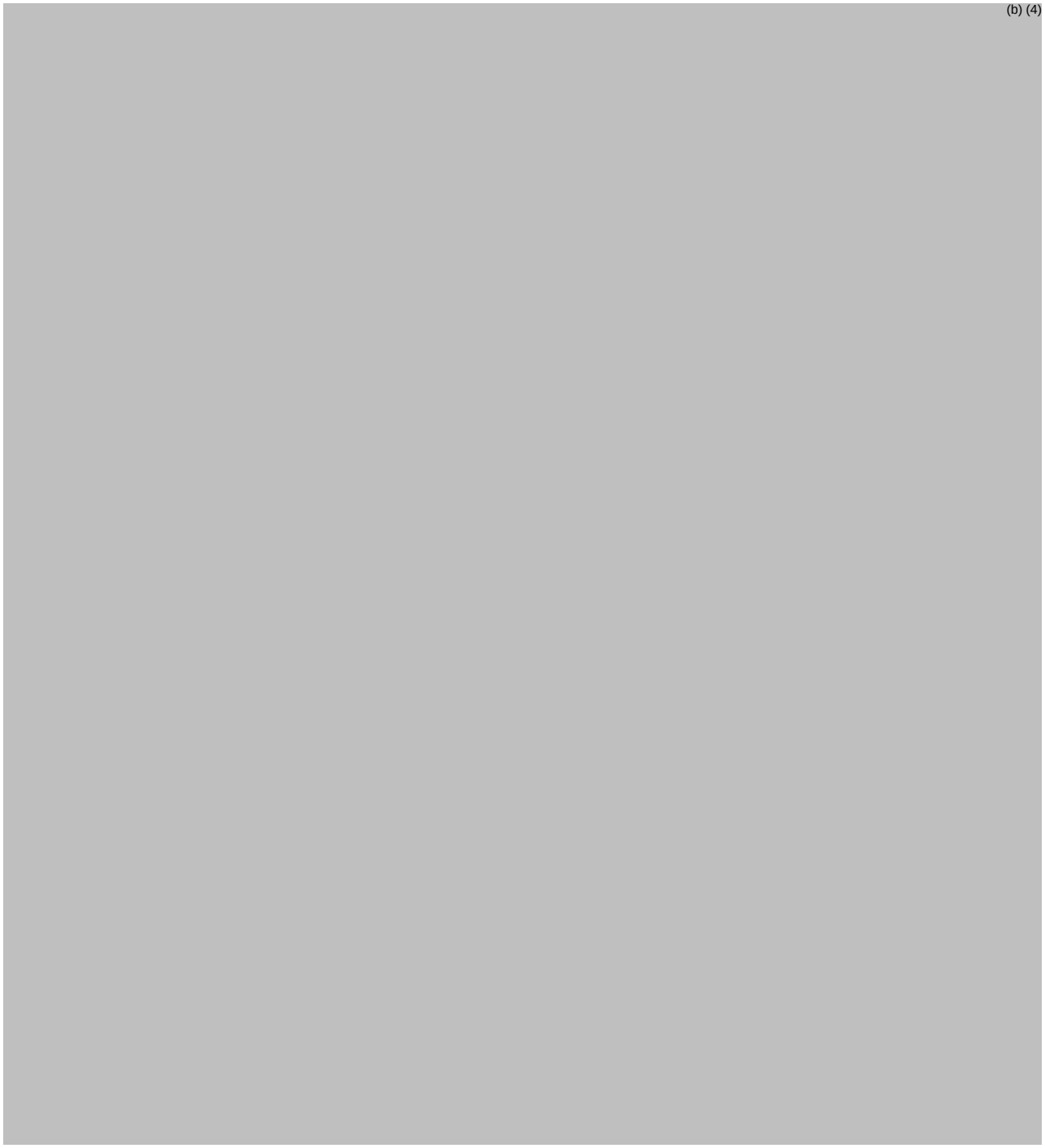
Requested Action and DDOP answers:

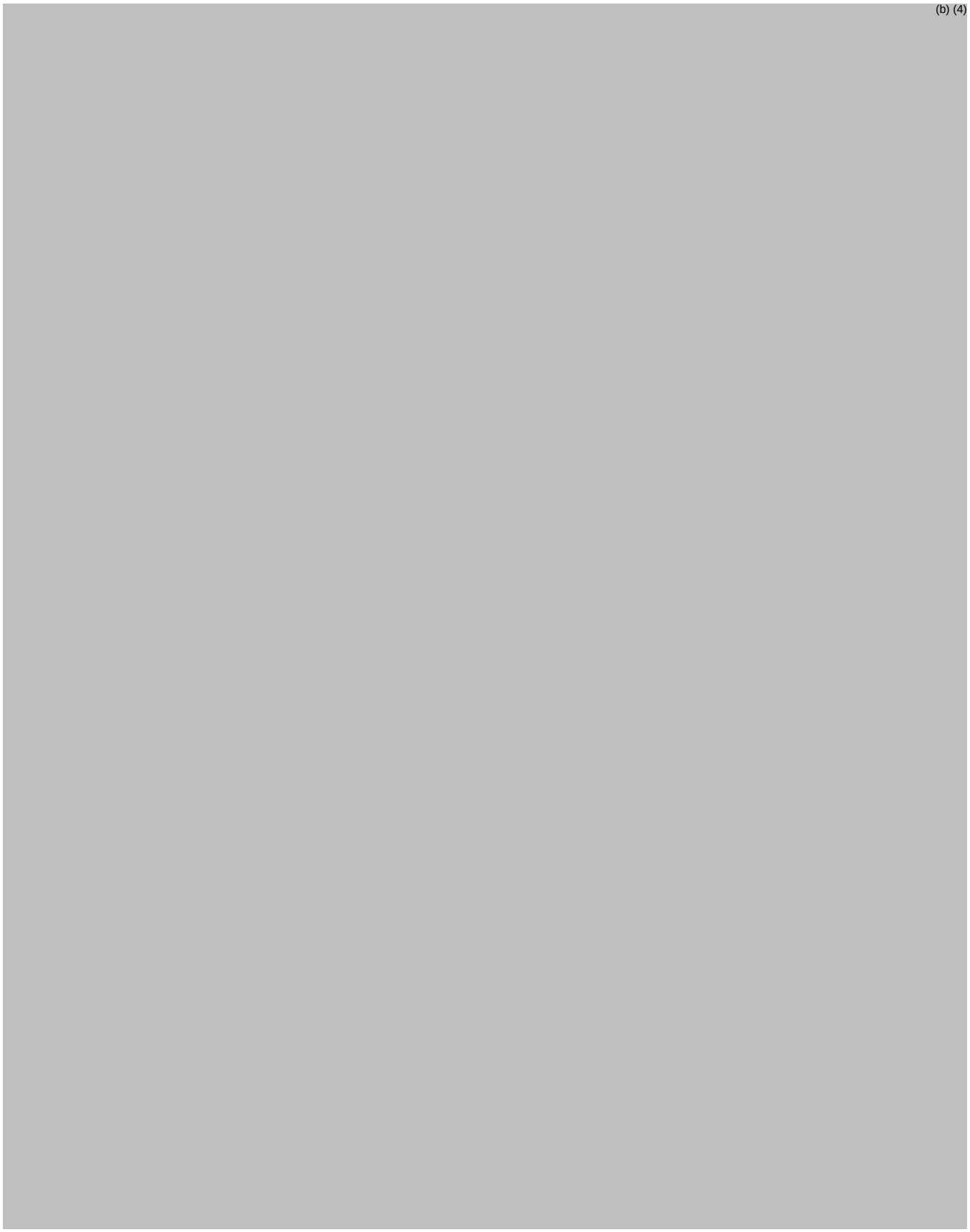
DMIP requests DOP2/OHOP to help answer the following questions:

1. In the adult population, besides breast cancer and melanoma, are there other cancer types the lymphatic mapping procedure is used?

OHOP response: Although multiple publications can be found in the literature regarding the use of ILM, the only diseases where ILM is widely used include malignant melanoma and breast cancer. Other indications where the use of ILM has been reported but remains situational, experimental or controversial include gastric cancer, colon cancer, Merkel cell carcinoma, GU tumors, head and neck cancer, non-small cell lung cancer, soft tissue sarcomas and thyroid tumors.

2. Please comment on the (b) (4) study proposals presented in the Sponsor's pediatric Plan.




(b) (4)

(b) (4)

Consultant review:

BACKGROUND

Intra-operative Lymphnode Mapping (ILM) with a radiopharmaceutical is an intra-operative examination wherein the surgeon utilizes a handheld gamma detection device that aids in the identification and localization of gamma emitting isotopically-labeled lymphatic detection agents. This process identifies for the surgeon the first lymph node(s) to receive lymphatic flow from the primary tumor site or tumor bed. Technetium Tc 99m Lymphoseek® Injection (abbreviated Tc 99m Lymphoseek) is a radiotracer that accumulates in lymphatic tissue by binding to a mannose binding receptor (MBR) protein that resides on the surface of macrophages and dendritic cells. Chemically, Tc 99m Lymphoseek (drug substance: tilmanocept) is technetium-99m labeled diethylenetriaminepentaacetic acid (DTPA) mannosyl dextran.

Navidea Biopharmaceuticals on August 22, 2011 submitted NDA 202207. The indication sought by the applicant was:

(b) (4)

The applicant had previously requested a full waiver from performing any pediatric studies required by PREA arguing that "the available pediatric populations will not provide adequate patient accrual to result in a statistically structured study for the evaluation of Lymphoseek in pediatric breast cancer or melanoma." However, based on PMH review a full waiver of required pediatric studies can only be granted if any of the following criteria are met (505B(a)(4) of the Federal Food, Drug, and Cosmetic Act):

1. Necessary studies are impossible or highly impracticable (e.g. the number of pediatric patients is so small or is geographically dispersed).

2. There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups.
3. The drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and is not likely to be used in a substantial number of pediatric patients.

Based on DPMH review however, the sponsor had not provided adequate epidemiologic data to support their position in regards to pursuit of a pediatric indication. The sponsor's request for waiver was subsequently denied.

In response the sponsor has submitted a pediatric development plan on 2/2 (b) (4)

(b) (4)

DMIP and DPMH request that the OHOP team evaluate the applicant's proposed plans and provide advice regarding the feasibility of performing these studies.

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/s/

AMIR SHAHLAEE
03/15/2012

JOSEPH E GOOTENBERG
03/15/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 9, 2012

TO: Alberta Davis-Warren, Regulatory Project Manager
Brenda Ye, M.D., Medical Officer
Division of Medical Imaging Products

FROM John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 202-207

APPLICANT: Neoprobe Corporation

DRUG: Lymphoseek® (technetium Tc 99m tilmanocept)

NME: Yes

INDICATION: (b) (4)

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: October 13, 2011

INSPECTION SUMMARY GOAL DATE: June 1, 2012

DMIP ACTION GOAL DATE: June 8, 2012

PDUFA DUE DATE: June 10, 2012

I. BACKGROUND

Intraoperative lymphatic mapping (**ILM**) using radiopharmaceuticals has evolved as an important adjunct to surgical evaluation of the lymphatic tissue draining a solid tumor (lymph node metastases). In the United States, ILM to facilitate lymph node biopsy and/or dissection is considered to be standard practice in surgery for breast cancer or melanoma. Imaging agents currently available for use in ILM are typically not targeted to the lymphatic tissue, and their imaging performance is affected greatly by fluid dynamics and passive dispersion. Low tissue specificity has limited the clinical utility of Tc 99m sulfur colloid or vital blue dye (**VBD**), two major currently available agents for imaging use in ILM.

Study Kit and Study Drug

The subject product of this inspection assignment is Lymphoseek® Kit for the preparation of a diagnostic radiopharmaceutical (technetium 99m tilmanocept, or Tc 99m Lymphoseek®). The Lymphoseek® Kit has been developed for (b) (4) Lyophilized Lymphoseek® is to be reconstituted and radiolabeled with Tc 99m prior to injection for ILM.

Lymphoseek® is a synthetic macromolecule engineered to accumulate rapidly and specifically within lymphatic tissue. It consists of multiple repeating units of mannose and diethylenetriaminepentaacetic acid (**DTPA**) synthetically attached to a 10-kilodalton dextran core: the mannose moiety allows the molecule to be specifically targeted the lymphatic tissue, and the DTPA moiety allows the molecule to be clinically detected as the chelation site for Tc 99m. The small 7 nm diameter of Lymphoseek® allows it to be susceptible to the pulse dynamics of lymphatic channels and capillaries, and within the lymphatic tissue, it binds specifically to macrophages and dendritic cells via the cellular mannose binding receptor (CD 206).

Pivotal Studies NEO3-05 and NEO3-09

Two open-label phase 3 studies of nearly identical study design were conducted to demonstrate that Lymphoseek® identifies tumor-draining lymph nodes with high sensitivity and clinical utility:

- NEO3-05 was a prospective, open-label, single-arm, within-patient comparison study (Tc 99m Lymphoseek® versus VBD) conducted at 14 U.S. centers plus one center in Israel (179 subject enrollment) over a period of 12 months, from June 2008 to June 2009. The primary study objective was to determine the concordance between Tc 99m Lymphoseek® and VBD, using VBD as the "truth standard," in the *in vivo* detection of tumor-positive lymph nodes.
  - Adult patients (age ≥ 18 years) with surgically resectable node-negative melanoma or breast cancer (and with Grade 0-2 ECOG performance status) were given a single 50 µg injection of Lymphoseek® radiolabeled with Tc 99m (0.5 or 1.0 mCi, depending on the timing of subsequent ILM) in close proximity to the primary tumor (intradermal, subcutaneous, subareolar, or peritumoral).
  - At ILM, a VBD (either isosulfan blue or sulfan blue, whichever was available at the study center) was also given as described in the VBD product insert. Lymph nodes identified as “hot” (gamma probe) and/or “blue” (visual identification) were surgically excised and examined histologically using standard methods (serial H&E sections, tumor-specific immunohistochemstry as needed).
  - The primary efficacy endpoint/analysis was Lymphoseek®-to-VBD concordance at the lymph node level, or the proportion of lymph nodes identified at ILM to be both "blue" (visual detection of VBD) and "hot" (gamma probe detection of Lymphoseek®) using the number of "blue" lymph nodes as the denominator ("truth standard").
  - Major secondary endpoints/analyses were: (1) Lymphoseek®-to-VBD concordance at the patient level, using the number of patients with any "blue" lymph node as the denominator; and (2) sensitivity and false negative rate for each detection method in patients undergoing

lymphadenectomy, using histopathology to confirm (or resolve) concordant (or discordant) findings:

- At the lymph node level, the overall concordance was 93% (239 of 256 lymph nodes), with higher concordance in melanoma (98%) than in breast cancer (90%).
- At the patient level (N=158, ITT population), the overall concordance was 92%, with higher concordance in melanoma (96%) than in breast cancer (89%).
- Of the 380 lymph nodes excised (safety population), 41 were tumor-positive by histopathology, of which 38 were identified by Lymphoseek®, 33 by VBD, and 32 by both methods. Using histopathology as the "truth standard," the sensitivity in detecting tumor-positive lymph nodes was higher for Lymphoseek (93%) than for VBD (80%); the false negative rate for VBD (20%) was nearly 3-fold that for Lymphoseek (7%).
- Although not prospectively defined, VBD-to-Lymphoseek® *reverse* concordance was also determined (at lymph node and patient levels) using the number of "hot" lymph nodes (or the number of patients with "hot" lymph nodes) as the denominator. The *reverse* concordance was 70% at the lymph node level (239 of 343 lymph nodes) and 57% at the patient level (N = 167).

- NEO3-09 was also a prospective, open-label, single-arm, within-patient comparison study of Tc 99m Lymphoseek® versus VBD, with the following major differences from NEO3-05:
  - This second pivotal study was conducted at 8 US centers over a period of 9 months, from July 2010 to April 2011 (after NEO3-005 had been completed), and enrolled 165 patients, of whom 153 were injected with Lymphoseek®.
  - The overall study design (including major endpoints/analyses) was the same as in NEO3-05. In NEO3-09, however, the secondary endpoint/analysis of *reverse* concordance (to demonstrate superiority of Lymphoseek® over VBD) was prospectively defined:
    - Concordance was 100%, at the lymph node level (229 lymph nodes) and at the patient level (N=133, ITT population). *Reverse* concordance was 61% at the lymph node level (229 of 378 lymph nodes) and 50% at the patient level (N = 76).
    - Of the 379 lymph nodes excised (safety population), 40 were tumor-positive by histopathology, all of which were identified by Lymphoseek®. VBD detected 30 of the 40 tumor-positive lymph nodes. Using histopathology as the "truth standard," the sensitivity in detecting tumor-positive lymph nodes was higher for Lymphoseek (100%) than for VBD (75%); the false negative rate was 25% for VBD. False negative results were not seen for Lymphoseek®.
    - Of the 33 patients with at least one tumor-positive lymph node, VBD missed at least one tumor-positive lymph node in 10 patients, and missed all tumor-positive lymph nodes in 6 patients; none (lymph nodes or patients) were missed by Lymphoseek®.

For both NEO3-05 and NEO3-09, safety evaluation, performed through 30 days post-injection, consisted of adverse event monitoring, clinical laboratory tests, vital signs, ECGs, and physical examination. The sponsor noted no significant drug-related safety signal in either study. Based on these results, the sponsor claims excellent clinical utility of Lymphoseek® in (b) (4)

In this NDA, Neoprobe seeks the following Lymphoseek® indication for use statement: (b) (4)

II. INSPECTION RESULTS

Five good clinical practice (**GCP**) inspections were conducted: two clinical study sites for Study NEO3-05, two clinical study sites for Study NEO3-09, and the sponsor site (Navidea, formerly Neoprobe). All study sites were selected based on large subject enrollment. Site 05 in Study NEO3-05 (Kenneth Deck) was selected specifically to evaluate the effect of a systematic error in study drug preparation on the primary efficacy endpoint data: the use of incorrect diluent volumes in reconstituting the lyophilized study drug for injection (10-fold larger than the volume specified in the study protocol).

	Inspected Entity	Protocol Site Number Subjects	Inspection Dates	Classification
1	Anne Wallace, MD Department of General Surgery UCSD Medical Center 3855 Health Sciences Drive #0987 La Jolla, CA 92093-0987	NEO3-05 Site 02 55 subjects	Nov 7 - 30, 2011	Pending (Preliminary VAI)
2	Anne Wallace, MD Department of General Surgery UCSD Medical Center 3855 Health Sciences Drive 0987 La Jolla, CA 92093-0987	NEO3-09 Site 01 56 subjects	Nov 7 - 30, 2011	Pending (Preliminary VAI)
3	Kenneth Deck, MD South Orange County Medical Center SOC Surgical Medical Group 24411 Health Center Drive, Suite 350 Laguna Hills, CA 92653	NEO3-05 Site 05 20 subjects	Nov 14 - Dec 6, 2011	Pending (Preliminary VAI)
4	Vernon Sondak, MD Department of Cutaneous Oncology Moffitt Cancer Ctr & Research Inst 12902 Magnolia Drive Tampa, FL 33612	NEO3-09 Site 02 41 subjects	Oct 31 - Nov 3, 2011	Pending (Preliminary VAI)
5	Navidea Corporation (formerly Neoprobe) c/o Rodger Brown, Vice President Regulatory Affairs and Quality Assurance 425 Metro Place North, Suite 300 Dublin, Ohio 43017	NEO3-05 NEO3-09	Dec 12 - 15, 2011	Pending (Preliminary NAI)

Classification:

NAI = no deviation from regulations
VAI = deviation from regulations
OAI = significant deviation from regulations and/or data unreliable

Pending:

Preliminary classification is based on information on Form FDA 483 and preliminary communication with the field investigator. The final establishment inspection report (**EIR**) has not been received from the field office and OSI's complete review of the EIR remains pending as of this clinical inspection summary (**CIS**).

1. Anne Wallace (NEO3-05, Site 02)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
- Data verification: primary endpoint, adverse events, subject randomization, protocol deviations, subject discontinuations, and concomitant medications
- Subjects: 55 subjects were screened, 55 enrolled, and 55 completed the study. Subject records for all enrolled subjects were reviewed, including complete review of informed consent documentation and primary endpoint data.

b. General observations and comments:

- A Form FDA 483 was issued for the following GCP deficiencies:
  - The drug accountability records indicated inconsistent drug lot numbers for one subject. Specifically, for Subject 050220:
    - The drug disposition log indicated that the subject received the study medication from Lot NMK 002-058, but the case report form (**CRF**) for the same subject indicated a different lot number, Lot NMK 002-056.
    - This inconsistency appeared to be an isolated transcription error. The number shown on the drug disposition log appeared to be correct, and the number shown on the CRF incorrect.
  - For one subject, the percent radiolabeling yield calculation results for the study medication to be administered were not exactly the same as shown on the quality control (**QC**) worksheet and on the CRF. Specifically, for Subject 050206:
    - The percent radiolabeling yield shown on the QC worksheet was 99%, above the > 97% QC specification. The yield shown on the CRF was 96%, below the > 97% QC specification.
    - The radiolabeled study medication was prepared by (b) (4) a contract research organization (CRO). The study site had no control over the preparation of the study medication, including radiolabeling and QC.
    - This inconsistency apparently resulted from not adjusting for the background radiation count when the study site used the raw radiation count data provided by (b) (4) to calculate the radiolabeling yield for documentation on the CRF.

      Reviewer's Comments:

      The inconsistent percent radiolabeling yields resulted from inconsistent calculation methods; the study protocol does not explicitly specify the need to adjust for the background radiation count. The study protocol could have been amended to ensure that study sites and (b) (4) use the same calculation method. This inconsistency is not expected to have a significant impact on the study results or subject safety.
  - In obtaining informed consent from one Spanish-speaking subject (Subject 050220), an English version of the information consent form was used.

- Other than as cited on the Form FDA 483, no significant GCP deficiencies were observed:
  - Drug accountability was well documented.
  - Source records appeared to be accurate and matched corresponding case report forms.
  - Informed consent appeared to have been obtained properly from all subjects.
  - Primary endpoint data were verifiable.
  - Underreporting of adverse events was not observed.
  - IRB oversight and study monitoring appeared to have been adequate.

c. Assessment of data integrity: The observed deficiencies (cited on Form FDA 483) appear to be isolated occurrences of minor significance. The data from this study site appear reliable.

Note: Observations noted above for this inspection site are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Anne Wallace (NEO3-09, Site 01)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
- Data verification: primary endpoint, adverse events, subject randomization, protocol deviations, subject discontinuations, and concomitant medications
- Subjects: 57 subjects were screened, 56 enrolled, and 54 completed the study. Subject records for all enrolled subjects were reviewed, including complete review of informed consent documentation and primary endpoint data.

b. General observations and comments:

- A Form FDA 483 was issued for the following GCP deficiencies:
  - The study protocol specifies the designation of a separate study medication vial for each subject, but two subjects appeared to have shared a common vial. Specifically, Subjects 090147 and 090150 received doses from the same Vial 2, Lot NMK OO5A-022.
  - For Subject 090129, the drug disposition log showed that the subject received the study medication from Vial 4 (Lot NMK 003B-025), but the CRF indicated Vial 3 (same lot).

    Reviewer's Comments:

    Since Study NEO3-09 was an open-label, single-arm, within-patient comparison study of Tc 99m Lymphoseek® versus VBD, these three subjects did receive the drug to which they were "randomized."
  - For one subject, the percent radiolabeling yield calculation was not exactly the same on the QC worksheet and on the CRF. Specifically, for Subject 090111:
    - The percent radiolabeling yield on the QC worksheet was 98%, but the yield on the CRF was 97.03%. Both calculation results were above the > 97% QC specification.
    - As in Study NEO3-05 (also conducted at this site), (b) (4) prepared the study medication. The study site had no control over the preparation of the study medication, including radiolabeling and QC.

- This inconsistency apparently resulted from not adjusting for the background radiation count when the study site used the raw radiation count data provided by (b) (4) to calculate the radiolabeling yield for documentation on the CRF.

  Reviewer's Comments:

  The inconsistent percent radiolabeling yields resulted from inconsistent calculation methods; the study protocol does not explicitly specify the need to adjust for the background radiation count. The study protocol could have been amended to ensure that study sites and (b) (4) use the same calculation method. This inconsistency is not expected to have a significant impact on the study results or subject safety.

- For Subject 090107, intraoperative source records indicated that Lymph Node 1 was detected by both Lymphoseek and VBD detection methods, but the CRF for this subject indicated that neither method detected Lymph Node 1.

  Reviewer's Comments:

  - In deviation from the study protocol (apparent oversight), the radiation count from Lymph Node 1 was not measured *ex vivo* after surgical resection, and the *ex vivo* radiation count data could not be reported on the CRF.
  - The intraoperative source records refer to the *in vivo* detection of Lymph Node 1 (prior to surgical resection, for identification as a lymph node to be resected). Since the source records and the CRF refer to different circumstances *(in vivo* or *ex vivo*), the source records and the CRF are not inconsistent.

- In obtaining informed consent from Subject 090149, the subject signed the consent form but the study coordinator dated the form/signature.

- Other than as cited on the Form FDA 483, no significant GCP deficiencies were observed:
  - Drug accountability was well documented.
  - Source records appeared to be accurate and matched corresponding CRFs.
  - Informed consent appeared to have been obtained properly from all subjects.
  - Primary endpoint data were verifiable.
  - Underreporting of adverse events was not observed.
  - IRB oversight and study monitoring appeared to have been adequate.

c. Assessment of data integrity: The observed deficiencies (cited on Form FDA 483) appear to be isolated occurrences of minor significance. The data from this study site appear reliable.

Note: Observations noted above for this inspection site are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

3. Kenneth Deck (NEO3-05, Site 05)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
- Data verification: primary endpoint, adverse events, subject randomization, protocol deviations, subject discontinuations, and concomitant medications

- Subjects: 20 subjects were screened, 19 enrolled, and 19 completed the study. Subject records for all enrolled subjects were completely reviewed.

b. General observations and comments:

- A Form FDA 483 was issued for the following deficiencies:
  - For all subjects, the administered study medication volumes were above the 0.2 - 0.4 mL range specified in the study protocol, as shown in Table 1 below:

Table 1: Injection volumes used at NEO3-05 Site 05 (Kenneth Deck)

Subject	mL	Subject	mL	Subject	mL
0501	4.0	0508	1.2	0515	4.0
0502	1.2	0509	4.0	0517	4.0
0503	1.2	0510	4.0	0518	4.0
0504	I.0	0511	4.0	0519	4.0
0505	4.0	0512	1.2	0520	4.0
0506	4.0	0513	4.0		
0507	4.0	0514	4.0		

Reviewer's Comments:

- As at other study sites, [redacted] (b) (4), see above under *Anne Wallace, NEO3-05, Site 02*), prepared and radiolabeled the study medication and provided it in pre-filled syringes, ready for injection. The study site had no control over the preparation of the study medication, including radiolabeling and QC.
- (b) (4) prepared the study medication according to the standard of care at this site for the particular malignancy being treated (apparently upon request from the site). The diluent volumes were up to 10-fold larger than the upper limit of the protocol-specified volume range. Neither the study site nor (b) (4) asked the sponsor to amend the study protocol (or requested a waiver) to permit the use of these diluent/injection volumes.

  - Two subjects were given incorrect doses of Tc-99m. Specifically, Subjects 0503 and 0504 received the study medication one day prior to surgery, but were injected with 1.0 mCi Tc-99m (dose for same-day surgery) instead of 0.5 mCi Tc-99m (dose for next-day surgery).
  - Two ineligible subjects were enrolled into the study. Specifically, Subjects 0504 and 0512 (melanoma, Breslow depths of 0.7 and 0.5 mm, respectively) were enrolled and given the study medication, in deviation of the study protocol which specifies that patients with melanoma of Breslow depth less than 0.75 mm are to be excluded.

- The drug accountability records were not always consistent. Specifically, for five subjects, records of injection volumes at the study site's Radiology Department conflicted with the records at Nuclear Medicine Department, as shown below in Table 2:

Table 2: Discrepant study medication volumes, Radiology vs Nuclear Medicine

Subject	Radiology Worksheet (mL)	Nuclear Medicine Report (mL)
0505	4.0	0.44
0507	4.0	0.42
0512	1.2	2.0
0514	4.0	0.10
0515	4.0	4.4

  - The records maintained at Radiology were to document the actual injection volumes administered to the study subjects. The same volumes were documented on the records maintained by the study coordinator.
  - The records maintained at Nuclear Medicine were to verify receipt of the pre-filled syringes from (b) (4). Both automated barcode (primary) and manual (back up) data entry procedures were used.

    Reviewer's Comments:

    The study medication from (b) (4) was received by Nuclear Medicine, not by the hospital pharmacy accustomed to medication recordkeeping. In Table 2 above, the volumes recorded on the Nuclear Medicine Report appear to be "syringe receipt documentation" volumes, and the actual volumes appear not to have been important and prone to manual data entry error. The volumes recorded on the Radiology Worksheet match those shown in Table 1 (recorded by the study coordinator).

- The percent radiolabeling yields for the study medication differed between the QC worksheet and the CRF. Specifically, discrepant results were noted in four subjects as shown below in Table 3, with the results on the CRFs for two subjects failing to meet the > 97% product release QC specification:

Table 3: Discrepant radiolabeling yield results, QC worksheet vs CRF

Subject	QC Worksheet (%)	CRF (%)
0503	99.0	97.2
0511	99.2	97.0
0515	99.4	86.9
0519	99.5	89.1

Reviewer's Comments:

- (b) (4) prepared and radiolabeled the study medication and provided it in pre-filled syringes, ready for injection. The study site had no control over the preparation of the study medication, including radiolabeling and QC.
- The inconsistency in percent radiolabeling yield apparently resulted from not adjusting for the background radiation count when the study site used the raw radiation count data provided by (b) (4) to calculate the radiolabeling yield for documentation on the CRF.
- For Subjects 0503 and 0511, the discrepancy in the percent radiolabeling yield (QC worksheet vs CRF) is small, and the lower value noted on the CRF is still above the > 97% product release specification.
- For Subjects 0515 and 0519, the CRF value does not meet the > 97% product release specification. A detailed review of the calculations for these two subjects showed that the background count does reconcile the apparent discrepancy between the QC worksheet and the CRF. The calculations for Subject 0515 is shown below, as an example:
  - The "bound" count (lower separation zone), the "unbound" count (upper separation zone), and the background count were 3188, 479, and 465, respectively. The percent radiolabeling yield was calculated as: lower count x 100 / (lower count + upper count).
  - The percent yield as noted on the CRF was: 3188 x 100 / (3188 + 479) = 86.9%. When the background count was considered, the yield as noted on the QC worksheet was: (3188 - *465*) x 100 / [(3188 - *465*) + (479 - *465*)] = 99.5%.
- For the percent radiolabeling yield calculation, the study protocol does not explicitly specify the need to adjust for the background radiation count. The study protocol could have been amended to ensure that different study participants (study sites and any CRO) use the same calculation method.
- Although cited as a GCP deficiency on Form FDA 483, the inconsistent percent radiolabeling yields resulted from inconsistent calculation methods. This inconsistency is not expected to have affected the study results or subject safety.

- Other than as cited on the Form FDA 483, no significant GCP deficiencies were observed:
  - Source records appeared to be accurate and matched corresponding case report forms.
  - Informed consent appeared to have been obtained properly from all subjects.
  - Primary endpoint data were verifiable.
  - Underreporting of adverse events was not observed.
  - IRB oversight and study monitoring appeared to have been adequate.

c. Assessment of data integrity: The observed deficiencies appear to be isolated occurrences of minor significance. The data from this study site appear reliable, with the following caveats regarding incorrect diluent/injection volumes of the study medication used at this study site.

- (b) (4) prepared and radiolabeled the study medication and provided it to the study site in pre-filled syringes, ready for injection. Apparently upon request from the study site, (b) (4) prepared the study medication according to standard practice at this site. The diluent/injection volumes that (b) (4) used differed for each subject (as requested by the study site, depending on the particular malignancy being treated) and were up to 10-fold larger than the upper limit of the volume range specified in the study protocol.

- The study site appeared not to have recognized the diluent/injection volumes as being inconsistent with the study protocol (as protocol violations). The protocol was not formally amended to include the diluent/injection volumes used at this study site. Apparently no safety/comfort concerns were encountered with the use of larger than protocol-specified diluent/injection volumes.
- These inspectional findings were discussed with the review division (2/8/2012). Given this inspectional verification of the incorrect diluent/injection volumes used at this study site, the review division considers the data from this site to be reliable and plans to include the data in evaluating Lymphoseek® efficacy.
- The effect of the diluent/injection volumes used at this site on the study results is unclear (concordance of Lymphoseek® with VBD). In the NDA, the sponsor has provided site-specific analyses to support the claim that the use of diluent/injection volumes that are larger than recommended decreases Lymphoseek® efficacy (concordance of Lymphoseek® with VBD). The sponsor's claim and supporting site-specific analyses are currently under evaluation by the review division, and the review findings (about impact on efficacy) may be reflected in the product labeling, if Lymphoseek® were to be approved.

Note: Observations noted above for this inspection site are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

4. Vernon Sondak (NEO3-09, Site 02)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
- Data verification: primary endpoint, adverse events, subject randomization, protocol deviations, subject discontinuations, and concomitant medications
- Subjects: 42 subjects were screened, 41 enrolled, and 37 completed the study. Subject records for 28 enrolled subjects were reviewed, including complete review in 14 subjects.

b. General observations and comments:

- A Form FDA 483 was issued for not promptly reporting serious adverse events (**SAEs**) to the sponsor. Two SAEs in two subjects were reported to the sponsor later than the protocol-specified timeframe. Specifically:
  - Subject 0219 experienced bradycardia (heart rate 32/min), an SAE considered unrelated to the study medication. Patient management was prompt, appropriate, and included cardiology consultation. The event was reported to the sponsor after uneventful patient recovery, one day later than the protocol-specified timeframe of within 24 hours.
  - Subject 0220 experienced chills, rigors, and tender left axilla due to an infected seroma. Given the patient's history, this condition was an expected SAE considered unrelated to the study medication. Patient management was prompt and appropriate, and consisted of incision, drainage, and the administration of intravenous antibiotics. The event was reported to the sponsor after uneventful patient recovery, five days later than the protocol-specified timeframe of within 24 hours.

- Primary endpoint data were verifiable; the data matched among source records, CRFs, and data listings reported in the NDA. Underreporting of adverse events was not observed.
- Informed consent was properly obtained from all subjects. Source records appeared factual, complete, and matched corresponding CRFs. Drug accountability was well documented. IRB oversight and study monitoring appeared to be adequate.

c. Assessment of data integrity: Although regulatory violations were noted, these are considered isolated in nature and unlikely to significantly impact data reliability. Data from this study site appear reliable.

Note: Observations noted above for this inspection site are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

5. Navidea Corporation (formerly Neoprobe)

a. What was inspected:

- Review of standard operating procedures (**SOPs**) for: study monitoring, compliance audits, data management, and test article handling and accountability
- Review of electronic and hard copies of CRFs

b. General observations:

- No Form FDA 483 was issued at the close of the inspection. The sponsor's records indicated adequate control over the various aspects of the audited studies.
- The sponsor's study monitoring records indicated that the study monitors (CRO) did alert the sponsor about NEO3-05 Site 05 (Kenneth Deck) using incorrect diluent/injection volumes of the study medication; however, the sponsor apparently failed to review and/or take corrective action in a timely manner. However, after study data were locked in April 2009:
  - The sponsor alerted CDER that incorrect diluent/injection volumes of the study medication were used at Site 05 (and also Site 06), and proposed to exclude the affected data from efficacy analyses.
  - The sponsor's site-specific efficacy analyses indicated that the use of larger than recommended Lymphoseek® diluent/injection volumes decreases its apparent clinical utility.

    Reviewer's Comments:

    - The sponsor claimed that retaining these data (not collected according to the study protocol, at NEO3-05 Site 05 and Site 06) would make Lymphoseek® appear less effective than when correct diluent/injection volumes are used (according to the study protocol). The following review concerns were discussed with the review division (2/8/2012):
      - Given the inspectional verification of the incorrect diluent/injection volumes used at NEO3-05 Site 05 (Kenneth Deck), the review division considers the data from this site (and also NEO3-05 Site 06, by extrapolation althouth not inspected) to be reliable and advised the sponsor to retain the affected data in evaluating Lymphoseek® efficacy.
      - Although concerned about this diluent/injection volume protocol violation, the review division advised the sponsor to retain the affected data since demonstration of efficacy despite retaining the affected data would support the ***robustness*** of Lymphoseek® efficacy. In other words, such demonstration of Lymphoseek® efficacy (despite

retaining the affected data) would show that the efficacy of Lymphoseek® is not so "fragile" as to require product reconstitution ***exactly*** as recommended at all participating study centers.

- Demonstration of efficacy despite retaining the affected data would provide ***reassurance*** that, although recommended reconstitution procedures should be followed, minor deviation from the recommended procedures (anticipated in clinical practice) will not render Lymphoseek® ineffective. Efficacy analyses, both with and without the data affected by this diluent/injection volume protocol violation, would be useful in writing the ***instructions for use*** in the final product label, if Lymphoseek® were to be approved.

c. Assessment of data integrity: The inspectional findings indicate that the data reported by the sponsor in the NDA accurately reflect the data reported by the clinical sites.

Note: Observations noted above for this inspection site are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In support of this NDA review, five GCP inspections (four clinical study sites and the sponsor site) were conducted between November 7, 2011 and December 15, 2011.

Four of the five inspections (NEO3-05 Site 02, NEO3-09 Site 01, NEO3-09 Site 02, and the sponsor site) revealed no major deficiencies; observed deficiencies at these four sites appeared to be isolated occurrences of minor significance. The data from three clinical study sites (NEO3-05 Site 02, NEO3-09 Site 01, and NEO3-09 Site 02) as reported by the sponsor under NDA 202-207 are considered acceptable in support of the proposed indication.

The deficiencies observed at NEO3-05 Site 05 (Kenneth Deck) also appeared to be isolated occurrences of minor significance, except for the systematic use of diluent/injection volumes of the study medication that were up to 10-fold larger than the upper limit of the protocol-specified volume range.

- (b) (4) prepared and provided the study medication in pre-filled syringes to contain large/varying volumes "customized" to each subject (particular malignancy being treated) according to standard practice at NEO3-05 Site 05 (Kenneth Deck), upon request by this study site. (b) (4) operated as multiple satellite centers, each located at/near the "assigned" study site, and the diluent/injection volumes for most study sites were within the protocol-specified volume range.
- This inspectional verification of incorrect diluent/injection volulmes used at this study site was discussed with the review division (2/8/2012). Given the inspectional verification, the review division considers the data from this site to be reliable and plans to include the data in evaluating Lymphoseek® efficacy. In the NDA, the sponsor has provided site-specific analyses to support the claim that the use of diluent/injection volumes that are larger than recommended decreases Lymphoseek® efficacy (concordance of Lymphoseek® with VBD). This sponsor's claim and supporting analyses are currently under review, and the review finding may be incorporated into Lymphoseek® labeling if Lymphoseek® were to be approved.

The data from NEO3-05 Site 05 (Kenneth Deck) as reported by the sponsor under NDA 202-207 also appear to be acceptable in support of the proposed indication. As unintended study data (but data nonetheless), the inspectional verification of the incorrect diluent/injection volumes may be useful in evaluating the robustness of Lymphoseek® efficacy: in clinical practice, the efficacy may differ

significantly from that determined under a well-monitored clinical trial, partly owing to the use of inconsistent diluent/injection volumes.

Note: For all five inspections, the final EIR has not been received from the field office and the final classification of the inspection outcome remains pending. The observations noted above are based on preliminary communications with the field investigator. An addendum to this clinical inspection summary will be forwarded to the review division if any final classification changes from the pending classification, or if additional observations of clinical or regulatory significance are discovered after completing the EIR review.

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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02/09/2012

SUSAN D THOMPSON
02/09/2012

TEJASHRI S PUROHIT-SHETH
02/09/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
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Pediatric and Maternal Health Staff Memorandum

Date: December 20, 2011 **Date Consulted:** November 22, 2011

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Team Leader – Pediatric Team
Pediatric and Maternal Health Staff

Lisa Mathis, MD, OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Medical Imaging Products (DMIP)

Drug: Lymphoseek Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection, NDA 202207

Subject: PREA Waiver Request, Pediatric Use Labeling

Materials Reviewed:

- PREA Waiver Request, submitted August 10, 2011

Consult Question:
Review labeling and address the Sponsor's request for a full waiver of pediatric studies. Specifically, respond to the following three questions:

1. How often is lymphatic mapping performed in the pediatric population?
2. Would you recommend a full waiver of pediatric studies based on your response to question 1?
3. If a partial pediatric waiver is granted, what would be the appropriate age cut-off?

INTRODUCTION

On August 22, 2011, Neoprobe Corporation submitted a New Drug Application, NDA 202207, Lymphoseek Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection.

(b) (4)

DMIP consulted the Pediatric and Maternal Health Staff (PMHS) – Pediatrics to review labeling and address the Sponsor's request for a full waiver of pediatric studies. Specifically, respond to the following three questions:

1. How often is lymphatic mapping performed in the pediatric population?
2. Would you recommend a full waiver of pediatric studies based on your response to question 1?
3. If a partial pediatric waiver is granted, what would be the appropriate age cut-off?

BACKGROUND

PREA Waiver Request

Neoprobe Corporations submitted a request for waiver of pediatric studies with Lymphoseek for the following reason**:**[1]

> "The available pediatric populations will not provide adequate patient accrual to result in a statistically structured study for the evaluation of Lymphoseek in pediatric breast cancer or melanoma."

In addition, Neoprobe states "that Lymphoseek might be employed off-label in some pediatric patients. To the extent that Lymphoseek might be employed for use in this patient population, Neoprobe, in the previous discussion, has presented strong evidence that Lymphoseek presents minimal and acceptable risk to this population of patients."

Sponsor Proposed Labeling

8.4 Pediatric Use

(b) (4)

DISCUSSION

PREA

A Sponsor is required to adequately address the Pediatric Research Equity Act (PREA) of 2007, with the submission of a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. A full waiver of required pediatric studies can be granted if any of the following criteria are met (505B(a)(4) of the Federal Food, Drug, and Cosmetic Act):

[1] See PREA waiver request, August 10, 2011

1. Necessary studies are impossible or highly impracticable (e.g. the number of pediatric patients is so small or is geographically dispersed).
2. There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups.
3. The drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and is not likely to be used in a substantial number of pediatric patients.

At this time, the sponsor has not presented sufficient evidence for PMHS to agree with, and/or recommend a full waiver of studies for Lymphoseek in the pediatric population, as insufficient data has been submitted to support any of the full waiver criteria. The Sponsor's proposed indication for Lymphoseek is for the intraoperative evaluation of tumor-draining lymph nodes. No specific tumor types are mentioned in the indication, yet the Sponsor based their full waiver request of required pediatric studies on the evaluation of Lymphoseek in pediatric breast cancer or melanoma, both of which occur rarely in the pediatric populations. Our pediatric oncology colleagues report that Lymphoseek could potentially be used in the intraoperative mapping of lymph nodes in multiple pediatric malignancies, including soft tissue sarcomas, germ cell tumors, neuroblastoma, Wilms tumor, and melanoma, etc.; however, pediatric surgery experts would need to be consulted to provide further information.

The Sponsor reports that there would not be any safety concerns with the off-label use of Lymphoseek in pediatric patients, a use that they are anticipating after product approval, as intraoperative lymph mapping is currently performed in pediatric patients. The Sponsor also reports that the performance of Lymphoseek should be similar between adults and children.

Pediatric Use Labeling
The Pediatric Use subsection of labeling should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted.

CONCLUSIONS
The Sponsor is required to adequately address PREA before the approval of Lymphoseek. Neoprobe Corporation has not presented sufficient data to support a request for a full waiver of pediatric studies under PREA. The Sponsor is required to provide data to support their waiver request. Such information should include complete epidemiologic data describing the prevalence of pediatric tumors likely to metastasize to lymph nodes. In addition, if the Sponsor can provide evidence to support that the indication is sufficiently similar between adults and children AND if efficacy was established in adults using adequate and well-controlled trials, then considering whether efficacy could be extrapolated to the pediatric population may be appropriate. Thus, the Sponsor should also submit their rationale for extrapolation from adequate and well-controlled studies in adults to the pediatric population, as they reported that the performance of Lymphoseek should be similar between adults and children. If the Sponsor chooses to provide a rationale for extrapolation from adult studies to the pediatric population, they will need to provide a plan to obtain dose-ranging and safety data in the pediatric population. Furthermore,

the sponsor must provide justification for the deferral of any pediatric studies and any pediatric partial waiver requests.

PMHS has the following responses to the PREA consult questions:

1. How often is lymphatic mapping performed in the pediatric population?

PMHS Response: Despite the requirement to submit data to support a PREA waiver request, the Sponsor has not submitted sufficient data to evaluate how often lymphatic mapping is performed. In addition to possible use in melanoma, our pediatric oncology colleagues report that Lymphoseek could potentially be used in the intraoperative mapping of lymph nodes in multiple pediatric malignancies, including soft tissue sarcomas, germ cell tumors, neuroblastoma, and Wilms tumor. However, pediatric surgery experts may also need to be consulted to provide further information. DMIP should send an information request to the Sponsor

4. Would you recommend a full waiver of pediatric studies based on your response to question 1?

PMHS Response: No, the Sponsor has not provided sufficient evidence to support a full waiver of required pediatric studies. Additional information is required to assess the waiver request

5. If a partial pediatric waiver is granted, what would be the appropriate age cut-off?

PMHS Response: The Sponsor must provide the rationale and justification for any partial pediatric waiver in their pediatric drug development plan.

The Sponsor's proposed pediatric use language is acceptable, unless safety concerns arise during the Lymphoseek review that precludes the use of Lymphoseek in any pediatric age group. Any pediatric use safety concern must be placed in labeling.

RECOMMENDATIONS
Issue a Pediatric Waiver Denied Letter and request that the Sponsor submit a pediatric drug development plan that includes:

- Epidemiologic data on pediatric malignancies likely to spread to the lymph nodes for which Lymphoseek could be used intraoperatively for evaluation of tumor-draining lymph nodes;

- A rationale for extrapolating efficacy from adult studies to the pediatric population based on dosimetry, if extrapolation of efficacy would be appropriate; and,

- A complete justification for any partial waiver of pediatric studies.

- A request for deferral and a plan that outlines the pediatric studies to be conducted.

The PMHS regulatory project management staff will assist you with the apprpriate letter and PREA template language to sent to the Sponsor. In addition, PMHS will be glad to assist in the review of the revised pediatric plan after submission.

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

/s/

JEANINE A BEST
12/20/2011

HARI C SACHS
12/20/2011
I agree with the recommendations contained within this consult. PMHS also participated in a teleconference on Dec 20, 2011 to inform the Sponsor that the waiver is going to be denied and provided a general outline of what needed to be submitted.

LISA L MATHIS
12/21/2011

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 202207

Name of Drug: Lymphoseek® (Tilmanocept) Powder for injection

Applicant: Neoprobe Corporation

Labeling Reviewed

Submission Date: August 10, 2011

Receipt Date: August 10, 2011

Background and Summary Description

On August 10, 2011 Neoprobe Corporation submitted a new drug application to the Division of Medical Imaging Products for their product called Lymphoseek. The proposed indication for Lymphoseek i (b) (4)

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with an "X" in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

1. All cross referencing needs to be italicized.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by November 11, 2011. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager Date

Chief, Project Management Staff Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☒ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**

  ☒ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**" (The Entire Highlights limitation statement is present however it needs to be all bolded)

- **Product Title**

  ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

  ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

  ☐ All text in the boxed warning is **bolded**.

  ☐ Summary of the warning must not exceed a length of 20 lines.

  ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").

  ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

  ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

  ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."

  ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.

  ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

  ☐ Removal of a section or subsection should be noted. For example, "Dosage and

Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**
  - ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

    http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**
  - ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."
  - ☐ All contraindications listed in the FPI must also be listed in HL.
  - ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
  - ☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
  - ☐ For drug products other than vaccines, the verbatim **bolded** statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**
  - ☐ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

- **Revision Date**
  - ☐ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.

☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.

☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.

☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

8.1 Pregnancy

8.3 Nursing Mothers (not 8.2)

8.4 Pediatric Use (not 8.3)

8.5 Geriatric Use (not 8.4)

☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**

☒ A horizontal line must separate the TOC and FPI.

☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.

☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.

☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.
  - ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."
  - ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

    "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**
  - ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "See FDA-approved patient labeling (Medication Guide)"
    - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information)"
    - "See FDA-approved patient labeling (Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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

/s/

ALBERTA E DAVIS WARREN
10/21/2011

KYONG A KANG
10/21/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202207 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Lymphoseek Established/Proper Name: Tilmanocept Dosage Form: Powder for Injection Strengths: 0.25 mg per vial		
Applicant: Neoprobe Corporation Agent for Applicant (if applicable):		
Date of Application: August 10, 2011 Date of Receipt: August 10, 2011 Date clock started after UN:		
PDUFA Goal Date: June 10, 2012	Action Goal Date (if different): June 8, 2012	
Filing Date: October 9, 2011	Date of Filing Meeting: September 19, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s):		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 61757	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☒ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	NA this is an electronic submission

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			X	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			PeRC meeting scheduled for March 28, 2011.
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Requested a full waiver of pediatric studies.

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			Full waiver of pediatric studies
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***			X	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☒ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Consult sent 8-16-11
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			Consult sent 8-16-11
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Consult sent 8-16-11
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 10-24-2007 ***If yes, distribute minutes before filing meeting***	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 10-4-10 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 19, 2011

BLA/NDA/Supp #: 202207

PROPRIETARY NAME: Lymphoseek®

ESTABLISHED/PROPER NAME: Tilmanocept

DOSAGE FORM/STRENGTH: Powder for Injection/0.25 mg per vial

APPLICANT: Neoprobe Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): (b) (4)

BACKGROUND: Pre-NDA meeting was held on October 4, 2010 under IND 61757. New Drug application submitted to the Agency on August 10, 2011.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alberta Davis-Warren	Y
	CPMS/TL:	Kyong Kaye Kang	N
Cross-Discipline Team Leader (CDTL)	Alex Gorovets		Y
Clinical	Reviewer:	Brenda Ye	Y
	TL:	Alex Gorovets	Y
Social Scientist Review (*for OTC products*)	Reviewer:	NA	
	TL:	NA	
OTC Labeling Review (*for OTC products*)	Reviewer:	NA	
	TL:	NA	
Clinical Microbiology (*for antimicrobial*	Reviewer:	NA	

products)			
	TL:	NA	

Clinical Pharmacology	Reviewer:	Christy John	Y
	TL:	Gene Williams	Y
Biostatistics	Reviewer:	Satish Misra	N
	TL:	Anthony Mucci	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Olayinka Dina	Y
	TL:	Adebayo Laniyonu	Y
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC)	Reviewer:	Ravindra Kasliwal	Y
	TL:	Eldon Leutzinger	Y
Quality Microbiology *(for sterile products)*	Reviewer:	John Metcalfe	Y
	TL:	James McVey	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	Y
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		

	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	James Dvorsky DDMAC, John Lee DSI,		N
Other attendees	Dwaine Rieves, Louis Marzella, Charles Ganley, Shaw Chen, Ali Al Hakim, Sandra Griffith, Frank Lutterodt		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: the product is not first in its

reason. For example: o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	class.
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Comments:	

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Charles Ganley, M.D.

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

ALBERTA E DAVIS WARREN
10/12/2011